PTO/AIA/15 (03-13)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	13211-713.302
First Named Inventor	Adam BOWEN
Title	NICOTINE SALT FORMULATIONS FOR ...
Express Mail Label No.	FILED VIA EFS ON 10/28/2015

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☐ **Applicant asserts small entity status.** See 37 CFR 1.27
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☑ **Specification** [*Total Pages* 95] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. ☑ **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 8]
6. **Inventor's Oath or Declaration** [*Total Pages* 2] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☑ A copy from a prior application (37 CFR 1.63(d))
7. ☑ **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

ACCOMPANYING APPLICATION PAPERS

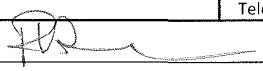
10. ☐ **Assignment Papers** (cover sheet & document(s)) Name of Assignee _____
11. ☐ **37 CFR 3.73(c) Statement** (*when there is an assignee*) ☐ **Power of Attorney**
12. ☐ **English Translation Document** (*if applicable*)
13. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
14. ☐ **Preliminary Amendment**
15. ☐ **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. ☐ **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. ☐ **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. ☑ **Other:** Certification and Request for Prioritized Examination (Track 1), Fee Transmittal

*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 66854 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature		Date	October 28, 2015
Name (Print/Type)	Richard D. Shoop	Registration No. (Attorney/Agent)	45,763

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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EX1031
NJOY v. JUUL
IPR2026-00161

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Adam BOWEN	Nonprovisional Application Number (if known):	
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature 	Date October 28, 2015
Name (Print/Typed) Richard D. Shoop	Practitioner Registration Number 45,763

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of one forms are submitted.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on October 28, 2015.

/Jennifer Capizzi/ October 28, 2015
Jennifer Capizzi Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	Unassigned	Confirmation No.	: Unassigned
First Named Inventor	:	Adam BOWEN		
Filing Date	:	Herewith		
Art Unit	:	Unassigned		
Examiner	:	Unassigned		
Title	:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Customer No.	:	66854		

FEE TRANSMITTAL

Transmitted herewith are the following fees:

(1) Basic Filing Fee - Utility	$280
(2) Utility Search Fee	$600
(3) Utility Examination Fee	$720
(4) Claims in Excess of 20 (3 x $80)	$240
(5) Independent Claims in Excess of 3 (0 x $420)	$0
(6) Processing fee (1.17(i))	$140
(7) Prioritized Examination Fee (Track 1) (1.17(c))	$4,000
(8) Application Size Fee (0 x $400)	$0
Total	**$5,980**

☒ The above fees have been paid via EFS to Deposit Account No. 50-4050. Please also deduct from or credit to said Deposit Account any other fees attendant with this matter.

Respectfully submitted,

Dated: October 28, 2015 By: _____
Richard D. Shoop, Reg. No. 45,763

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SG Docket No.: 13211-713.302

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ■ United States application or PCT international application number 14/271,071 filed on May 6, 2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Adam Bowen Date (Optional): 5/14/14

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

■ United States application or PCT international application number 14/271,071 filed on May 6, 2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Chenyue Xing Date (Optional): 05/19/14

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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UNITED STATES PATENT APPLICATION

NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

Inventor(s):

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/Jennifer Capizzi/ October 28, 2015
Jennifer Capizzi Date

NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

CROSS REFERENCE

[0001] This application is a continuation of U.S. Patent Application No. 14/271,071, filed May 6, 2014, titled "NICOTINE SALT FORMULATIONS FOR AEROLSOL DEVICES AND METHODS THEREOF," now U.S. Patent Publication No. 2014-0345631-A1, which claims the benefit of U.S. Provisional Patent Application No. 61/820,128, filed May 6, 2013, and U.S. Provisional Patent Application No. 61/912,507, filed December 5, 2013, which are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

[0002] Provided herein is a method of delivering nicotine to a user comprising operating an electronic cigarette to a user wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

[0003] Provided herein is a method of delivering nicotine to a user comprising operating an electronic cigarette to a user wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

[0004] Provided herein is a method of delivering nicotine to a user comprising operating an electronic cigarette wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

[0005] Provided herein is a method of delivering nicotine to a user comprising providing an electronic cigarette to a user wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

[0006] Provided herein is a method of delivering nicotine to the blood of a user, said method comprising providing an aerosol that is inhaled by the user from an electronic cigarette that comprises a nicotine salt formulation wherein providing the aerosol comprises the electronic cigarette heating the formulation thereby generating the aerosol, wherein the aerosol is effective in delivering a level of nicotine in the blood of the user that is at least 5ng/mL at about 1.5 minutes after a first puff of ten puffs of the aerosol, each puff taken at 30 second intervals.

[0007] Provided herein is a nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C.

[0008] Provided herein is a nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C.

[0009] Provided herein is a nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

[0010] Provided herein is a nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the

cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

[0011] Provided herein is a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C.

[0012] Provided herein is a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C.

[0013] Provided herein is a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

[0014] Provided herein is a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

[0015] Provided herein is a nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C.

[0016] Provided herein is a nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid

carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

[0017] Provided herein is a nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

[0018] Provided herein is a nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

[0019] Provided herein is a use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

[0020] Provided herein is a use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

[0021] Provided herein is a use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

[0022] Provided herein is a use of a nicotine salt formulation for delivery of nicotine to the blood of a user from an electronic cigarette, wherein the nicotine salt formulation in the

electronic cigarette is heated to form an aerosol which delivers a level of nicotine in the blood of the user that is at least 5 ng/mL at about 1.5 minutes after a first puff of ten puffs of the aerosol, each puff taken at 30 second intervals.

[0023] Provided herein is a use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

[0024] Provided herein is a cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

[0025] Provided herein is a cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

[0026] Provided herein is a cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

[0027] Provided herein is a cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

[0028] Provided herein is an electronic cigarette for generating an inhalable aerosol comprising:

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C;

a battery; and

a mouthpiece.

[0029] Provided herein is an electronic cigarette for generating an inhalable aerosol comprising:

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C;

a battery; and

a mouthpiece.

[0030] Provided herein is an electronic cigarette for generating an inhalable aerosol comprising:

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point;

a battery; and

a mouthpiece.

[0031] Provided herein is an electronic cigarette for generating an inhalable aerosol comprising:

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point;

a battery; and

a mouthpiece.

[0032] Provided herein is a cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 ^{o}C.

[0033] Provided herein is a cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

[0034] Provided herein is a cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

[0035] Provided herein is a cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

[0036] Provided herein is a kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

[0037] Provided herein is a kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

[0038] Provided herein is a kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

[0039] Provided herein is a kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature

of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

INCORPORATION BY REFERENCE

[0040] All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are used, and the accompanying drawings of which:

[0042] **Figure 1** illustrates results of heart rate data measured for six minutes from start of puffing. Y-axis is heart rate (bpm) and X-axis represent duration of the test (-60 to 180 seconds);

[0043] **Figure 2** illustrates results of heart rate data measured for ten minutes from start of puffing. Y-axis is heart rate (bpm) and X-axis represents duration of the test (0 to 10 minutes);

[0044] **Figure 3** illustrates the calculated vapor pressures of various acids relative to nicotine;

[0045] **Figure 4** illustrates the pharmacokinetic profiles for eight test articles in a blood plasma study;

[0046] **Figure 5** illustrates the comparison of C_{max} and T_{max} for eight test articles in a blood plasma study;

[0047] **Figure 6** illustrates the comparison of C_{max} and AUC for eight test articles in a blood plasma study;

[0048] **Figure 7** depicts an example embodiment of an electronic cigarette having a fluid storage compartment comprising an embodiment nicotine salt formulation described herein; and

[0049] **Figure 8** depicts an example embodiment of an electronic cigarette cartomizer having a fluid storage compartment, a heater, and comprising an embodiment nicotine salt formulation described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0050] Nicotine is a chemical stimulant and increases heart rate and blood pressure when provided to an individual or animal. Nicotine transfer to an individual is associated with a feeling of physical and/or emotional satisfaction. Conflicting reports have been published regarding the transfer efficiency of free base nicotine in comparison to mono- or di-protonated nicotine salts. Studies on the transfer efficiency of free base nicotine and nicotine salts are complex and have yielded unpredictable results. Further, such transfer efficiency studies have been performed under extremely high temperature conditions, comparable to smoking; therefore, they offer scant guidance on the transfer efficiency of free base nicotine and nicotine salts under low-temperature vaporization conditions. Some reports have posited that nicotine free base should give rise to a greater satisfaction in a user than any corresponding nicotine salt.

[0051] It has been unexpectedly discovered herein that certain nicotine salt formulations provide satisfaction in an individual superior to that of free base nicotine, and more comparable to the satisfaction in an individual smoking a traditional cigarette. The satisfaction effect is consistent with an efficient transfer of nicotine to the lungs of an individual and a rapid rise of nicotine absorption in the plasma as shown, for non-limiting example, in Example 8, at least. It has also been unexpectedly discovered herein that certain nicotine salt formulations provide greater satisfaction than other nicotine salt formulations, and such effect has been shown in blood plasma levels of example nicotine salt formulations herein, for non-limiting example, in Example 8, at least. These results show a difference in rate of nicotine uptake in the blood that is higher for some nicotine salt formulations aerosolized by an electronic cigarette than for other nicotine salt formulations, and likewise higher than nicotine freebase formulations, while the peak concentration of the nictoine in the blood and total amount of nicotine delivered appears comparable to a traditional cigarette, and do not appear to vary significantly between the various nicotine formulations. Therefore, described herein are nicotine salt formulations for use in an electronic cigarette, or the like, that provide a general satisfaction effect consistent with an efficient transfer of nicotine to the lungs of an individual and a rapid rise of nicotine absorption

in the plasma. Provided herein, therefore, are devices, formulation of nicotine salts, systems, cartomizers, kits and methods that are used to inhale an aerosol generated from a nicotine salt liquid formulation through the mouth or nose as described herein or as would be obvious to one of skill in the art upon reading the disclosure herein.

[0052] Consistent with these satisfaction effects, it has unexpectedly been found herein that there is a difference between the C_{max} (maximum concentration) and T_{max} (time at which the maximum concentration is measured) when measuring blood plasma nicotine levels of freebase nicotine formulations inhaled using a low temperature vaporization device, i.e. electronic cigarette, as compared to the C_{max} and T_{max} (similarly measuring blood plasma nicotine levels) of a traditional cigarette. Also consistent with these satisfaction effects, it has unexpectedly been found herein that there is a difference between the C_{max} (maximum concentration) and T_{max} (time at which the maximum concentration is measured) when measuring blood plasma nicotine levels of freebase nicotine formulations inhaled using a low temperature vaporization device, i.e. electronic cigarette, as compared to the C_{max} and T_{max} (similarly measuring blood plasma nicotine levels) of nicotine salt formulations inhaled using a low temperature vaporization device, i.e. electronic cigarette. Additionally, it has unexpectedly been found that there is a difference between the rate of nicotine uptake in the plasma of users inhaling freebase nicotine formulations using a low temperature vaporization device, i.e. electronic cigarette, as compared to the rate of nicotine uptake in the plasma of users inhaling smoke of a traditional cigarette. Furthermore, it has unexpectedly been found that there is a difference between the rate of nicotine uptake in the plasma of users inhaling freebase nicotine formulations using a low temperature vaporization device, i.e. electronic cigarette, as compared to the rate of nicotine uptake in the plasma of users inhaling nicotine salt formulations using a low temperature vaporization device, i.e. electronic cigarette.

[0053] Thus, looking at freebase nicotine as a source of nicotine in compositions used in e-cigarettes, freebase nicotine compositions' delivery of nicotine to blood when inhaled using is not necessarily comparable in blood plasma levels (C_{max} and T_{max}) to a traditional cigarette's nicotine delivery to blood when inhaled. Freebase nicotine compositions' delivery of nicotine to blood when inhaled using is not necessarily comparable in blood plasma levels (C_{max} and T_{max}) to nicotine salt formulations' nicotine delivery to blood when inhaled. Freebase nicotine compositions' delivery of nicotine to blood when inhaled using is not necessarily comparable in

blood plasma levels when measuring the rate of nicotine uptake in the blood within the first 0-5 minutes to a traditional cigarette's nicotine delivery to blood when inhaled. Freebase nicotine compositions' delivery of nicotine to blood when inhaled using necessarily is not comparable in blood plasma levels when measuring the rate of nicotine uptake in the blood within the first 0-5 minutes to nicotine salt formulations' nicotine delivery to blood when inhaled.

[0054] Also consistent with these satisfaction effects, it has unexpectedly been found herein that while there appears to be comparable C_{max} and T_{max} values (measuring blood plasma nicotine levels) of nicotine salt formulations inhaled using a low temperature vaporization device, i.e. electronic cigarette, as compared to the C_{max} and T_{max} (similarly measuring blood plasma nicotine levels) of a traditional cigarette, there is a demonstrable difference between the rate of nicotine uptake in the plasma of users inhaling certain nicotine salt formulations using a low temperature vaporization device, i.e. electronic cigarette, as compared to the rate of nicotine uptake in the plasma of users inhaling other nicotine salt formulations using a low temperature vaporization device, i.e. electronic cigarette. It is also unexpected that while the C_{max} and T_{max} values are comparable to those of a traditional cigarette, (or are approaching that of a traditional cigarette), the rate of nicotine uptake in the plasma of blood of users is higher in certain nicotine salt formulations than that of the traditional cigarette. The nicotine salt formulations which demonstrate the quickest rate of nicotine uptake in the plasma were more preferred in satisfaction evaluations, and were rated more equivalent to cigarette satisfaction than the nicotine salt formulations showing the slowest rates of rise of nicotine in the subjects' blood plasma. In addition, doubling the concentration of the nicotine salt in the formulation may not necessarily impact the rate of absorption of nicotine in the blood (see, for non-limiting example Example 8, nicotine benzoate tested in 4% and 2% concentrations).

[0055] Thus, looking at nicotine salt formulations used in e-cigarettes, nicotine salt formulations delivered using an e-cigarette appear comparable in C_{max} and T_{max} values (measuring blood plasma nicotine levels), however, not all nicotine salts perform similarly to each other or to a traditional cigarette with respect to the rate of nicotine uptake in the blood at early time periods (0-1.5 minutes). These results are unexpected. Nicotine salt formulations made using acids having a Vapor Pressure between 20 – 300 mmHg @ 200 °C, or Vapor Pressure > 20 mmHg @ 200 °C, or a Vapor Pressure from 20 to 300 mmHg @ 200 °C, or a Vapor Pressure from 20 to 200 mmHg @ 200 °C, a Vapor Pressure between 20 and 300 mmHg

@ 200 °C appear to have a higher rate of nicotine uptake in the blood at early time periods (0-1.5 minutes, 0-3 minutes, 0-2 minutes, 0-4 minutes for non-limiting example) than other nicotine salt formulations, however, they also provide satisfaction comparable to a traditional cigarette or closer to a traditional cigarette (as compared to other nicotine salt formulations or as compared to nicotine freebase formulations). For non-limiting example, acids that meet one or more criteria of the prior sentence include salicylic acid, sorbic acid, benzoic acid, lauric acid, and levulinic acid. Nicotine salt formulations made using acids that have a difference between boiling point and melting point of at least 50 °C, and a boiling point greater than 160 °C, and a melting point less than 160 °C appear to have a higher rate of nicotine uptake in the blood at early time periods (0-1.5 minutes, 0-3 minutes, 0-2 minutes, 0-4 minutes for non-limiting example) than other nicotine salt formulations, however, they also provide satisfaction comparable to a traditional cigarette or closer to a traditional cigarette (as compared to other nicotine salt formulations or as compared to nicotine freebase formulations). For non-limiting example, acids that meet the criteria of the prior sentence include salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid. Nicotine salt formulations made using acids that have a difference between boiling point and melting point of at least 50 °C, and a boiling point at most 40 °C less than operating temperature, and a melting point at least 40 °C lower than operating temperature appear to have a higher rate of nicotine uptake in the blood at early time periods (0-1.5 minutes, 0-3 minutes, 0-2 minutes, 0-4 minutes for non-limiting example) than other nicotine salt formulations, however, they also provide satisfaction comparable to a traditional cigarette or closer to a traditional cigarette (as compared to other nicotine salt formulations or as compared to nicotine freebase formulations). Operating temperature can be 100 °C to 300°C, or about 200°C, about 150°C to about 250°C, 180C to 220°C, about 180°C to about 220°C, 185°C to 215°C, about 185°C to about 215°C, about 190°C to about 210°C, 190°C to 210°C, 195°C to 205°C, or about 195°C to about 205°C. For non-limiting example, acids that meet the criteria of the prior sentence include salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid. Combinations of these criteria for preference of certain nicotine salt formulations are contemplated herein.

[0056] Other reasons for excluding certain acids from formulations may be unrelated to the rate of nicotine uptake, however. For example, an acid may be inappropriate for use with the device materials (corrosive or otherwise incompatible). Sulfuric acid is an example of this, which

may be inappropriate for the e-cigarette device. An acid may be inappropriate for use in inhalation or for toxicity reasons – thus not be compatible for human consumption, ingestion, or inhalation. Sulfuric acid again is an example of this, which may be inappropriate for a user of an e-cigarette device, depending on the embodiment of the composition. An acid that is bitter or otherwise bad-tasting may also provide a reason for exclusion, such as acetic acid in some embodiments. Acids that oxidize at room temperature or at operating temperature may be inappropriate for certain embodiments, for example, sorbic acid, as this indicates a decomposition or reaction or instability that may be undesirable in the formulation. Decomposition of acids at room or operating temperatures may also indicate that the acid is inappropriate for use in the embodiment formulations. For example, citric acid decomposes at 175°C, and malic acid decomposes at 140°C, thus for a device operating at 200°C, these acids may not be appropriate. Acids that have poor solubility in the composition constituents may be inappropriate for use in certain embodiments of the compositions herein. For example, nicotine bitartrate with a composition of nicotine and tartaric acid as 1:2 molar ratio will not produce a solution at a concentration of 0.5%(w/w) nicotine or higher and 0.9%(w/w) tartaric acid or higher in propylene glycol (PG) or vegetable glycerin (VG) or any mixture of PG and VG at ambient conditions. As used herein, weight percentage (w/w) refers to the weight of the individual component over the weight of the total formulation.

[0057] As used in this specification and the claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0058] The term "organic acid" as used herein, refers to an organic compound with acidic properties (e.g., by Brønsted-Lowry definition, or Lewis definition). A common organic acid is the carboxylic acids, whose acidity is associated with their carboxyl group –COOH. A dicarboxylic acid possesses two carboxylic acid groups. The relative acidity of an organic is measured by its pK_a value and one of skill in the art knows how to determine the acidity of an organic acid based on its given pKa value. The term "keto acid" as used herein, refers to organic compounds that contain a carboxylic acid group and a ketone group. Common types of keto acids include alpha-keto acids, or 2-oxoacids, such as pyruvic acid or oxaloacetic acid, having the keto group adjacent to the carboxylic acid; beta-keto acids, or 3-oxoacids, such as acetoacetic acid, having the ketone group at the second carbon from the carboxylic acid; gamma-keto acids,

or 4-oxoacids, such as levulinic acid, having the ketone group at the third carbon from the carboxylic acid.

[0059] The term "electronic cigarette" or "e-cigarette" or "low temperature vaporization device" as used herein, refers to an electronic inhaler that vaporizes a liquid solution into an aerosol mist, simulating the act of tobacco smoking. The liquid solution comprises a formulation comprising nicotine. There are many electronic cigarettes which do not resemble conventional cigarettes at all. The amount of nicotine contained can be chosen by the user via the inhalation. In general, an electronic cigarette contains three essential components: a plastic cartridge that serves as a mouthpiece and a reservoir for liquid, an "atomizer" that vaporizes the liquid, and a battery. Other embodiment electronic cigarettes include a combined atomizer and reservoir, called a "cartomizer" that may or may not be disposable, a mouthpiece that may be integrated with the cartomizer or not, and a battery.

[0060] As used in this specification and the claims, unless otherwise stated, the term "about" refers to variations of 1%, 2%, 3%, 4%, 5%, 10%, 15%, or 25%, depending on the embodiment.

[0061] Suitable carriers (e.g.., a liquid solvent) for the nicotine salts described herein include a medium in which a nicotine salt is soluble at ambient conditions, such that the nicotine salt does not form a solid precipitate. Examples include, but are not limited to, glycerol, propylene glycol, trimethylene glycol, water, ethanol and the like, as well as combinations thereof. In some embodiments, the liquid carrier comprises 0% to 100% of propylene glycol and 100% to 0% of vegetable glycerin. In some embodiments, the liquid carrier comprises 10% to 70% of propylene glycol and 90% to 30% of vegetable glycerin. In some embodiments, the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin. In some embodiments, the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

[0062] The formulations described herein vary in concentration. In some formulations, a dilute concentration of the nicotine salt in the carrier is utilized. In some formulations, a less dilute concentration of the nicotine salt in the carrier is utilized. In some formulations the concentration of nicotine in the nicotine salt formulation is about 1% (w/w) to about 25% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is about 1% (w/w) to about 20% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is about 1% (w/w) to about 18% (w/w). In some embodiments the concentration of nicotine in the nicotine salt formulation is about 1% (w/w) to about 15% (w/w). In some

formulations the concentration of nicotine in the nicotine salt formulation is about 4% (w/w) to about 12% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is about 4% (w/w). In some embodiments the concentration of nicotine in the nicotine salt formulation is about 2% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 1% (w/w) to 25% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 1% (w/w) to 20% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 1% (w/w) to 18% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 1% (w/w) to 15% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 4% (w/w) to 12% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 4% (w/w). In some formulations the concentration of nicotine in the nicotine salt formulation is 2% (w/w). In some formulations, a less dilute concentration of one nicotine salt is used in conjunction with a more dilute concentration of a second nicotine salt. In some formulations, the concentration of nicotine in the first nicotine salt formulation is about 1% to about 20%, and is combined with a second nicotine salt formulation having a concentration of nicotine therein from about 1% to about 20% or any range or concentration therein. In some formulations, the concentration of nicotine in the first nicotine salt formulation is 1% to 20%, and is combined with a second nicotine salt formulation having a concentration of nicotine therein from 1% to 20% or any range or concentration therein. As used with respect to concentrations of nicotine in the nicotine salt formulations, the term "about" refers to ranges of 0.05% (i.e. if the concentration is about 2%, the range is 1.95%-2.05%), 0.1 (i.e. if the concentration is about 2%, the range is 1.9%-2.1%), 0.25 (i.e. if the concentration is about 2%, the range is 1.75%-2.25%), 0.5 (i.e. if the concentration is about 2%, the range is 1.5%-2.5%), or 1 (i.e. if the concentration is about 4%, the range is 3%-5%), depending on the embodiment.

[0063] Nicotine salts are formed by the addition of a suitable acid, including organic or inorganic acids. In some formulations provided herein, suitable organic acids are carboxylic acids. Examples of organic carboxylic acids disclosed herein are monocarboxylic acids, dicarboxylic acids (organic acid containing two carboxylic acid groups), carboxylic acids containing an aromatic group such as benzoic acids, hydroxycarboxylic acids, heterocyclic carboxylic acids, terpenoid acids, sugar acids; such as the pectic acids, amino acids, cycloaliphatic acids, aliphatic carboxylic acids, keto carboxylic acids, and the like. In some

formulations provided herein, the organic acids used herein are monocarboxylic acids. Nicotine salts are formed from the addition of a suitable acid to nicotine. In some formulations provided herein, the stoichiometric ratios of the nicotine to acid (nicotine:acid) are 1:1, 1:2, 1:3, 1:4, 2:3, 2:5, 2:7, 3:4, 3:5, 3:7, 3:8, 3:10, 3:11, 4:5, 4:7, 4:9, 4:10, 4:11, 4:13, 4:14, 4:15, 5:6, 5:7, 5:8, 5:9, 5:11, 5:12, 5:13, 5:14, 5:16, 5:17, 5:18, or 5:19. In some formulations provided herein, the stoichiometric ratios of the nicotine to acid are 1:1, 1:2, 1:3, or 1:4 (nicotine:acid).

[0064] Nicotine is an alkaloid molecule that comprises two basic nitrogens. It may occur in different states of protonation. For example, if no protonation exists, nicotine is referred to as the "free base." If one nitrogen is protonated, then the nicotine would be "mono-protonated."

[0065] Nicotine salt formulations may be formed by adding a suitable acid to nicotine, stirring the neat mixture at ambient temperature or at elevated temperature, and then diluting the neat mixture with a carrier mixture, such as a mixture of propylene glycol and glycerin. In some embodiments, the suitable acid is completely dissolved by the nicotine prior to dilution. The suitable acid may not completely dissolved by the nicotine prior to dilution. The addition of the suitable acid to the nicotine to form a neat mixture may cause an exothermic reaction. The addition of the suitable acid to the nicotine to form a neat mixture may be conducted at 55 °C. The addition of the suitable acid to the nicotine to form a neat mixture may be conducted at 90 °C. The neat mixture may be cooled to ambient temperature prior to dilution. The dilution may be carried out at elevated temperature.

[0066] Nicotine salt formulations may be prepared by combining nicotine and a suitable acid in a carrier mixture, such as a mixture of propylene glycol and glycerin. The mixture of nicotine and a first carrier mixture is combined with a mixture of a suitable acid in a second carrier mixture. In some embodiments, the first and second carrier mixtures are identical in composition. In some embodiments, the first and second carrier mixtures are not identical in composition. In some embodiments, heating of nicotine/acid/carrier mixture is required to facilitate complete dissolution.

[0067] In some embodiments, nicotine salt formulations may be prepared and added to a solution of 3:7 ratio by weight of propylene glycol (PG)/vegetable glycerin (VG), and mixed thoroughly. While described herein as producing 10g of each of the formulations, all procedures noted *infra* are scalable. Other manners of formulation may also be employed form the

formulations noted infra, without departing from the disclosure herein, and as would be known to one of skill in the art upon reading the disclosure herein.

[0068] The optimal nicotine salt formulation may be determined by the vapor pressure of the constituent acid. In some embodiments, the nicotine salt formulations comprise an acid with a vapor pressure that is similar to the vapor pressure of free base nicotine. In some embodiments, the nicotine salt formulations are formed from an acid with a vapor pressure that is similar to the vapor pressure of free base nicotine at the heating temperature of the device. Figure 3 illustrates this trend. Nicotine salts formed from nicotine and benzoic acid; nicotine and salicylic acid; or nicotine and levulinic acid are salts that produce a satisfaction in an individual user consistent with efficient transfer of nicotine and a rapid rise in nicotine plasma levels. This pattern may be due to the mechanism of action during heating of the nicotine salt formulation. The nicotine salt may disassociate at, or just below, the heating temperature of the device, resulting in a mixture of free base nicotine and the individual acid. At that point, if both the nicotine and acid have similar vapor pressures, they may aerosolize at the same time, giving rise to a transfer of both free base nicotine and the constituent acid to the user.

[0069] The nicotine salt liquid formulation for generating an inhalable aerosol upon heating in an electronic cigarette may comprise a nicotine salt in a biologically acceptable liquid carrier; wherein the acid used to form said nicotine salt is characterized by a vapor pressure between 20 – 4000 mmHg at 200 °C. In some embodiments, the acid used to form the nicotine salt is characterized by vapor pressure between 20 – 2000 mmHg at 200 °C. In some embodiments, the acid used to form the nicotine salt is characterized by vapor pressure between 100 – 300 mmHg at 200 °C.

[0070] Unexpectedly, different nicotine salt formulations produced varying degrees of satisfaction in an individual. In some embodiments, the extent of protonation of the nicotine salt affected satisfaction, such that more protonation was less satisfying as compared to less protonation. The nicotine salt formed may be monoprotonated. The nicotine salt formed may be diprotonated. The nicotine salt may exist in more than one protonation state, e.g., an equilibrium of mono-protonated and di-protonated nicotine salts. The extent of protonation of the nicotine molecule may be dependent upon the stoichiometric ratio of nicotine:acid used in the salt formation reaction. The extent of protonation of the nicotine molecule may be dependent upon the solvent. The extent of protonation of the nicotine molecule may be unknown. In some

embodiments, monoprotonated nicotine salts produced a high degree of satisfaction in the user. For example, nicotine benzoate and nicotine salicylate are mono-protonated nicotine salts and all produce a high degree of satisfaction in the user. The reason for this trend may be explained by a mechanism of action wherein the nicotine is first deprotonated prior to transfer to the vapor with the constituent acid and then retained and stabilized after re-protonated by the acid going down stream to the lungs of the user. It may be easier to remove one proton versus two protons, thus resulting in better transfer efficiency. In addition, the lack of satisfaction of free base nicotine indicates that a second factor may be important. A nicotine salt may be best performing when it is at its optimal extent of protonation, depending on the salt. For example, nicotine pyruvate is a nicotine salt with 1:2 nicotine:acid ratio. The formulation containing nicotine pyruvate (1:2) may deliver more satisfaction to the user than the one containing same amount of nicotine but only half amount of pyruvic acid, i.e. nicotine pyruvate (1:1). This may be explained as 1 mole of nicotine produces a salt with 2 moles of pyruvic acid. When there is not enough pyruvic acid to associate with all nicotine molecules, the free base nicotine left unprotonated in the formulation may reduce the satisfaction the formulation provides.

[0071] The flavor of the constituent acid used in the salt formation may be a consideration in choosing the acid. A suitable acid may have minimal or no toxicity to humans in the concentrations used. A suitable acid may be compatible with the electronic cigarette components it contacts or could contact at the concentrations used. That is, such acid does not degrade or otherwise react with the electronic cigarette components it contacts or could contact. The odor of the constituent acid used in the salt formation may be a consideration in choosing a suitable acid. The concentration of the nicotine salt in the carrier may affect the satisfaction in the individual user. In some embodiments, the flavor of the formulation is adjusted by changing the acid. In some embodiments, the flavor of the formulation is adjusted by adding exogenous flavorants. In some embodiments, an unpleasant tasting or smelling acid is used in minimal quantities to mitigate such characteristics. In some embodiments, exogenous pleasant smelling or tasting acid is added to the formulation. Examples of salts which can provide flavor and aroma to the mainstream aerosol at certain levels include nicotine acetate, nicotine oxalate, nicotine malate, nicotine isovalerate, nicotine lactate, nicotine citrate, nicotine phenylacetate and nicotine myristate.

[0072] Nicotine salt formulations may generate an inhalable aerosol upon heating in an electronic cigarette. The amount of nicotine or nicotine salt aerosol inhaled may be user-determined. The user may, for example, modify the amount of nicotine or nicotine salt inhaled by adjusting his inhalation strength.

[0073] Formulations are described herein comprising two or more nicotine salts. In some embodiments, wherein a formulation comprises two or more nicotine salts, each individual nicotine salt is formed as described herein.

[0074] Nicotine salt formulations, as used herein, refer to a single or mixture of nicotine salts with other suitable chemical components used for e-cigarette, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the nicotine salt formulation is stirred at ambient conditions for 20 minutes. In certain embodiments, the nicotine salt formulation is heated and stirred at 55C for 20 minutes. In certain embodiments, the nicotine salt formulation is heated and stirred at 90C for 60 minutes. In certain embodiments, the formulation facilitates administration of nicotine to an organism (e.g., lung).

[0075] The nicotine of nicotine salt formulations provided herein is either naturally occurring nicotine (e.g., from extract of nicotineous species such as tobacco), or synthetic nicotine. In some embodiments, the nicotine is (-)-nicotine, (+)-nicotine, or a mixture thereof. In some embodiments, the nicotine is employed in relatively pure form (e.g., greater than about 80% pure, 85% pure, 90% pure, 95% pure, or 99 % pure). In some embodiments, the nicotine for nicotine salt formulation provided herein is "water clear" in appearance in order to avoid or minimize the formation of tarry residues during the subsequent salt formation steps.

[0076] Nicotine salt formulations used for e-cigarettes described herein, in some embodiments, have a nicotine concentration of about 0.5% (w/w) to about 20% (w/w), wherein the concentration is of nicotine weight to total solution weight, i.e. (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 20% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 18% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 15% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 4% (w/w) to about 12% (w/w). In certain

embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 18% (w/w), about 3% (w/w) to about 15% (w/w), or about 4% (w/w) to about 12% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 0.5% (w/w) to about 10% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 0.5% (w/w) to about 5% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 0.5% (w/w) to about 4% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 0.5% (w/w) to about 3% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 0.5% (w/w) to about 2% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 0.5% (w/w) to about 1% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 10% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 5% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 4% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 3% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 1% (w/w) to about 2% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 2% (w/w) to about 10% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 2% (w/w) to about 5% (w/w). In certain embodiments, nicotine salt formulations provided herein have a nicotine concentration of about 2% (w/w) to about 4% (w/w). Certain embodiments provide a nicotine salt formulation having a nicotine concentration of about 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% (w/w), or more, including any increments therein. Certain embodiments provide a nicotine salt formulation having a nicotine concentration of about 5% (w/w). Certain embodiments provide a nicotine salt formulation having a nicotine concentration of about 4% (w/w). Certain

embodiments provide a nicotine salt formulation having a nicotine concentration of about 3% (w/w). Certain embodiments provide a nicotine salt formulation having a nicotine concentration of about 2% (w/w). Certain embodiments provide a nicotine salt formulation having a nicotine concentration of about 1% (w/w). Certain embodiments provide a nicotine salt formulation having a nicotine concentration of about 0.5% (w/w).

[0077] The formulation further may comprise one or more flavorants.

[0078] Thee suitable acid for the nicotine salt formulation may have a vapor pressure >20 mmHg at 200 °C and is non-corrosive to the electronic cigarette or is non-toxic to humans. In some embodiments, the suitable acid for nicotine salt formation is selected from the group consisting of salicylic acid, formic acid, sorbic acid, acetic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

[0079] Thee suitable acid for the nicotine salt formulation may have a vapor pressure of about 20 to 200 mmHg at 200 °C and is non-corrosive to the electronic cigarette or is non-toxic to humans. In some embodiments, the suitable acid for nicotine salt formation is selected from the group consisting of salicylic acid, benzoic acid, lauric acid, and levulinic acid.

[0080] Thee suitable acid for the nicotine salt formulation may have a melting point <160 °C, a boiling point >160 °C, at least a 50-degree difference between the melting point and the boiling point, and is non-corrosive to the electronic cigarette or is non-toxic to humans. In some embodiments, the suitable acid for nicotine salt formation has a melting point at least 40 degrees lower than the operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, at least a 50-degree difference between the melting point and the boiling point, and is non-corrosive to the electronic cigarette or is non-toxic to humans; wherein the operating temperature is 200 °C. In some embodiments, the suitable acid for nicotine salt formation is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

[0081] Thee suitable acid for the nicotine salt formulation does not decompose at the operating temperature of the electronic cigarette. In some embodiments, the suitable acid for nicotine salt formation does not oxidize at the operating temperature of the electronic cigarette. In some embodiments, the suitable acid for nicotine salt formation does not oxidize at room temperature. In some embodiments, the suitable acid for nicotine salt formation does not provide

an unpleasant taste. In some embodiments, the suitable acid for nicotine salt formation has good solubility in a liquid formulation for use in an electronic cigarette.

[0082] Provided herein is an electronic cigarette 2 having a fluid storage compartment 4 comprising an embodiment nicotine salt formulation of any embodiment described herein within the fluid storage compartment described herein. An embodiment is shown in FIG. 7. The electronic cigarette 2 of FIG. 7 includes a mouth end 6, and a charging end 8. The mouth-end 6 includes a mouthpiece 10. The charging end 8 may connect to a battery or a charger or both, wherein the battery is within a body of the electronic cigarette, and the charger is separate from the battery and couples to the body or the battery to charge the battery. In some embodiments the electronic cigarette comprises a rechargeable battery within a body 14 of the electronic cigarette and the charge end 8 comprises a connection 12 for charging the rechargeable battery. In some embodiments, the electronic cigarette comprises a cartomizer that comprises the fluid storage compartment and an atomizer. In some embodiments, the atomizer comprises a heater. In some embodiments the fluid storage compartment 4 is separable from an atomizer. In some embodiments the fluid storage compartment 4 is replaceable as part of a replaceable cartridge. In some embodiments the fluid storage compartment 4 is refillable. In some embodiments, the mouthpiece 10 is replaceable.

[0083] Provided herein is a cartomizer 18 for an electronic cigarette 2 having a fluid storage compartment 4 comprising an embodiment nicotine salt formulation of any embodiment described herein within the fluid storage compartment described herein. The cartomizer 18 embodiment of FIG. 8 includes a mouth end 6, and a connection end 16. The connection end 16 in the embodiment of FIG. 8 couples the cartomizer 14 to a body of an electronic cigarette, or to a battery of the electronic cigarette, or both. The mouth end 6 includes a mouthpiece 10. In some embodiments, the cartomizer does not include a mouthpiece, and in such embodiments, the cartomizer can be coupled to a mouthpiece of an electronic cigarette, or the cartomizer can be coupled to a battery or body of an electronic cigarette, while the mouthpiece is also coupled to the battery or the body of the electronic cigarette. In some embodiments, the mouthpiece is integral with the body of the electronic cigarette. In some embodiments, including the embodiment of FIG. 8, the cartomizer 18 comprises the fluid storage compartment 4 and an atomizer (not shown). In some embodiments, the atomizer comprises a heater (not shown)

Examples

Example 1: Preparation of Nicotine salt Formulations

[0084] Various nicotine formulations were prepared and added to a solution of 3:7 ratio by weight of propylene glycol (PG)/vegetable glycerin (VG), and mixed thoroughly. The examples shown below were used to make 10g of each of the formulations. All procedures are scalable.

[0085] For example, in order to make nicotine formulations with a final nicotine free base equivalent concentration of 2% (w/w), the following procedures were applied to each individual formulation.

- Nicotine benzoate salt formulation: 0.15g benzoic acid was added to a beaker followed by adding 0.2g nicotine to the same beaker. The mixture was stirred at 55 °C for 20 minutes until benzoic acid was completely dissolved and an orange oily mixture was formed. The mixture was cooled down to ambient conditions. 9.65g PG/VG (3:7) solution was added to the orange nicotine benzoate salt and the mixture was stirred until a visually homogenous formulation solution was achieved.
- Nicotine benzoate salt formulation can also be made by adding 0.15g benzoic acid to a beaker followed by adding 0.2g nicotine and 9.65g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 55 °C for 20 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine citrate salt formulation was made by adding 0.47g citric acid to a beaker followed by adding 0.2g nicotine and 9.33g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine malate salt formulation was made by adding 0.33g L-malic acid to a beaker followed by adding 0.2g nicotine and 9.47g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine succinate salt formulation was made by adding 0.29g succinic acid to a beaker followed by adding 0.2g nicotine and 9.51g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.

- Nicotine salicylate salt formulation was made by adding 0.17g salicylic acid to a beaker followed by adding 0.2g nicotine and 9.63g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine salicylate salt formulation can also be made by adding 0.17g salicylic acid to a beaker followed by adding 0.2g nicotine to the same beaker. The mixture was stirred at 90 °C for 60 minutes until salicylic acid was completely dissolved and an orange oily mixture was formed. The mixture was either cooled to ambient conditions or kept at 90 °C when 9.63g PG/VG (3:7) solution was added. The mixture was then stirred at 90 °C until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine free base formulation was made by adding 0.2g nicotine to a beaker followed by adding 9.8g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at ambient conditions for 10 minutes until a visually homogenous formulation solution was achieved.

[0086] For example, in order to make nicotine salt formulations with a final nicotine free base equivalent concentration of 3% (w/w), the following procedures were applied to each individual formulation.

- Nicotine benzoate salt formulation: 0.23g benzoic acid was added to a beaker followed by adding 0.3g nicotine to the same beaker. The mixture was stirred at 55 °C for 20 minutes until benzoic acid was completely dissolved and an orange oily mixture was formed. The mixture was cooled down to ambient conditions. 9.47g PG/VG (3:7) solution was added to the orange nicotine benzoate salt and the blend was stirred until a visually homogenous formulation solution was achieved.
- Nicotine benzoate salt formulation can also be made by adding 0.23g benzoic acid to a beaker followed by adding 0.3g nicotine and 9.47g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 55 °C for 20 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine citrate salt formulation was made by adding 0.71g citric acid to a beaker followed by adding 0.3g nicotine and 8.99g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.

- Nicotine malate salt formulation was made by adding 0.5g L-malic acid to a beaker followed by adding 0.3g nicotine and 9.2g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine levulinate salt formulation was made by adding melted 0.64g levulinic acid to a beaker followed by adding 0.3g nicotine to the same beaker. The mixture was stirred at ambient conditions for 10 minutes. Exothermic reaction took place and oily product was produced. The mixture was allowed to cool down to ambient temperature and 9.06g PG/VG (3:7) solution was added to the same beaker. The mixture was then stirred at ambient conditions for 20 minutes until a visually homogenous formulation solution was achieved.
- Nicotine pyruvate salt formulation was made by adding 0.33g pyruvic acid to a beaker followed by adding 0.3g nicotine to the same beaker. The mixture was stirred at ambient conditions for 10 minutes. Exothermic reaction took place and oily product was produced. The mixture was allowed to cool down to ambient temperature and 9.37g PG/VG (3:7) solution was added to the same beaker. The mixture was then stirred at ambient conditions for 20 minutes until a visually homogenous formulation solution was achieved.
- Nicotine succinate salt formulation was made by adding 0.44g succinic acid to a beaker followed by adding 0.3g nicotine and 9.26g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine salicylate salt formulation was made by adding 0.26g salicylic acid to a beaker followed by adding 0.3g nicotine and 9.44g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine salicylate salt formulation can also be made by adding 0.26g salicylic acid to a beaker followed by adding 0.3g nicotine to the same beaker. The mixture was stirred at 90 °C for 60 minutes until salicylic acid was completely dissolved and an orange oily mixture was formed. The mixture was either cooled to ambient conditions or kept at 90 °C when 9.44g PG/VG (3:7) solution was added. The blend was then stirred at 90C until a visually homogenous formulation solution was achieved with no undissolved chemicals.

- Nicotine free base formulation was made by adding 0.3g nicotine to a beaker followed by adding 9.7g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at ambient conditions for 10 minutes until a visually homogenous formulation solution was achieved.

[0087] For example, in order to make nicotine salt formulations with a final nicotine free base equivalent concentration of 4% (w/w), the following procedures were applied to each individual formulation.

- Nicotine benzoate salt formulation: 0.3g benzoic acid was added to a beaker followed by adding 0.4g nicotine to the same beaker. The mixture was stirred at 55 °C for 20 minutes until benzoic acid was completely dissolved and an orange oily mixture was formed. The mixture was cooled down to ambient conditions. 9.7g PG/VG (3:7) solution was added to the orange nicotine benzoate salt and the blend was stirred until a visually homogenous formulation solution was achieved.
- Nicotine benzoate salt formulation can also be made by adding 0.3g benzoic acid to a beaker followed by adding 0.4g nicotine and 9.7g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 55 °C for 20 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.

For example, in order to make nicotine salt formulations with a final nicotine free base equivalent concentration of 5% (w/w), the following procedures were applied to each individual formulation.

- Nicotine benzoate salt formulation: 0.38g benzoic acid was added to a beaker followed by adding 0.5g nicotine to the same beaker. The mixture was stirred at 55 °C for 20 minutes until benzoic acid was completely dissolved and an orange oily mixture was formed. The mixture was cooled down to ambient conditions. 9.12g PG/VG (3:7) solution was added to the orange nicotine benzoate salt and the blend was stirred until a visually homogenous formulation solution was achieved.
- Nicotine benzoate salt formulation can also be made by adding 0.38g benzoic acid to a beaker followed by adding 0.5g nicotine and 9.12g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 55 °C for 20 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine malate salt formulation was made by adding 0.83g L-malic acid to a beaker followed by adding 0.5g nicotine and 8.67g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.

- Nicotine levulinate salt formulation was made by adding melted 1.07g levulinic acid to a beaker followed by adding 0.5g nicotine to the same beaker. The mixture was stirred at ambient conditions for 10 minutes. Exothermic reaction took place and oily product was produced. The mixture was allowed to cool down to ambient temperature and 8.43g PG/VG (3:7) solution was added to the same beaker. The mixture was then stirred at ambient conditions for 20 minutes until a visually homogenous formulation solution was achieved.
- Nicotine pyruvate salt formulation was made by adding 0.54g pyruvic acid to a beaker followed by adding 0.5g nicotine to the same beaker. The mixture was stirred at ambient conditions for 10 minutes. Exothermic reaction took place and oily product was produced. The mixture was allowed to cool down to ambient temperature and 8.96g PG/VG (3:7) solution was added to the same beaker. The mixture was then stirred at ambient conditions for 20 minutes until a visually homogenous formulation solution was achieved.
- Nicotine succinate salt formulation was made by adding 0.73g succinic acid to a beaker followed by adding 0.5g nicotine and 8.77g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine salicylate salt formulation was made by adding 0.43g salicylic acid to a beaker followed by adding 0.5g nicotine and 9.07g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at 90 °C for 60 minutes until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine salicylate salt formulation can also be made by adding 0.43g salicylic acid to a beaker followed by adding 0.5g nicotine to the same beaker. The mixture was stirred at 90 °C for 60 minutes until salicylic acid was completely dissolved and an orange oily mixture was formed. The mixture was either cooled to ambient conditions or kept at 90C when 9.07g PG/VG (3:7) solution was added. The blend was then stirred at 90 °C until a visually homogenous formulation solution was achieved with no undissolved chemicals.
- Nicotine free base formulation was made by adding 0.5g nicotine to a beaker followed by adding 9.5g PG/VG (3:7) solution to the same beaker. The mixture was then stirred at ambient conditions for 10 minutes until a visually homogenous formulation solution was achieved.

[0088] Various formulations comprising different nicotine salts can be prepared similarly, or different concentrations of the above-noted nicotine formulations or other nicotine salt

formulations can be prepared as one of skill in the art would know to do upon reading the disclosure herein.

[0089] Various formulations comprising two or more nicotine salts can be prepared similarly in a solution of 3:7 ratio of propylene glycol (PG)/vegetable glycerin (VG). For example, 0.43g (2.5% w/w nicotine) of nicotine levulinate salt and 0.34 g (2.5% w/w nicotine) of nicotine acetate salt are added to 9.23g of PG/VG solution, to achieve a 5% w/w nicotine formulation.

[0090] Also provided is another exemplary formulation. For example, 0.23g (1.33% w/w nicotine) of nicotine benzoate salt (molar ratio 1:1 nicotine/benzoic acid), 0.25g (1.33% w/w nicotine) of nicotine salicylate salt(molar ratio 1:1 nicotine/salicylic acid) and 0.28 g (1.34% w/w nicotine) of nicotine pyruvate salt (molar ratio 1:2 nicotine/pyruvic acid) are added to 9.25g of PG/VG solution, to achieve a 5% w/w nicotine formulation.

Example 2: Heart rate study of nicotine solutions via e-cigarette

[0091] Exemplary formulations of nicotine levulinate, nicotine benzoate, nicotine succinate, nicotine salicylate, nicotine malate, nicotine pyruvate, nicotine citrate, nicotine freebase, and a control of propylene glycol were prepared as noted in Example 1 in 3% w/w solutions and were administered in the same fashion by an electronic cigarette to the same human subject. About 0.5 mL of each solution was loaded into an "eRoll" cartridge atomizer (joyetech.com) to be used in the study. The atomizer was then attached to an "eRoll" e-cigarette (same manufacturer). The operating temperature was from about 150°C to about 250 °C, or from about 180°C to about 220 °C.

[0092] Heart rate measurements were taken for 6 minutes; from 1 minute before start of puffing, for 3 minutes during puffing, and continuing until 2 minutes after end of puffing. The test participant took 10 puffs over 3 minutes in each case. The base heart rate was the average heart rate over the first 1 minute before start of puffing. Heart rate after puffing started was averaged over 20-second intervals. Puffing (inhalation) occurred every 20 seconds for a total of 3 minutes. Normalized heart rate was defined as the ratio between individual heart rate data point and the base heart rate. Final results were presented as normalized heart rate, shown for the first 4 minutes in FIG. 1.

[0093] FIG. 1 summarizes results from heart rate measurements taken for a variety of nicotine salt formulations. For ease of reference in reviewing FIG. 1, at the 180-second

timepoint, from top to bottom (highest normalized heart rate to lowest normalized heart rate), the nicotine formulations are as follows: nicotine salicylate formulation, nicotine malate formulation, nicotine levulinate formulation (nearly identical to nicotine malate formulation at 180 seconds, thus, as a second reference point: the nicotine malate formulation curve is lower than the nicotine levulinate formulation curve at the 160-second time point), nicotine pyruvate formulation, nicotine benzoate formulation, nicotine citrate formulation, nicotine succinate formulation, and nicotine free base formulation. The bottom curve (lowest normalized heart rate) at the 180-second timepoint is associated with the placebo (100% propylene glycol). The test formulations comprising a nicotine salt cause a faster and more significant rise in heart rate than the placebo. The test formulations comprising a nicotine salt also cause faster and more significant rise when compared with a nicotine freebase formulation with the same amount of nicotine by weight. In addition, the nicotine salts (e.g., nicotine benzoate and nicotine pyruvate) prepared from the acids having calculated vapor pressures between 20 - 200 mmHg at 200 ^{o}C (benzoic acid (171.66 mmHg), with the exception of pyruvic acid (having a boiling point of 165C), respectively) cause a faster rise in heart rate than the rest. The nicotine salts (e.g., nicotine levulinate, nicotine benzoate, and nicotine salicylate) prepared from the acids (benzoic acid, levulinic acid and salicylic acid, respectively) also cause a more significant heart rate increase. Thus, other suitable nicotine salts formed by the acids with the similar vapor pressure and/or similar boiling point may be used in accordance with the practice of the present invention. This experience of increased heart rate theoretically approaching or theoretically comparable to that of a traditional burned cigarette has not been demonstrated or identified in other electronic cigarette devices. Nor has it been demonstrated or identified in low temperature tobacco vaporization devices (electronic cigarettes) that do not burn the tobacco, even when a nicotine salt was used (a solution of 20% (w/w) or more of nicotine salt) as an additive to the tobacco. Thus the results from this experiment are surprising and unexpected.

Example 3: Satisfaction Study of Nicotine salt Solution via e-cigarette

[0094] In addition to the heart rate study shown in Example 2, nicotine formulations (using 3% w/w nicotine formulations as described in Example 1) were used to conduct a satisfaction study in a single test participant. The test participant, an e-cigarette and/or traditional cigarette user, was required to have no nicotine intake for at least 12 hours before the test. The participant

took 10 puffs using an e-cigarette (same as used in Example 2) over 3 minutes in each case, and then was asked to rate the level of physical and emotional satisfaction he or she felt on a scale of 0 - 10, with 0 being no physical or emotional satisfaction. The results indicated that the least satisfying compound was the nicotine free base. Nicotine benzoate, nicotine salicylate, and nicotine succinate all performed well, followed by nicotine pyruvate, nicotine citrate, and nicotine pyruvate.

[0095] Based on the Satisfaction Study, the nicotine salts formulations with acids having vapor pressure ranges between >20 mmHg @ 200 °C, or 20-200 mmHg @ 200 °C, or 100 – 300 mmHg @ 200 °C provide more satisfaction than the rest (except the pyruvic acid which has boiling point of 165 °C). For reference, it has been determined that salicylic acid has a vapor pressure of about 135.7 mmHg @ 200 °C, benzoic acid has a vapor pressure of about 171.7 mmHg @ 200 °C, lauric acid has a vapor pressure of about 38 mmHg @ 200 °C, and levulinic acid has a vapor pressure of about 149 mmHg @ 200 °C.

Example 4: Test formulation 1 (TF1):

[0096] A solution of nicotine levulinate in glycerol comprising nicotine salt used: 1.26g (12.6% w/w) of 1:3 nicotine levulinate 8.74g (87.4% w/w) of glycerol - Total weight 10.0g.

[0097] Neat nicotine levulinate was added to the glycerol, and mixed thoroughly. L-Nicotine has a molar mass of 162.2g, and levulinic acid molar mass is 116.1g. In a 1:3 molar ratio, the percentage of nicotine in nicotine levulinate by weight is given by: 162.2g / (162.2g + (3 x 116.1g)) = 31.8% (w/w).

Example 5: Test formulation 2 (TF2):

[0098] A solution of free base nicotine in glycerol comprising 0.40g (4.00% w/w) of L-nicotine was dissolved in 9.60g (96.0% w/w) of glycerol and mixed thoroughly.

Example 6: Heart rate study of nicotine solutions via e-cigarette:

[0099] Both formulations (TF1 and TF2) were administered in the same fashion by an electronic cigarette to the same human subject: about 0.6 mL of each solution was loaded into "eGo-C" cartridge atomizer (joyetech.com). The atomizer was then attached to an "eVic" e-cigarette (same manufacturer). This model of e-cigarette allows for adjustable voltage, and

therefore wattage, through the atomizer. The operating temperature of the e-cigarette is from about 150°C to about 250 °C, or from about 180°C to about 220 °C.

[00100] The atomizer in both cases has resistance 2.4ohms, and the e-cigarette was set to 4.24V, resulting in 7.49W of power. **(P = V^2 / R)**

[00101] Heart rate was measured in a 30-second interval for ten minutes from start of puffing. Test participants took 10 puffs over 3 minutes in each case (solid line (2nd highest peak): cigarette, dark dotted line (highest peak): test formulation 1 (TF1-nicotine salt formulation), light dotted line: test formulation 2 (TF2 — nicotine formulation). Comparison between cigarette, TF1, and TF2 is shown in FIG. 2.

[00102] It is clearly shown in FIG. 2 that the test formulation with nicotine levulinate (TF1) causes a faster rise in heart rate than just nicotine (TF2). Also, TF1 more closely resembles the rate of increase for a cigarette. Other salts were tried and also found to increase heart rate relative to a pure nicotine solution. Thus, other suitable nicotine salts that cause the similar effect may be used in accordance with the practice of the present invention. For example, other keto acids (alpha-keto acids, beta-keto acids, gamma-keto acids, and the like) such as pyruvic acid, oxaloacetic acid, acetoacetic acid, and the like. This experience of increased heart rate comparable to that of a traditional burned cigarette has not been demonstrated or identified in other electronic cigarette devices, nor has it been demonstrated or identified in low temperature tobacco vaporization devices that do not burn the tobacco, even when a nicotine salt was used (a solution of 20% (W/W) or more of nicotine salt) as an additive to the tobacco. Thus the results from this experiment are surprising and unexpected.

[00103] In addition, the data appears to correlate well with the previous findings shown in FIG. 2.

[00104] As previously noted in the Satisfaction Study, the nicotine salts formulations with acids having vapor pressures between 20 – 300 mmHg @ 200 °C provide more satisfaction than the rest, with the exception of the nicotine salt formulation made with pyruvic acid, which has a boiling point of 165 °C, as noted in FIG. 3. Based on the findings herein, it was anticipated that these nicotine salt formulations having either:

- a Vapor Pressure between 20 – 300 mmHg @ 200 °C,
- a Vapor Pressure > 20 mmHg @ 200 °C,

- a difference between boiling point and melting point of at least 50 °C, and a boiling point greater than 160 °C, and a melting point less than 160 °C,
- a difference between boiling point and melting point of at least 50 °C, and a boiling point greater than 160 °C, and a melting point less than 160 °C,
- a difference between boiling point and melting point of at least 50 °C, and a boiling point at most 40 °C less than operating temperature, and a melting point at least 40 °C lower than operating temperature, or
- a combination thereof produce one or more of the following effects:

[00105] T_{max} – Time to maximum blood concentration: Based on the results established herein, a user of an e-cigarette comprising the nicotine salt formulation will experience a comparable rate of physical and emotional satisfaction from using a formulation comprising a mixture of nicotine salts prepared with an appropriate acid at least 1.2X to 3X faster than using a formulation comprising a freebase nicotine. As illustrated in FIG. 1: Nicotine from a nicotine salts formulation appears to generate a heartbeat that is nearly 1.2 times that of a normal heart rate for an individual approximately 40 seconds after the commencement of puffing; whereas the nicotine from a nicotine freebase formulation appears to generate a heartbeat that is nearly 1.2 times that of a normal heart rate for an individual approximately 110 seconds after the commencement of puffing; a 2.75 X difference in time to achieve a comparable initial satisfaction level.

[00106] Again this would not be inconsistent with the data from FIG. 2, where the data illustrated that at approximately 120 seconds (2 minutes), the heart rate of test participants reached a maximum of 105 – 110 bpm with either a regular cigarette or a nicotine salt formulation (TF1); whereas those same participants heart rates only reached a maximum of approximately 86 bpm at approximately 7 minutes with a nicotine freebase formulation (TF2); also a difference in effect of 1.2 times greater with nicotine salts (and regular cigarettes) versus freebase nicotine.

[00107] Further, when considering peak satisfaction levels (achieved at approximately 120 seconds from the initiation of puffing (time =0) and looking at the slope of the line for a normalized heart rate, the approximate slope of those nicotine salt formulations that exceeded the freebase nicotine formulation range between 0.0054 hr_n/sec and 0.0025 hr_n/sec. By comparison, the slope of the line for the freebase nicotine formulation is about 0.002. This would suggest that

the concentration of available nicotine will be delivered to the user at a rate that is between 1.25 and 2.7 times faster than a freebase formulation.

[00108] In another measure of performance; C_{max} – Maximum blood nicotine concentration; it is anticipated that similar rates of increase will be measured in blood nicotine concentration, as those illustrated above. That is, it was anticipated based on the findings herein, and unexpected based on the art known to date, that there would be comparable C_{max} between the common cigarette and certain nicotine salt formulations, but with a lower C_{max} in a freebase nicotine solution.

[00109] Similarly, anticipated based on the findings herein, and unexpected based on the art known to date, that certain nicotine salt formulations would have higher rate of nicotine uptake levels in the blood at early time periods. Indeed, Example 8 presents data for multiple salt formulations consistent with these predictions which were made based on the findings and tests noted herein, and unexpected compared to the art available to date.

Example 7: Heart rate study of nicotine solutions via e-cigarette

[00110] Exemplary formulations of nicotine levulinate, nicotine benzoate, nicotine succinate, nicotine salicylate, nicotine malate, nicotine pyruvate, nicotine citrate, nicotine sorbate, nicotine laurate, nicotine freebase, and a control of propylene glycol are prepared as noted in Example 1 and are administered in the same fashion by an electronic cigarette to the same human subject. About 0.5 mL of each solution is loaded into an "eRoll" cartridge atomizer (joyetech.com) to be used in the study. The atomizer is then attached to an "eRoll" e-cigarette (same manufacturer). The operating temperature of the e-cigarette is from about 150°C to about 250 °C, or from about 180°C to about 220 °C.

[00111] Heart rate measurements are taken for 6 minutes; from 1 minute before start of puffing, for 3 minutes during puffing, and continuing until 2 minutes after end of puffing. The test participant takes 10 puffs over 3 minutes in each case. The base heart rate is the average heart rate over the first 1 minute before start of puffing. Heart rate after puffing started is averaged over 20-second intervals. Normalized heart rate is defined as the ratio between individual heart rate data point and the base heart rate. Final results are presented as normalized heart rate.

Example 8: Blood Plasma testing

[00112] Blood plasma testing was conducted on three subjects (n = 3). Eight test articles were used in this study: one reference cigarette and seven blends used in an e-cigarette device having an operating temperature of the e-cigarette from about 150°C to about 250 °C, or from about 180°C to about 220 °C. The reference cigarette was Pall Mall (New Zealand). Seven blends were tested in the e-cigarette: 2% free base, 2% benzoate, 4% benzoate, 2% citrate, 2% malate, 2% salicylate, and 2% succinate. Except for 2% succinate (n = 1), all other blends have n = 3. The seven blends were liquid formulations prepared as described in Example 1.

[00113] The concentration of nicotine in each of the formulations was confirmed using UV spectrophotometer (Cary 60, manufactured by Agilent). The sample solutions for UV analysis were made by dissolving 20mg of each of the formulations in 20mL 0.3% HCl in water. The sample solutions were then scanned in UV spectrophotometer and the characteristic nicotine peak at 259nm was used to quantify nicotine in the sample against a standard solution of 19.8 □g/mL nicotine in the same diluent. The standard solution was prepared by first dissolving 19.8mg nicotine in 10mL 0.3% HCl in water followed by a 1:100 dilution with 0.3% HCl in water. Nicotine concentrations reported for all formulations were within the range of 95%-105% of the claimed concentrations

[00114] All subjects were able to consume 30-55 mg of the liquid formulation of each tested blend using the e-cigarette.

[00115] Literature results: C. Bullen et al, Tobacco Control 2010, 19:98-103

Cigarette (5min adlib, n=9): T_{max} = 14.3 (8.8-19.9), C_{max} = 13.4 (6.5-20.3)

1.4% E-cig (5min adlib, n=8): T_{max} = 19.6 (4.9-34.2), C_{max} = 1.3 (0.0-2.6)

Nicorette Inhalator (20mg/20min, n=10): T_{max} = 32.0 (18.7-45.3), C_{max} = 2.1 (1.0-3.1)

[00116] Estimated C_{max} of 2% nicotine blends:

C_{max} = Mass consumed * Strength * Bioavailability / (Vol of Distribution * Body Weight) = 40mg * 2% * 80% / (2.6L/kg * 75kg) = 3.3 ng/mL

[00117] Estimated C_{max} of 4% nicotine blends:

C_{max} = Mass consumed * Strength * Bioavailability / (Vol of Distribution * Body Weight) = 40mg * 4% * 80% / (2.6L/kg * 75kg) = 6.6 ng/mL

[00118] Pharmacokinetic profiles of the blood plasma testing are shown in FIG. 4; showing blood nicotine concentrations (ng/mL) over time after the first puff (inhalation) of the aerosol

from the e-cigarette or the smoke of the Pall Mall. Ten puffs were taken at 30 sec intervals starting at time =0 and continuing for 4.5 minutes. For ease of reference and review of FIG. 4, at the 5-minute timepoint, the curves on the graph show from top to bottom (highest average blood nicotine concentration to lowest average blood nicotine concentration) are 4% benzoate, 2% succinate, 2% salicylate, 2% citrate, Pall Mall cigarette, 2% benzoate, 2% malate, and 2% free base blend. Although noted as highest to lowest at this time point, this is not to say that there is a statistically significant difference between any of the salt formulations, or between any of the salt formulations and the Pall Mall cigarette. However, it is possible there may be a statistically significant difference between the C_{max} of particular salt formulations, and it is also likely based on the data shown in FIG. 4 and in other studies herein that the freebase formulation is statistically different from salt formulations and/or the Pall Mall with respect to C_{max}, since it appears lower than others tested at several time points. One of skill in the art, upon review of the disclosure herein could properly power a test to determine actual statistically-based differences between one or more formulations and the cigarette, or between the formulations themselves in an e-cigarette. For ease of reference Tables 1 & 2 present the amount of nicotine detected (as an average of all users) for each formulation and the Pall Mall, presented in ng/mL, along with C_{max} and T_{max} and AUC. Data from these tables, along with the raw data therefore, was used to generate FIG. 4, 5, and 6.

Table 1

Time	Pall Mall	2% Freebase	2% Benzoate	4% Benzoate
-2	0.46	0.03	0.09	0.05
0	-0.46	-0.03	-0.09	-0.05
1.5	1.54	0.08	5.67	6.02
3	9.98	1.19	8.60	11.47
5	11.65	1.70	11.44	15.06
7.5	11.34	3.09	6.43	12.12

10	9.24	3.42	5.03	11.08
12.5	8.85	3.35	4.68	10.10
15	8.40	2.81	4.47	8.57
30	5.51	1.74	2.72	5.56
60	3.39	0.79	1.19	3.60
T_{max} (min)	**5.17**	**10.00**	**6.67**	**5.83**
C_{max} (ng/mL)	**11.65**	**3.42**	**11.44**	**15.06**
AUC (ng*min/mL)	**367.5**	**106.2**	**207.8**	**400.2**

Table 2

Time	**2% Citrate**	**2% Malate**	**2% Salicylate**	**2% Succinate**
-2	0.06	-0.17	-0.19	-0.06
0	-0.06	0.17	0.19	0.06
1.5	4.80	1.09	6.14	2.10
3	8.33	5.30	12.04	10.81
5	12.09	10.02	13.46	13.81
7.5	6.93	5.93	5.21	5.15
10	6.01	4.85	4.60	5.18
12.5	5.34	4.17	3.83	4.17

15	4.72	3.79	3.52	3.41
30	3.40	1.56	2.19	2.01
60	1.70	0.46	0.55	1.00
T_{max} (min)	**5.83**	**5.00**	**4.33**	**5.00**
C_{max} (ng/mL)	**12.09**	**10.02**	**13.46**	**13.81**
AUC (ng*min/mL)	**238.0**	**146.1**	**182.9**	**179.5**

[00119] Comparison of T_{max} and C_{max} of the seven blends and reference cigarette are shown in FIG. 5. Comparison of C_{max} and AUC of the seven blends and reference cigarette are shown in FIG. 6. Due to the time limit of the wash-period, baseline blood nicotine concentration (at t=-2 and t=0 min) was higher for samples consumed at a later time on the test day. The data in FIGS. 4-6 show corrected blood nicotine concentration values (i.e. apparent blood nicotine concentration at each time point minus baseline nicotine concentration of the same sample).

[00120] Rates of nicotine uptake in the blood of the users of each sample within the first 90 seconds are shown in Table 3.

Table 3

Sample	Rate of nicotine uptake (ng/mL/min)
2% Salicylate	4.09
2% Benzoate	3.78
2% Citrate	3.20
2% Succinate	1.40
Pall Mall (reference)	1.03
2% Malate	0.73
2% Freebase	0.05
4% Benzoate	4.01

[00121] Although the T_{max} and C_{max} values are comparable between the tested blends and the reference cigarette (with the exception of the 2% free base blend), the rates of nicotine absorption within the first 90 seconds differed among the test articles. In particular, four blends (2% salicylate, 2% benzoate, 4% benzoate, and 2% citrate) showed markedly higher rates of absorption within the first 90 seconds compared to the other blends and with the reference cigarette. These four blends contain salts (salicylate, benzoate, and citrate) which performed well in the Satisfaction Study of Example 3. Moreover, 2% benzoate and 4% benzoate had comparable rates of absorption, suggesting that a lower concentration of nicotinic salt may not adversely impact the rate of absorption.

Example 9: Blood Plasma testing

[00122] Blood plasma testing is conducted on 24 subjects (n = 24). Eight test articles are used in this study: one reference cigarette and seven blends delivered to a user in an e-cigarette as an aerosol. The operating temperature of the e-cigarette is from about 150°C to about 250 °C, or from about 180°C to about 220 °C. The reference cigarette is Pall Mall (New Zealand). Seven blends are tested: 2% free base, 2% benzoate, 4% benzoate, 2% citrate, 2% malate, 2% salicylate, and 2% succinate. The seven blends are liquid formulations prepared according to protocols similar to that described *infra* and in Example 1.

[00123] All subjects are to consume 30-55 mg of the liquid formulation of each tested blend. Ten puffs are to be taken at 30 sec intervals starting at time =0 and continuing for 4.5 minutes. Blood plasma testing is to occur for at least 60 minutes from the first puff (t=0) Pharmacokinetic data (e.g., C_{max}, T_{max}, AUC) for nicotine in the plasma of users are obtained at various time periods during those 60 minutes, along with rates of nicotine absorption within the first 90 seconds for each test article.

Example 10: Blood Plasma testing

[00124] Blood plasma testing is conducted on twenty-four subjects (n = 24). Eleven test articles are used in this study: one reference cigarette and ten blends delivered to a user in an e-cigarette as an aerosol. The reference cigarette is Pall Mall (New Zealand). The operating temperature of the e-cigarette is from about 150°C to about 250 °C, or from about 180°C to about 220 °C. Ten blends are tested: 2% free base, 2% benzoate, 2% sorbate, 2% pyruvate, 2%

laurate, 2% levulinate, 2% citrate, 2% malate, 2% salicylate, and 2% succinate. The ten blends are liquid formulations prepared according to protocols similar to that described *infra* and in Example 1.

[00125] All subjects are to consume 30-55 mg of the liquid formulation of each tested blend. Ten puffs are to be taken at 30 sec intervals starting at time =0 and continuing for 4.5 minutes. Blood plasma testing is to occur for at least 60 minutes from the first puff (t=0) . Pharmacokinetic data (e.g., C_{max}, T_{max}, AUC) for nicotine in the plasma of users are obtained at various time periods during those 60 minutes, along with rates of nicotine absorption within the first 90 seconds for each test article.

Example 11: Blood Plasma testing

[00126] Blood plasma testing is conducted on twenty-four subjects (n = 24). Twenty-one test articles are used in this study: one reference cigarette and twenty blends delivered to a user in an e-cigarette as an aerosol. The reference cigarette is Pall Mall (New Zealand). The operating temperature of the e-cigarette is from about 150°C to about 250 °C, or from about 180°C to about 220 °C. Twenty blends are tested: 2% free base, 4% free base, 2% benzoate, 4% benzoate, 2% sorbate, 4% sorbate, 2% pyruvate, 4% pyruvate, 2% laurate, 4% laurate, 2% levulinate, 4% levulinate, 2% citrate, 4% citrate, 2% malate, 4% malate, 2% salicylate, 4% salicylate, 2% succinate, and 4% succinate. The twenty blends are liquid formulations prepared according to protocols similar to that described *infra* and in Example 1.

[00127] All subjects are to consume 30-55 mg of the liquid formulation of each tested blend. Ten puffs are to be taken at 30 sec intervals starting at time =0 and continuing for 4.5 minutes. Blood plasma testing is to occur for at least 60 minutes from the first puff (t=0) . Pharmacokinetic data (e.g., C_{max}, T_{max}, AUC) for nicotine in the plasma of users are obtained at various time periods during those 60 minutes, along with rates of nicotine absorption within the first 90 seconds for each test article.

Example 12: Blood Plasma testing

[00128] Blood plasma testing is conducted on twenty-four subjects (n = 24). Twenty-one test articles are used in this study: one reference cigarette and twenty blends delivered to a user in an e-cigarette as an aerosol. The reference cigarette is Pall Mall (New Zealand). The operating

temperature of the e-cigarette is from about 150°C to about 250 °C, or from about 180°C to about 220 °C. Twenty blends are tested: 2% free base, 1% free base, 2% benzoate, 1% benzoate, 2% sorbate, 1% sorbate, 2% pyruvate, 1% pyruvate, 2% laurate, 1% laurate, 2% levulinate, 1% levulinate, 2% citrate, 1% citrate, 2% malate, 1% malate, 2% salicylate, 1% salicylate, 2% succinate, and 1% succinate. The twenty blends are liquid formulations prepared according to protocols similar to that described *infra* and in Example 1.

[00129] All subjects are to consume 30-55 mg of the liquid formulation of each tested blend. Ten puffs are to be taken at 30 sec intervals starting at time =0 and continuing for 4.5 minutes. Blood plasma testing is to occur for at least 60 minutes from the first puff (t=0) . Pharmacokinetic data (e.g., C_{max}, T_{max}, AUC) for nicotine in the plasma of users are obtained at various time periods during those 60 minutes, along with rates of nicotine absorption within the first 90 seconds for each test article.

[00130] Further understanding may be gained through contemplation of the numbered embodiments below.

1. A method of delivering nicotine to a user comprising operating an electronic cigarette to a user wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

2. A method of delivering nicotine to a user comprising operating an electronic cigarette to a user wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

3. A method of delivering nicotine to a user comprising operating an electronic cigarette wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

4. A method of delivering nicotine to a user comprising providing an electronic cigarette to a user wherein the electronic cigarette comprises a nicotine salt formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point, and inhaling an aerosol generated from the nicotine salt formulation heated by the electronic cigarette.

5. The method of any one of embodiments 1-3, wherein an operating temperature is from 150 °C to 250 °C.

6. The method of any one of embodiments 1-3, wherein an operating temperature is from 180 °C to 220 °C.

7. The method any one of embodiments 1-3, wherein an operating temperature is about 200 °C.

8. The method of embodiment 4, wherein the operating temperature is from 150 °C to 250 °C.

9. The method of embodiment 4, wherein the operating temperature is from 180 °C to 220 °C.

10. The method of embodiment 4, wherein the operating temperature is about 200 °C.

11. The method any one of embodiments 1-10, wherein the aerosol comprises condensate of the nicotine salt.

12. The method any one of embodiments 1-10, wherein the aerosol comprises condensate of freebase nicotine.

13. The method any one of embodiments 1-10, wherein the aerosol comprises condensate of freebase nicotine and condensate of the carrier.

14. The method any one of embodiments 1-10, wherein the aerosol comprises condensate of freebase nicotine and condensate of the acid.

15. The method any one of embodiments 1-14, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 5 microns.

16. The method any one of embodiments 1-14, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 1 or 2 microns.

17. The method any one of embodiments 1-14, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 0.7 microns.

18. The method any one of embodiments 1-14, wherein the aerosol comprises condensate in particle sizes from about 0.3 microns to about 0.4 microns.

19. The method any one of embodiments 1-18, wherein the acid is a carboxylic acid.

20. The method of any one of embodiments 1-18, wherein the acid used to form said nicotine salt is an organic acid.

21. The method of embodiment 20, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

22. The method of embodiment 20, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

23. The method of any one of embodiments 1-18, wherein the acid used to form the nicotine salt is salicylic acid.

24. The method of any one of embodiments 1-18, wherein the acid used to form the nicotine salt is benzoic acid.

25. The method of any one of embodiments 1-18, wherein the acid used to form the nicotine salt is pyruvic acid.

26. The method of any one of embodiments 1-18, wherein the acid used to form the nicotine salt is sorbic acid.

27. The method of any one of embodiments 1-18, wherein the acid used to form the nicotine salt is lauric acid.

28. The method of any one of embodiments 1-18, wherein the acid used to form the nicotine salt is levulinic acid.

29. The method of any one of embodiments 1-18, wherein said nicotine salt comprises nicotine pyruvate.

30. The method of any one of embodiments 1-18, wherein said nicotine salt comprises nicotine salicylate.

31. The method of any one of embodiments 1-18, wherein said nicotine salt comprises nicotine sorbate.

32. The method of any one of embodiments 1-18, wherein said nicotine salt comprises nicotine laurate.

33. The method of any one of embodiments 1-18, wherein said nicotine salt comprises nicotine levulinate.

34. The method of any one of embodiments 1-18, wherein said nicotine salt comprises nicotine benzoate.

35. The method of any one of embodiments 1-34, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

36. The method of any one of embodiments 1-34, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

37. The method of any one of embodiments 1-34, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

38. The method of any one of embodiments 1-34, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

39. The method of any one of embodiments 1-38, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

40. The method of any one of embodiments 1-38, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

41. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

42. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

43. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

44. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

45. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

46. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

47. The method of any one of embodiments 1-40, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

48. The method of any one of embodiments 1-47, wherein the formulation further comprises a flavorant.

49. The method of any one of embodiments 1-48, wherein the formulation is non-corrosive to an electronic cigarette.

50. The method of any one of embodiments 1-49, wherein the acid is stable at and below operating temperature or about 200 °C.

51. The method of any one of embodiments 1-50, wherein the acid does not decompose at and below operating temperature or about 200 °C.

52. The method of any one of embodiments 1-51, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

53. The method of any one of embodiments 1-52, wherein the formulation is non-corrosive to the electronic cigarette.

54. The method of any one of embodiments 1-53, wherein the formulation is non-toxic to a user of the electronic cigarette.

55. The method of any one of embodiments 1-54, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

56. The method of embodiment 55, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

57. A method of delivering nicotine to the blood of a user, said method comprising providing an aerosol that is inhaled by the user from an electronic cigarette that comprises a nicotine salt formulation wherein providing the aerosol comprises the electronic cigarette heating the formulation thereby generating the aerosol, wherein the aerosol is effective in delivering a level of nicotine in the blood of the user that is at least 5ng/mL at about 1.5 minutes after a first puff of ten puffs of the aerosol, each puff taken at 30 second intervals.

58. The method of embodiment 54, wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C.

59. The method of embodiment 54, wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

60. The method of embodiment 54, wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

61. The method of any one of embodiments 57-60, wherein the heating of the formulation is at a temperature from 150 °C to 250 °C.

62. The method of any one of embodiments 57-60, wherein the heating of the formulation is at a temperature from 180 °C to 220 °C.

63. The method of any one of embodiments 57-60, wherein the heating of the formulation is at a temperature of about 200 °C.

64. The method of embodiment 54, wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than the operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point; and the operating temperature is 200 °C.

65. The method of any one of embodiments 57-64, wherein the Cmax is over 10 ng/mL on average.

66. The method of any one of embodiments 57-64, wherein the Cmax is over 11 ng/mL on average.

67. The method of any one of embodiments 57-64, wherein the Cmax is between 10 ng/mL and 16 ng/mL on average.

68. The method of any one of embodiments 57-64, wherein the Cmax is between 11 ng/mL and 15 ng/mL on average.

69. The method of any one of embodiments 57-64, wherein the Cmax is between 11 ng/mL and 14 ng/mL on average.

70. The method of any one of embodiments 57-69, wherein the Tmax under 10 minutes on average.

71. The method of any one of embodiments 57-69, wherein the Tmax is under 9 minutes on average.

72. The method of any one of embodiments 57-69, wherein the Tmax is under 8 minutes on average.

73. The method of any one of embodiments 57-69, wherein the Tmax is under 7 minutes on average.

74. The method of any one of embodiments 54-63, wherein the Tmax is from 3 minutes to 10 minutes on average.

75. The method of any one of embodiments 57-69, wherein the Tmax is from 3 minutes to 7.5 minutes on average.

76. The method of any one of embodiments 57-75, wherein the aerosol comprises condensate of the nicotine salt.

77. The method of any one of embodiments 57-75, wherein the aerosol comprises condensate of freebase nicotine.

78. The method of any one of embodiments 57-75, wherein the aerosol comprises condensate of freebase nicotine and condensate of the carrier.

79. The method of any one of embodiments 57-75, wherein the aerosol comprises condensate of freebase nicotine and condensate of the acid.

80. The method of any one of embodiments 57-79, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 5 microns.

81. The method of any one of embodiments 57-79, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 1 or 2 microns.

82. The method of any one of embodiments 57-79, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 0.7 microns.

83. The method of any one of embodiments 57-79, wherein the aerosol comprises condensate in particle sizes from about 0.3 microns to about 0.4 microns.

84. The method of any one of embodiments 57-83, wherein the acid is a carboxylic acid.

85. The method of any one of embodiments 57-83, wherein the acid used to form said nicotine salt is an organic acid.

86. The method of embodiment 85, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

87. The method of embodiment 85, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

88. The method of any one of embodiments 57-83, wherein the acid used to form the nicotine salt is salicylic acid.

89. The method of any one of embodiments 57-83, wherein the acid used to form the nicotine salt is benzoic acid.

90. The method of any one of embodiments 57-83, wherein the acid used to form the nicotine salt is pyruvic acid.

91. The method of any one of embodiments 57-83, wherein the acid used to form the nicotine salt is sorbic acid.

92. The method of any one of embodiments 57-83, wherein the acid used to form the nicotine salt is lauric acid.

93. The method of any one of embodiments 57-83, wherein the acid used to form the nicotine salt is levulinic acid.

94. The method of any one of embodiments 57-83, wherein said nicotine salt comprises nicotine pyruvate.

95. The method of any one of embodiments 57-83, wherein said nicotine salt comprises nicotine salicylate.

96. The method of any one of embodiments 57-83, wherein said nicotine salt comprises nicotine sorbate.

97. The method of any one of embodiments 57-83, wherein said nicotine salt comprises nicotine laurate.

98. The method of any one of embodiments 57-83, wherein said nicotine salt comprises nicotine levulinate.

99. The method of any one of embodiments 57-83, wherein said nicotine salt comprises nicotine benzoate.

100. The method of any one of embodiments 57-99, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

101. The method of any one of embodiments 57-99, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

102. The method of any one of embodiments 57-99, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

103. The method of any one of embodiments 57-99, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

104. The method of any one of embodiments 57-103, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

105. The method of any one of embodiments 57-103, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

106. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

107. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

108. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

109. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

110. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

111. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

112. The method of any one of embodiments 57-105, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

113. The method of any one of embodiments 57-112, wherein the formulation further comprises a flavorant.

114. The method of any one of embodiments 57-113, wherein the formulation is non-corrosive to an electronic cigarette.

115. The method of any one of embodiments 57-114, wherein the acid is stable at and below operating temperature or about 200 °C.

116. The method of any one of embodiments 57-115, wherein the acid does not decompose at and below operating temperature or about 200 °C.

117. The method of any one of embodiments 57-116, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

118. The method of any one of embodiments 57-117, wherein the formulation is non-corrosive to the electronic cigarette.

119. The method of any one of embodiments 57-118, wherein the formulation is non-toxic to a user of the electronic cigarette.

120. The method of any one of embodiments 57-119, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

121. The method of embodiment 120, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

122. A nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C.

123. A nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

124. A nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine

salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

125. A nicotine salt liquid formulation in an electronic cigarette for generating an inhalable aerosol upon heating in the electronic cigarette, the formulation in the cigarette comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

126. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-124, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 150 °C to 250 °C.

127. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-124, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 180 °C to 220 °C.

128. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-124, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature of about 200 °C.

129. The nicotine salt liquid formulation in the electronic cigarette of embodiment 125, wherein the operating temperature is from 150 °C to 250 °C.

130. The nicotine salt liquid formulation in the electronic cigarette of embodiment 125, wherein the operating temperature is from 180 °C to 220 °C.

131. The nicotine salt liquid formulation in the electronic cigarette of embodiment 125, wherein the operating temperature is about 200 °C.

132. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid is a carboxylic acid.

133. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form said nicotine salt is an organic acid.

134. The nicotine salt liquid formulation in the electronic cigarette of embodiment 133, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

135. The nicotine salt liquid formulation in the electronic cigarette of embodiment 133, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

136. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form the nicotine salt is salicylic acid.

137. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form the nicotine salt is benzoic acid.

138. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form the nicotine salt is pyruvic acid.

139. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form the nicotine salt is sorbic acid.

140. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form the nicotine salt is lauric acid.

141. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein the acid used to form the nicotine salt is levulinic acid.

142. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein said nicotine salt comprises nicotine pyruvate.

143. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein said nicotine salt comprises nicotine salicylate.

144. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein said nicotine salt comprises nicotine sorbate.

145. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein said nicotine salt comprises nicotine laurate.

146. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein said nicotine salt comprises nicotine levulinate.

147. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-131, wherein said nicotine salt comprises nicotine benzoate.

148. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-147, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

149. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-147, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

150. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-147, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

151. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-147, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

152. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-151, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

153. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-151, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

154. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

155. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

156. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

157. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

158. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

159. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

160. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-153, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

161. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-160, wherein the formulation further comprises a flavorant.

162. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-161, wherein the formulation is non-corrosive to an electronic cigarette.

163. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-162, wherein the acid is stable at and below operating temperature or about 200 °C.

164. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-163, wherein the acid does not decompose at and below operating temperature or about 200 °C.

165. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-164, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

166. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-165, wherein the formulation is non-corrosive to the electronic cigarette.

167. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-166, wherein the formulation is non-toxic to a user of the electronic cigarette.

168. The nicotine salt liquid formulation in the electronic cigarette of any one of embodiments 122-167 further comprising one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

169. The nicotine salt liquid formulation in the electronic cigarette of embodiment 168, wherein a second acid used to form the additional nicotine salt is selected from the group

consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

170. A nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C.

171. A nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

172. A nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

173. A nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

174. The nicotine salt liquid formulation of any one of embodiments 170-172, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 150 °C to 250 °C.

175. The nicotine salt liquid formulation of any one of embodiments 170-172, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 180 °C to 220 °C.

176. The nicotine salt liquid formulation of any one of embodiments 170-172, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature of about 200 °C.

177. The nicotine salt liquid formulation of embodiment 173, wherein the operating temperature is from 150 °C to 250 °C.

178. The nicotine salt liquid formulation of embodiment 173, wherein the operating temperature is from 180 °C to 220 °C.

179. The nicotine salt liquid formulation of embodiment 173, wherein the operating temperature is about 200 °C.

180. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid is a carboxylic acid.

181. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid used to form said nicotine salt is an organic acid.

182. The nicotine salt liquid formulation of embodiment 181, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

183. The nicotine salt liquid formulation of embodiment 181, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

184. The liquid formulation of any one of embodiments 170-179, wherein the acid used to form the nicotine salt is salicylic acid.

185. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid used to form the nicotine salt is benzoic acid.

186. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid used to form the nicotine salt is pyruvic acid.

187. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid used to form the nicotine salt is sorbic acid.

188. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid used to form the nicotine salt is lauric acid.

189. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein the acid used to form the nicotine salt is levulinic acid.

190. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein said nicotine salt comprises nicotine pyruvate.

191. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein said nicotine salt comprises nicotine salicylate.

192. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein said nicotine salt comprises nicotine sorbate.

193. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein said nicotine salt comprises nicotine laurate.

194. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein said nicotine salt comprises nicotine levulinate.

195. The nicotine salt liquid formulation of any one of embodiments 170-179, wherein said nicotine salt comprises nicotine benzoate.

196. The nicotine salt liquid formulation of any one of embodiments 170-195, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

197. The nicotine salt liquid formulation of any one of embodiments 170-195, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

198. The nicotine salt liquid formulation of any one of embodiments 170-195, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

199. The nicotine salt liquid formulation of any one of embodiments 170-195, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

200. The nicotine salt liquid formulation of any one of embodiments 170-199, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

201. The nicotine salt liquid formulation of any one of embodiments 170-199, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

202. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

203. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

204. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

205. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

206. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

207. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

208. The nicotine salt liquid formulation of any one of embodiments 170-201, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

209. The nicotine salt liquid formulation of any one of embodiments 170-208, wherein the formulation further comprises a flavorant.

210. The nicotine salt liquid formulation of any one of embodiments 170-209, wherein the formulation is non-corrosive to an electronic cigarette.

211. The nicotine salt liquid formulation of any one of embodiments 170-210, wherein the acid is stable at and below operating temperature or about 200 °C.

212. The nicotine salt liquid formulation of any one of embodiments 170-211, wherein the acid does not decompose at and below operating temperature or about 200 °C.

213. The nicotine salt liquid formulation of any one of embodiments 170-212, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

214. The nicotine salt liquid formulation of any one of embodiments 170-213, wherein the formulation is non-corrosive to the electronic cigarette.

215. The nicotine salt liquid formulation of any one of embodiments 170-214, wherein the formulation is non-toxic to a user of the electronic cigarette.

216. The nicotine salt liquid formulation of any one of embodiments 170-215, further comprising one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

217. The nicotine salt liquid formulation of embodiment 216, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

218. A nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C.

219. A nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

220. A nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

221. A nicotine salt liquid formulation for use in an electronic cigarette the nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

222. The nicotine salt liquid formulation of any one of embodiments 218-220, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 150 °C to 250 °C.

223. The nicotine salt liquid formulation of any one of embodiments 218-220, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 180 °C to 220 °C.

224. The nicotine salt liquid formulation of any one of embodiments 218-220, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature of about 200 °C.

225. The nicotine salt liquid formulation of embodiment 221, wherein the operating temperature is from 150 °C to 250 °C.

226. The nicotine salt liquid formulation of embodiment 221, wherein the operating temperature is from 180 °C to 220 °C.

227. The nicotine salt liquid formulation of embodiment 221, wherein the operating temperature is about 200 °C.

228. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid is a carboxylic acid.

229. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid used to form said nicotine salt is an organic acid.

230. The nicotine salt liquid formulation of embodiment 229, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

231. The nicotine salt liquid formulation of embodiment 229, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

232. The liquid formulation of any one of embodiments 218-227, wherein the acid used to form the nicotine salt is salicylic acid.

233. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid used to form the nicotine salt is benzoic acid.

234. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid used to form the nicotine salt is pyruvic acid.

235. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid used to form the nicotine salt is sorbic acid.

236. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid used to form the nicotine salt is lauric acid.

237. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein the acid used to form the nicotine salt is levulinic acid.

238. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein said nicotine salt comprises nicotine pyruvate.

239. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein said nicotine salt comprises nicotine salicylate.

240. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein said nicotine salt comprises nicotine sorbate.

241. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein said nicotine salt comprises nicotine laurate.

242. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein said nicotine salt comprises nicotine levulinate.

243. The nicotine salt liquid formulation of any one of embodiments 218-227, wherein said nicotine salt comprises nicotine benzoate.

244. The nicotine salt liquid formulation of any one of embodiments 218-243, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

245. The nicotine salt liquid formulation of any one of embodiments 218-243, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

246. The nicotine salt liquid formulation of any one of embodiments 218-243, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

247. The nicotine salt liquid formulation of any one of embodiments 218-243, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

248. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

249. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

250. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

251. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

252. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

253. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

254. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

255. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

256. The nicotine salt liquid formulation of any one of embodiments 218-247, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

257. The nicotine salt liquid formulation of any one of embodiments 218-256, wherein the formulation further comprises a flavorant.

258. The nicotine salt liquid formulation of any one of embodiments 218-257, wherein the formulation is non-corrosive to an electronic cigarette.

259. The nicotine salt liquid formulation of any one of embodiments 218-258, wherein the acid is stable at and below operating temperature or about 200 °C.

260. The nicotine salt liquid formulation of any one of embodiments 218-259, wherein the acid does not decompose at and below operating temperature or about 200 °C.

261. The nicotine salt liquid formulation of any one of embodiments 218-260, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

262. The nicotine salt liquid formulation of any one of embodiments 218-261, wherein the formulation is non-corrosive to the electronic cigarette.

263. The nicotine salt liquid formulation of any one of embodiments 218-262, wherein the formulation is non-toxic to a user of the electronic cigarette.

264. The nicotine salt liquid formulation of any one of embodiments 218-263, further comprising one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

265. The nicotine salt liquid formulation of embodiment 264, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

266. Use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

267. Use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

268. Use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

269. Use of a nicotine salt formulation for delivery of nicotine to the blood of a user from an electronic cigarette, wherein the nicotine salt formulation in the electronic cigarette is heated to form an aerosol which delivers a level of nicotine in the blood of the user that is at least 5 ng/mL at about 1.5 minutes after a first puff of ten puffs of the aerosol, each puff taken at 30 second intervals.

270. Use of a nicotine salt formulation for delivery of nicotine to a user from an electronic cigarette wherein the nicotine salt formulation comprises a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point, and the nicotine salt formulation is heated by the electronic cigarette to generate an aerosol inhalable by the user.

271. The use of any one of embodiments 266-269, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature is from 150 °C to 250 °C.

272. The use of any one of embodiments 266-269, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature is from 180 °C to 220 °C.

273. The use of any one of embodiments 266-269, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature is about 200 °C.

274. The use of embodiment 270, wherein the operating temperature is from 150 °C to 250 °C.

275. The use of embodiment 270, wherein the operating temperature is from 180 °C to 220 °C.

276. The use of embodiment 270, wherein the operating temperature is about 200 °C.

277. The use of any one of embodiments 266-276, wherein the aerosol comprises condensate of the nicotine salt.

278. The use of any one of embodiments 266-276, wherein the aerosol comprises condensate of freebase nicotine.

279. The use of any one of embodiments 266-276, wherein the aerosol comprises condensate of freebase nicotine and condensate of the carrier.

280. The use of any one of embodiments 266-276, wherein the aerosol comprises condensate of freebase nicotine and condensate of the acid.

281. The use of any one of embodiments 266-280, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 5 microns.

282. The use of any one of embodiments 266-280, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 1 or 2 microns.

283. The use of any one of embodiments 266-280, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 0.7 microns.

284. The use of any one of embodiments 266-280, wherein the aerosol comprises condensate in particle sizes from about 0.3 microns to about 0.4 microns.

285. The use of any one of embodiments 266-284, wherein the acid is a carboxylic acid.

286. The use of any one of embodiments 266-284, wherein the acid used to form said nicotine salt is an organic acid.

287. The use of embodiment 286, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

288. The use of embodiment 286, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic

acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

289. The use of any one of embodiments 266-284, wherein the acid used to form the nicotine salt is salicylic acid.

290. The use of any one of embodiments 266-284, wherein the acid used to form the nicotine salt is benzoic acid.

291. The use of any one of embodiments 266-284, wherein the acid used to form the nicotine salt is pyruvic acid.

292. The use of any one of embodiments 266-284, wherein the acid used to form the nicotine salt is sorbic acid.

293. The use of any one of embodiments 266-284, wherein the acid used to form the nicotine salt is lauric acid.

294. The use of any one of embodiments 266-284, wherein the acid used to form the nicotine salt is levulinic acid.

295. The use of any one of embodiments 266-284, wherein said nicotine salt comprises nicotine pyruvate.

296. The use of any one of embodiments 266-284, wherein said nicotine salt comprises nicotine salicylate.

297. The use of any one of embodiments 266-284, wherein said nicotine salt comprises nicotine sorbate.

298. The use of any one of embodiments 266-284, wherein said nicotine salt comprises nicotine laurate.

299. The use of any one of embodiments 266-284, wherein said nicotine salt comprises nicotine levulinate.

300. The use of any one of embodiments 266-284, wherein said nicotine salt comprises nicotine benzoate.

301. The use of any one of embodiments 266-300, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

302. The use of any one of embodiments 266-300, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

303. The use of any one of embodiments 266-300, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

304. The use of any one of embodiments 266-300, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

305. The use of any one of embodiments 266-304, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

306. The use of any one of embodiments 266-304, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

307. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

308. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

309. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

310. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

311. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

312. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

313. The use of any one of embodiments 266-306, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

314. The use of any one of embodiments 266-313, wherein the formulation further comprises a flavorant.

315. The use of any one of embodiments 266-314, wherein the formulation is non-corrosive to an electronic cigarette.

316. The use of any one of embodiments 266-315, wherein the acid is stable at and below operating temperature or about 200 °C.

317. The use of any one of embodiments 266-316, wherein the acid does not decompose at and below operating temperature or about 200 °C.

318. The use of any one of embodiments 266-317, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

319. The use of any one of embodiments 266-318, wherein the formulation is non-corrosive to the electronic cigarette.

320. The use of any one of embodiments 266-319, wherein the formulation is non-toxic to a user of the electronic cigarette.

321. The use of any one of embodiments 266-320, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

322. The use of embodiment 321, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid

323. A cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

324. A cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

325. A cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

326. A cartomizer for an electronic cigarette comprising:

a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point;

an atomizer comprising a heating element in fluid communication with the nicotine salt liquid formulation; and

a fluid storage compartment that stores the nicotine salt liquid formulation.

327. The cartomizer of any one of embodiments 323-325, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 150 °C to 250 °C.

328. The cartomizer of any one of embodiments 323-325, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 180 °C to 220 °C.

329. The cartomizer of any one of embodiments 323-325, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature of about 200 °C.

330. The cartomizer of embodiment 326, wherein the operating temperature is from 150 °C to 250 °C.

331. The cartomizer of embodiment 326, wherein the operating temperature is from 180 °C to 220 °C.

332. The cartomizer of embodiment 326, wherein the operating temperature is about 200 °C.

333. The cartomizer of any one of embodiments 323-332, wherein the cartomizer further comprises a mouthpiece.

334. The cartomizer of any one of embodiments 323-333, wherein the acid is a carboxylic acid.

335. The cartomizer of any one of embodiments 323-333, wherein the acid used to form said nicotine salt is an organic acid.

336. The cartomizer of embodiment 335, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

337. The cartomizer of embodiment 335, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

338. The cartomizer of any one of embodiments 323-333, wherein the acid used to form the nicotine salt is salicylic acid.

339. The cartomizer of any one of embodiments 323-333, wherein the acid used to form the nicotine salt is benzoic acid.

340. The cartomizer of any one of embodiments 323-333, wherein the acid used to form the nicotine salt is pyruvic acid.

341. The cartomizer of any one of embodiments 323-333, wherein the acid used to form the nicotine salt is sorbic acid.

342. The cartomizer of any one of embodiments 323-333, wherein the acid used to form the nicotine salt is lauric acid.

343. The cartomizer of any one of embodiments 323-333, wherein the acid used to form the nicotine salt is levulinic acid.

344. The cartomizer of any one of embodiments 323-333, wherein said nicotine salt comprises nicotine pyruvate.

345. The cartomizer of any one of embodiments 323-333, wherein said nicotine salt comprises nicotine salicylate.

346. The cartomizer of any one of embodiments 323-333, wherein said nicotine salt comprises nicotine sorbate.

347. The cartomizer of any one of embodiments 323-333, wherein said nicotine salt comprises nicotine laurate.

348. The cartomizer of any one of embodiments 323-333, wherein said nicotine salt comprises nicotine levulinate.

349. The cartomizer of any one of embodiments 323-333, wherein said nicotine salt comprises nicotine benzoate.

350. The cartomizer of any one of embodiments 323-349, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

351. The cartomizer of any one of embodiments 323-349, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

352. The cartomizer of any one of embodiments 323-349, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

353. The cartomizer of any one of embodiments 323-349, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

354. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

355. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

356. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

357. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

358. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

359. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

360. The cartomizer of any one of embodiments 323-353, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

361. The cartomizer of any one of embodiments 323-360, wherein the electronic cigarette is configured to generate an aerosol inhalable by a user.

362. The cartomizer of embodiment 361, wherein the aerosol comprises condensate of the nicotine salt.

363. The cartomizer of embodiment 361, wherein the aerosol comprises condensate of freebase nicotine.

364. The cartomizer of embodiment 361, wherein the aerosol comprises condensate of freebase nicotine and condensate of the carrier.

365. The cartomizer of embodiment 361, wherein the aerosol comprises condensate of freebase nicotine and condensate of the acid.

366. The cartomizer of any one of embodiments 361-365, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 5 microns.

367. The cartomizer of any one of embodiments 361-365, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 1 or 2 microns.

368. The cartomizer of any one of embodiments 361-365, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 0.7 microns.

369. The cartomizer of any one of embodiments 361-365, wherein the aerosol comprises condensate in particle sizes from about 0.3 microns to about 0.4 microns.

370. The cartomizer of any one of embodiments 361-369, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

371. The cartomizer of any one of embodiments 361-369, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

372. The cartomizer of any one of embodiments 323-371, wherein the formulation further comprises a flavorant.

373. The cartomizer of any one of embodiments 323-372, wherein the formulation is non-corrosive to an electronic cigarette.

374. The cartomizer of any one of embodiments 323-373, wherein the acid is stable at and below operating temperature or about 200 °C.

375. The cartomizer of any one of embodiments 323-374, wherein the acid does not decompose at and below operating temperature or about 200 °C.

376. The cartomizer of any one of embodiments 323-375, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

377. The cartomizer of any one of embodiments 323-376, wherein the formulation is non-corrosive to the electronic cigarette.

378. The cartomizer of any one of embodiments 323-377, wherein the formulation is non-toxic to a user of the electronic cigarette.

379. The cartomizer of any one of embodiments 323-378, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

380. The cartomizer of embodiment 379, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

381. An electronic cigarette for generating an inhalable aerosol comprising

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C;

a battery; and

a mouthpiece.

382. An electronic cigarette for generating an inhalable aerosol comprising

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C;

a battery; and

a mouthpiece.

383. An electronic cigarette for generating an inhalable aerosol comprising

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point;

a battery; and

a mouthpiece.

384. An electronic cigarette for generating an inhalable aerosol comprising

a fluid storage compartment;

a heater; and

a nicotine salt liquid formulation in the fluid storage compartment, the liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point;

a battery; and

a mouthpiece.

385. The electronic cigarette of any one of embodiments 381-384, wherein the heater comprises a heater chamber, a fluid wick, and a resistive heating element in contact with the fluid wick.

386. The electronic cigarette of any one of embodiments 381-384, wherein the mouthpiece, the heater and the fluid storage compartment form a cartomizer separable from the battery.

387. The electronic cigarette of any one of embodiments 381-384, wherein the heater and the fluid storage compartment form a cartomizer separable from the battery and the mouthpiece.

388. The electronic cigarette of any one of embodiments 381-384, wherein the fluid storage compartment is separable from the heater, the battery and the mouthpiece.

389. The electronic cigarette of any one of embodiments 381-383, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 150 °C to 250 °C.

390. The electronic cigarette of any one of embodiments 381-383, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature from 180 °C to 220 °C.

391. The electronic cigarette of any one of embodiments 381-383, wherein the electronic cigarette heats the nicotine salt formulation to an operating temperature of about 200 °C.

392. The electronic cigarette of embodiment 384, wherein the operating temperature is from 150 °C to 250 °C.

393. The electronic cigarette of embodiment 384, wherein the operating temperature is from 180 °C to 220 °C.

394. The electronic cigarette of embodiment 384, wherein the operating temperature is about 200 °C.

395. The electronic cigarette of any one of embodiments 381-394, wherein the aerosol comprises condensate of the nicotine salt.

396. The electronic cigarette of any one of embodiments 381-394, wherein the aerosol comprises condensate of freebase nicotine.

397. The electronic cigarette of any one of embodiments 381-394, wherein the aerosol comprises condensate of freebase nicotine and condensate of the carrier.

398. The electronic cigarette of any one of embodiments 381-394, wherein the aerosol comprises condensate of freebase nicotine and condensate of the acid.

399. The electronic cigarette of any one of embodiments 381-398, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 5 microns.

400. The electronic cigarette of any one of embodiments 381-398, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 1 or 2 microns.

401. The electronic cigarette of any one of embodiments 381-398, wherein the aerosol comprises condensate in particle sizes from about 0.1 microns to about 0.7 microns.

402. The electronic cigarette of any one of embodiments 381-398, wherein the aerosol comprises condensate in particle sizes from about 0.3 microns to about 0.4 microns.

403. The electronic cigarette of any one of embodiments 381-402, wherein the acid is a carboxylic acid.

404. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form said nicotine salt is an organic acid.

405. The electronic cigarette of embodiment 404, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

406. The electronic cigarette of embodiment 404, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid,

malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

407. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form the nicotine salt is salicylic acid.

408. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form the nicotine salt is benzoic acid.

409. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form the nicotine salt is pyruvic acid.

410. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form the nicotine salt is sorbic acid.

411. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form the nicotine salt is lauric acid.

412. The electronic cigarette of any one of embodiments 381-402, wherein the acid used to form the nicotine salt is levulinic acid.

413. The electronic cigarette of any one of embodiments 381-402, wherein said nicotine salt comprises nicotine pyruvate.

414. The electronic cigarette of any one of embodiments 381-402, wherein said nicotine salt comprises nicotine salicylate.

415. The electronic cigarette of any one of embodiments 381-402, wherein said nicotine salt comprises nicotine sorbate.

416. The electronic cigarette of any one of embodiments 381-402, wherein said nicotine salt comprises nicotine laurate.

417. The electronic cigarette of any one of embodiments 381-402, wherein said nicotine salt comprises nicotine levulinate.

418. The electronic cigarette of any one of embodiments 381-402, wherein said nicotine salt comprises nicotine benzoate.

419. The electronic cigarette of any one of embodiments 381-419, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

420. The electronic cigarette of any one of embodiments 381-419, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

421. The electronic cigarette of any one of embodiments 381-419, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

422. The electronic cigarette of any one of embodiments 381-419, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

423. The electronic cigarette of any one of embodiments 381-422, wherein the nicotine salt is in an amount that forms about 0.5% to about 20% nicotine in the inhalable aerosol.

424. The electronic cigarette of any one of embodiments 381-422, wherein the nicotine salt is in an amount that forms about 1% to about 20% nicotine in the inhalable aerosol.

425. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

426. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

427. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

428. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

429. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

430. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

431. The electronic cigarette of any one of embodiments 381-424, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

432. The electronic cigarette of any one of embodiments 381-431, wherein the formulation further comprises a flavorant.

433. The electronic cigarette of any one of embodiments 381-432, wherein the formulation is non-corrosive to an electronic cigarette.

434. The electronic cigarette of any one of embodiments 381-433, wherein the acid is stable at and below operating temperature or about 200 °C.

435. The electronic cigarette of any one of embodiments 381-434, wherein the acid does not decompose at and below operating temperature or about 200 °C.

436. The electronic cigarette of any one of embodiments 381-435, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

437. The electronic cigarette of any one of embodiments 381-436, wherein the formulation is non-corrosive to the electronic cigarette.

438. The electronic cigarette of any one of embodiments 381-437, wherein the formulation is non-toxic to a user of the electronic cigarette.

439. The electronic cigarette of any one of embodiments 381-438, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

440. The electronic cigarette of embodiment 439, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

441. A cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C.

442. A cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

443. A cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

444. A cartridge in an electronic cigarette comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the

operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

445. The cartridge of any one of embodiments 441-444, wherein the cartridge is separable from the electronic cigarette.

446. The cartridge of any one of embodiments 441-445, wherein the acid is a carboxylic acid.

447. The cartridge of any one of embodiments 441-445, wherein the acid used to form said nicotine salt is an organic acid.

448. The cartridge of embodiment 447, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

449. The cartridge of embodiment 447, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

450. The cartridge of any one of embodiments 441-445, wherein the acid used to form the nicotine salt is salicylic acid.

451. The cartridge of any one of embodiments 441-445, wherein the acid used to form the nicotine salt is benzoic acid.

452. The cartridge of any one of embodiments 441-445, wherein the acid used to form the nicotine salt is pyruvic acid.

453. The cartridge of any one of embodiments 441-445, wherein the acid used to form the nicotine salt is sorbic acid.

454. The cartridge of any one of embodiments 441-445, wherein the acid used to form the nicotine salt is lauric acid.

455. The cartridge of any one of embodiments 441-445, wherein the acid used to form the nicotine salt is levulinic acid.

456. The cartridge of any one of embodiments 441-445, wherein said nicotine salt comprises nicotine pyruvate.

457. The cartridge of any one of embodiments 441-445, wherein said nicotine salt comprises nicotine salicylate.

458. The cartridge of any one of embodiments 441-445, wherein said nicotine salt comprises nicotine sorbate.

459. The cartridge of any one of embodiments 441-445, wherein said nicotine salt comprises nicotine laurate.

460. The cartridge of any one of embodiments 441-445, wherein said nicotine salt comprises nicotine levulinate.

461. The cartridge of any one of embodiments 441-445, wherein said nicotine salt comprises nicotine benzoate.

462. The cartridge of any one of embodiments 441-461, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

463. The cartridge of any one of embodiments 441-461, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

464. The cartridge of any one of embodiments 441-461, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

465. The cartridge of any one of embodiments 441-461, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

466. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

467. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

468. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

469. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

470. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

471. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

472. The cartridge of any one of embodiments 441-465, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

473. The cartridge of any one of embodiments 441-472, wherein the formulation further comprises a flavorant.

474. The cartridge of any one of embodiments 441-473, wherein the formulation is non-corrosive to an electronic cigarette.

475. The cartridge of any one of embodiments 441-474, wherein the acid is stable at and below operating temperature or about 200 °C.

476. The cartridge of any one of embodiments 441-475, wherein the acid does not decompose at and below operating temperature or about 200 °C.

477. The cartridge of any one of embodiments 441-476, wherein the acid does not oxidize at and below operating temperature or about 200 $^{\circ C}$.

478. The cartridge of any one of embodiments 441-477, wherein the formulation is non-corrosive to the electronic cigarette.

479. The cartridge of any one of embodiments 441-478, wherein the formulation is non-toxic to a user of the electronic cigarette.

480. The cartridge of any one of embodiments 441-479, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

481. The cartridge of embodiment 480, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

482. A kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 $^{\circ}$C;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

483. A kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 ^{o}C;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

484. A kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

485. A kit comprising:

(a) an electronic cigarette for generating an inhalable aerosol comprising

i. a device body comprising a cartridge receptacle;

ii. a cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is

further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point;

iii. a heater;

iv. a battery; and

v. a mouthpiece; and

(b) instructions for using the electronic cigarette to generate an inhalable aerosol.

486. The kit of any one of embodiments 482-485, wherein the acid is a carboxylic acid.

487. The kit of any one of embodiments 482-485, wherein the acid used to form said nicotine salt is an organic acid.

488. The kit of embodiment 487, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

489. The kit of embodiment 487, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

490. The kit of any one of embodiments 482-485, wherein the acid used to form the nicotine salt is salicylic acid.

491. The kit of any one of embodiments 482-485, wherein the acid used to form the nicotine salt is benzoic acid.

492. The kit of any one of embodiments 482-485, wherein the acid used to form the nicotine salt is pyruvic acid.

493. The kit of any one of embodiments 482-485, wherein the acid used to form the nicotine salt is sorbic acid.

494. The kit of any one of embodiments 482-485, wherein the acid used to form the nicotine salt is lauric acid.

495. The kit of any one of embodiments 482-485, wherein the acid used to form the nicotine salt is levulinic acid.

496. The kit of any one of embodiments 482-485, wherein said nicotine salt comprises nicotine pyruvate.

497. The kit of any one of embodiments 482-485, wherein said nicotine salt comprises nicotine salicylate.

498. The kit of any one of embodiments 482-485, wherein said nicotine salt comprises nicotine sorbate.

499. The kit of any one of embodiments 482-485, wherein said nicotine salt comprises nicotine laurate.

500. The kit of any one of embodiments 482-485, wherein said nicotine salt comprises nicotine levulinate.

501. The kit of any one of embodiments 482-485, wherein said nicotine salt comprises nicotine benzoate.

502. The kit of any one of embodiments 482-501, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

503. The kit of any one of embodiments 482-501, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

504. The kit of any one of embodiments 482-501, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

505. The kit of any one of embodiments 482-501, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

506. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

507. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

508. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

509. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

510. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

511. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

512. The kit of any one of embodiments 482-505, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

513. The kit of any one of embodiments 482-512, wherein the formulation further comprises a flavorant.

514. The kit of any one of embodiments 482-513, wherein the formulation is non-corrosive to an electronic cigarette.

515. The kit of any one of embodiments 482-514, wherein the acid is stable at and below operating temperature or about 200 °C.

516. The kit of any one of embodiments 482-515, wherein the acid does not decompose at and below operating temperature or about 200 °C.

517. The kit of any one of embodiments 482-516, wherein the acid does not oxidize at and below operating temperature or about 200 °C.

518. The kit of any one of embodiments 482-517, wherein the formulation is non-corrosive to the electronic cigarette.

519. The kit of any one of embodiments 482-518, wherein the formulation is non-toxic to a user of the electronic cigarette.

520. The kit of any one of embodiments 482-519, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

521. The kit of embodiment 520, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

522. A cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure >20 mmHg at 200 °C.

523. A cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically

acceptable liquid carrier wherein an acid used to form said nicotine salt is characterized by vapor pressure of about 20 to 200 mmHg at 200 °C.

524. A cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point <160 °C, a boiling point >160 °C, and at least a 50-degree difference between the melting point and the boiling point.

525. A cartridge comprising a fluid storage compartment, wherein the fluid storage compartment stores a nicotine salt liquid formulation comprising a nicotine salt in a biologically acceptable liquid carrier wherein an acid used to form said nicotine salt is further characterized by a melting point at least 40 degrees lower than an operating temperature of the electronic cigarette, a boiling point no more than 40 degrees lower than the operating temperature of the electronic cigarette, and at least a 50-degree difference between the melting point and the boiling point.

526. The cartridge of any one of embodiments 523-526, wherein the cartridge can be connected to an electronic cigarette.

527. The cartridge of any one of embodiments 523-527, wherein the acid is a carboxylic acid.

528. The cartridge of any one of embodiments 523-527, wherein the acid used to form said nicotine salt is an organic acid.

529. The cartridge of embodiment 529, wherein the organic acid is monocarboxylic acid, aromatic acid, or keto acid.

530. The cartridge of embodiment 529, wherein the organic acid is formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, capric acid, citric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, phenylacetic acid, benzoic acid, pyruvic acid, levulinic acid, tartaric acid, lactic acid, malonic acid, succinic acid, fumaric acid, finnaric acid, gluconic acid, saccharic acid, salicylic acid, sorbic acid, malonic acid, or malic acid.

531. The cartridge of any one of embodiments 523-527, wherein the acid used to form the nicotine salt is salicylic acid.

532. The cartridge of any one of embodiments 523-527, wherein the acid used to form the nicotine salt is benzoic acid.

533. The cartridge of any one of embodiments 523-527, wherein the acid used to form the nicotine salt is pyruvic acid.

534. The cartridge of any one of embodiments 523-527, wherein the acid used to form the nicotine salt is sorbic acid.

535. The cartridge of any one of embodiments 523-527, wherein the acid used to form the nicotine salt is lauric acid.

536. The cartridge of any one of embodiments 523-527, wherein the acid used to form the nicotine salt is levulinic acid.

537. The cartridge of any one of embodiments 523-527, wherein said nicotine salt comprises nicotine pyruvate.

538. The cartridge of any one of embodiments 523-527, wherein said nicotine salt comprises nicotine salicylate.

539. The cartridge of any one of embodiments 523-527, wherein said nicotine salt comprises nicotine sorbate.

540. The cartridge of any one of embodiments 523-527, wherein said nicotine salt comprises nicotine laurate.

541. The cartridge of any one of embodiments 523-527, wherein said nicotine salt comprises nicotine levulinate.

542. The cartridge of any one of embodiments 523-527, wherein said nicotine salt comprises nicotine benzoate.

543. The cartridge of any one of embodiments 523-543, wherein the liquid carrier comprises glycerol, propylene glycol, trimethylene glycol, water, ethanol or combinations thereof.

544. The cartridge of any one of embodiments 523-543, wherein the liquid carrier comprises propylene glycol and vegetable glycerin.

545. The cartridge of any one of embodiments 523-543, wherein the liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% of vegetable glycerin.

546. The cartridge of any one of embodiments 523-543, wherein the liquid carrier comprises 30% propylene glycol and 70% vegetable glycerin.

547. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 25% (w/w).

548. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 20% (w/w).

549. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 18% (w/w).

550. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 1% (w/w) to about 15% (w/w).

551. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 4% (w/w) to about 12% (w/w).

552. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 4% (w/w).

553. The cartridge of any one of embodiments 523-547, wherein the liquid formulation has a nicotine concentration of about 2% (w/w).

554. The cartridge of any one of embodiments 523-553, wherein the formulation further comprises a flavorant.

555. The cartridge of any one of embodiments 523-554, wherein the formulation is non-corrosive to an electronic cigarette.

556. The cartridge of any one of embodiments 523-555, wherein the acid is stable at and below operating temperature or about 200 ^{o}C.

557. The cartridge of any one of embodiments 523-556, wherein the acid does not decompose at and below operating temperature or about 200 ^{o}C.

558. The cartridge of any one of embodiments 523-557, wherein the acid does not oxidize at and below operating temperature or about 200 ^{o}C.

559. The cartridge of any one of embodiments 523-558, wherein the formulation is non-corrosive to the electronic cigarette.

560. The cartridge of any one of embodiments 523-559, wherein the formulation is non-toxic to a user of the electronic cigarette.

561. The cartridge of any one of embodiments 523-560, wherein the formulation further comprises one or more additional nicotine salts in a biologically acceptable liquid carrier suitable for generating the inhalable aerosol upon heating.

562. The cartridge of embodiment 561, wherein a second acid used to form the additional nicotine salt is selected from the group consisting of salicylic acid, sorbic acid, benzoic acid, pyruvic acid, lauric acid, and levulinic acid.

[00131] Although preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein can be employed in practicing the invention. It is intended that the following embodiments define the scope of the invention and that methods and structures within the scope of these embodiments and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w);

b. the nicotine is protonated;

c. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation to generate an inhalable aerosol comprising protonated nicotine.

2. The method of claim 1, wherein the nicotine salt formulation comprises nicotine lactate.

3. The method of claim 1, wherein the carboxylic acid comprises one or more of: pyruvic acid, salicylic acid, sorbic acid, lauric acid or benzoic acid.

4. The method of claim 1, wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

5. The method of claim 1, wherein a molar ratio of nicotine to carboxylic acid is between 1:1 and 1:3.

6. The method of claim 1, wherein the nicotine salt formulation further comprises at least one flavorant.

7. The method of claim 1, wherein the nicotine concentration is about 4.5%.

8. The method of claim 1, wherein inhalation of the aerosol into the user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min.

9. The method of claim 1, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

10. A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid comprising lactic acid, pyruvic acid, salicylic acid, sorbic acid, lauric acid or benzoic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w);
b. the nicotine is protonated;
c. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation to generate an inhalable aerosol comprising protonated nicotine.

11. The method of claim 10, wherein the nicotine salt formulation comprises nicotine lactate.

12. The method of claim 10, wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

13. The method of claim 10, wherein a molar ratio of nicotine to carboxylic acid is between 1:1 and 1:3.

14. The method of claim 10, wherein the nicotine salt formulation further comprises at least one flavorant.

15. The method of claim 10, wherein the nicotine concentration is about 4.5%.

16. The method of claim 10, wherein inhalation of the aerosol into the user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min.

17. The method of claim 10, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

18. A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, lactic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about .05% (w/w) to about 20% (w/w);
b. the nicotine formulation comprises protonated nicotine;
c. the nicotine salt formulation comprises nicotine lactate;
d. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation to generate an inhalable aerosol comprising nicotine lactate.

19. The method of claim 18, wherein a molar ratio of nicotine to organic acid is between 1:1 and 1:3.

20. The method of claim 18, wherein the nicotine salt formulation further comprises at least one flavorant.

21. The method of claim 18, wherein the nicotine concentration is about 4.5%.

22. The method of claim 18, wherein inhalation of the aerosol into the user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min.

23. The method of claim 18, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

ABSTRACT

A nicotine salt liquid formulation for generating an inhalable aerosol in an electronic cigarette comprising nicotine salt that forms about 0.5% to about 20% nicotine is provide.

FIG. 1

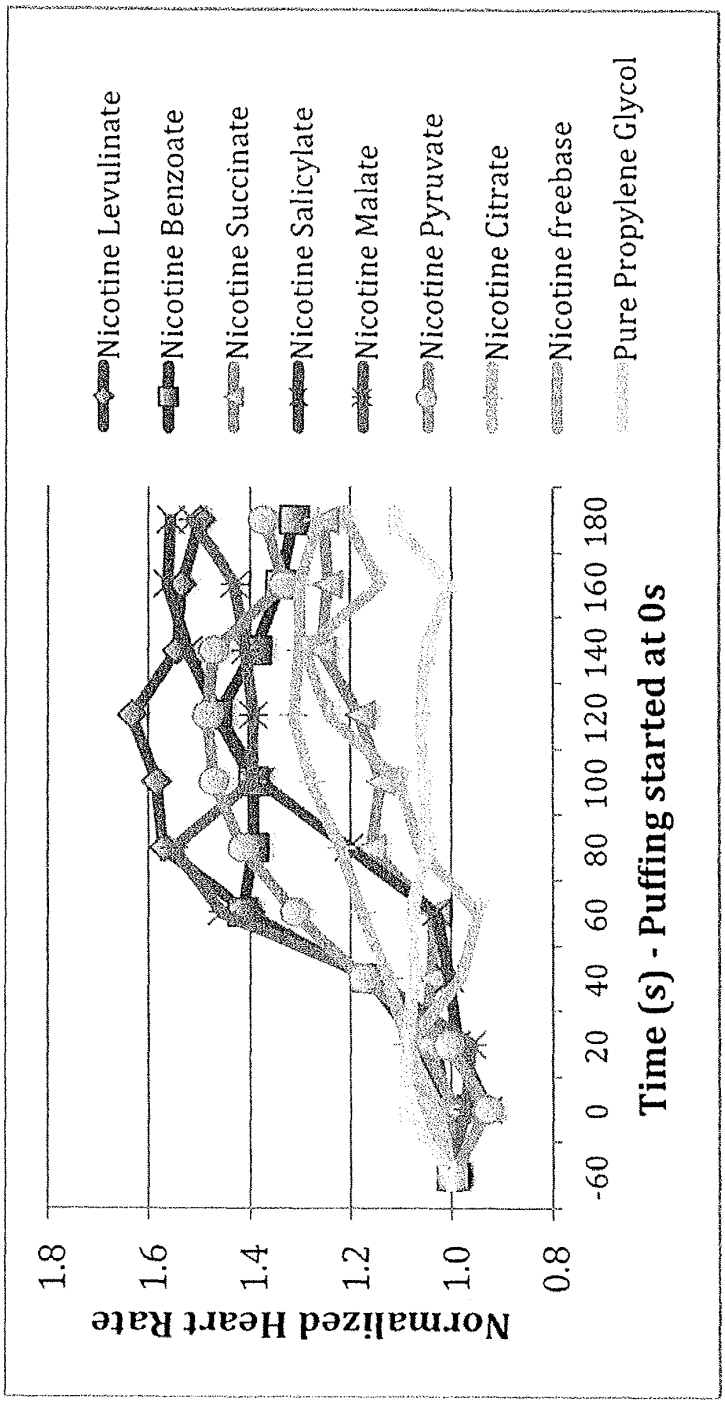

Nicotine Levulinate
Nicotine Benzoate
Nicotine Succinate
Nicotine Salicylate
Nicotine Malate
Nicotine Pyruvate
Nicotine Citrate
Nicotine freebase
Pure Propylene Glycol
Normalized Heart Rate
1.8
1.6
1.4
1.2
1.0
0.8
-60 0 20 40 60 80 100 120 140 160 180
Time (s) - Puffing started at 0s

FIG. 2

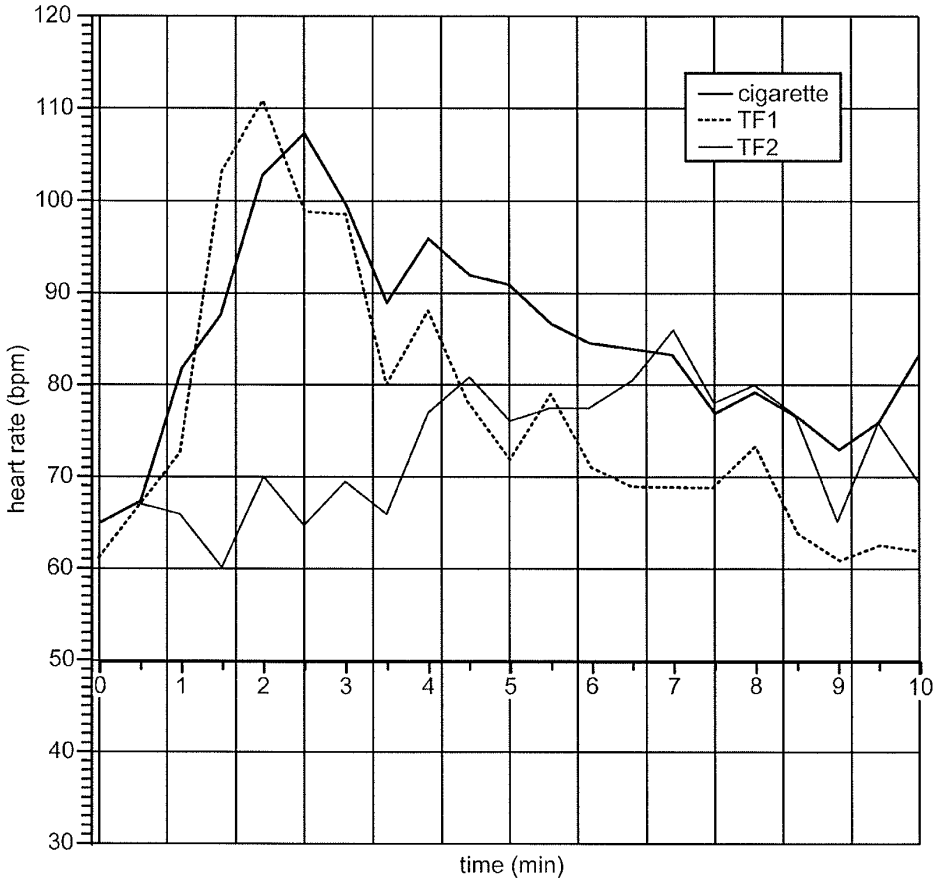

120
110
100
90
80
70
60
50
40
30
heart rate (bpm)
0
1
2
3
4
5
6
7
8
9
10
time (min)
cigarette
TF1
TF2

FIG. 3

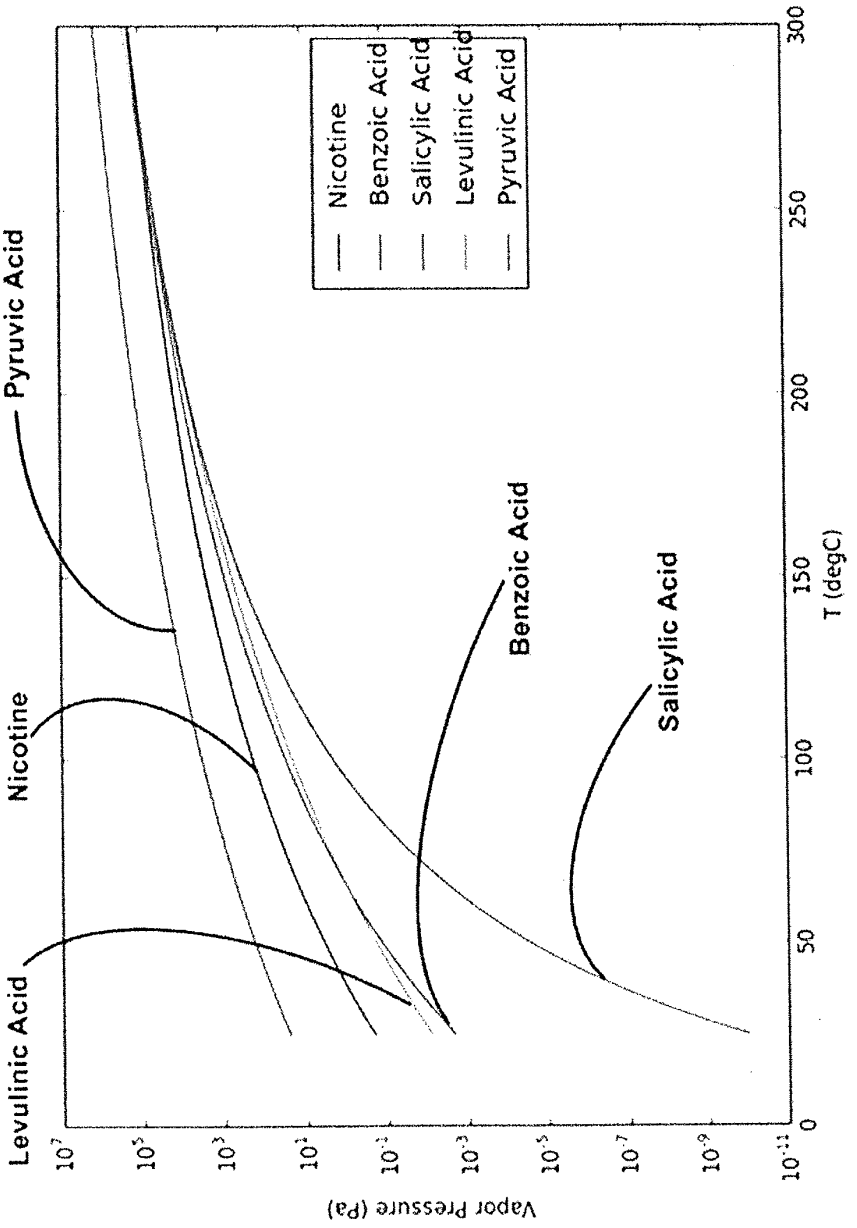

Nicotine
Benzoic Acid
Salicylic Acid
Levulinic Acid
Pyruvic Acid
Vapor Pressure (Pa)
T (degC)
0
50
100
150
200
250
300

FIG. 4

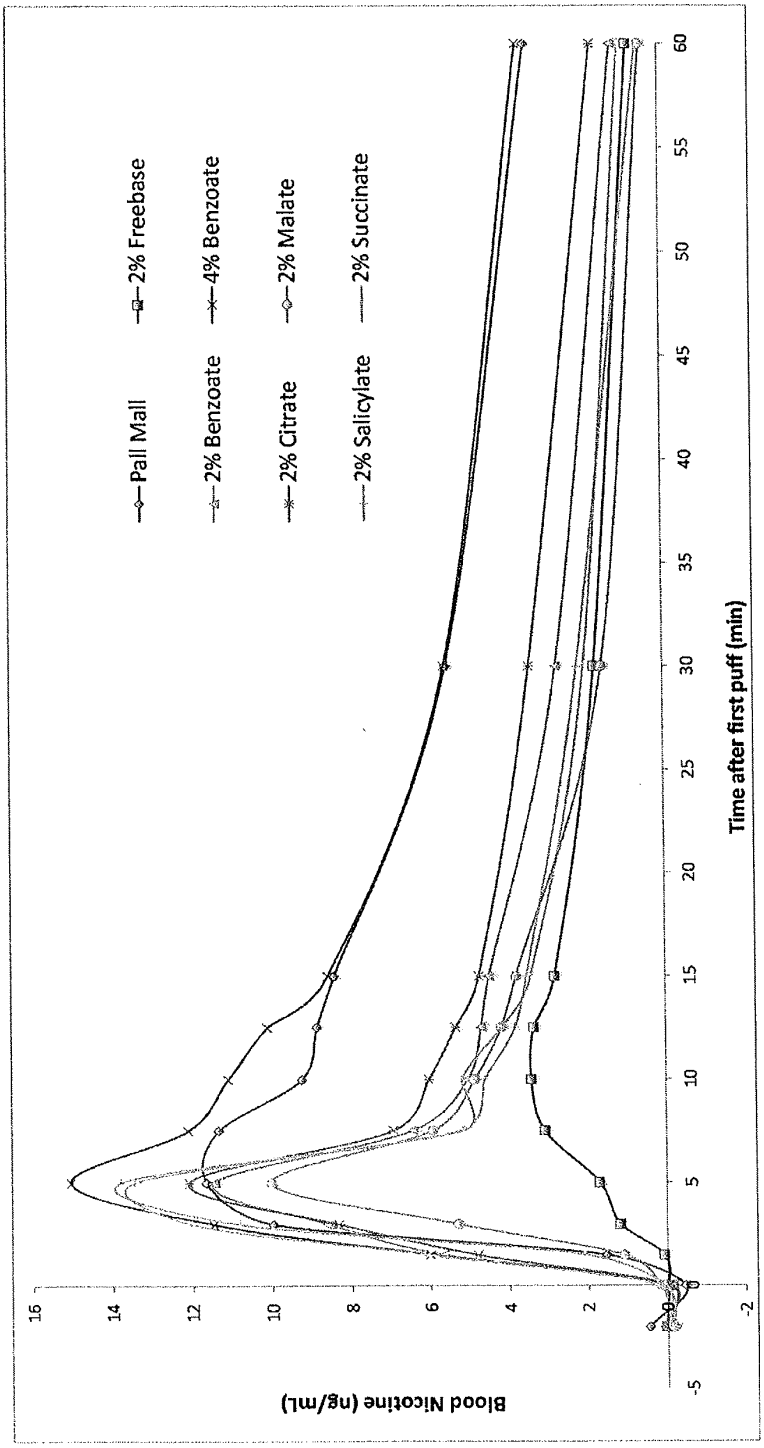

Pall Mall
2% Freebase
2% Benzoate
4% Benzoate
2% Citrate
2% Malate
2% Salicylate
2% Succinate
Blood Nicotine (ng/mL)
Time after first puff (min)
16
14
12
10
8
6
4
2
0
-2
-5
0
5
10
15
20
25
30
35
40
45
50
55
60

FIG. 5

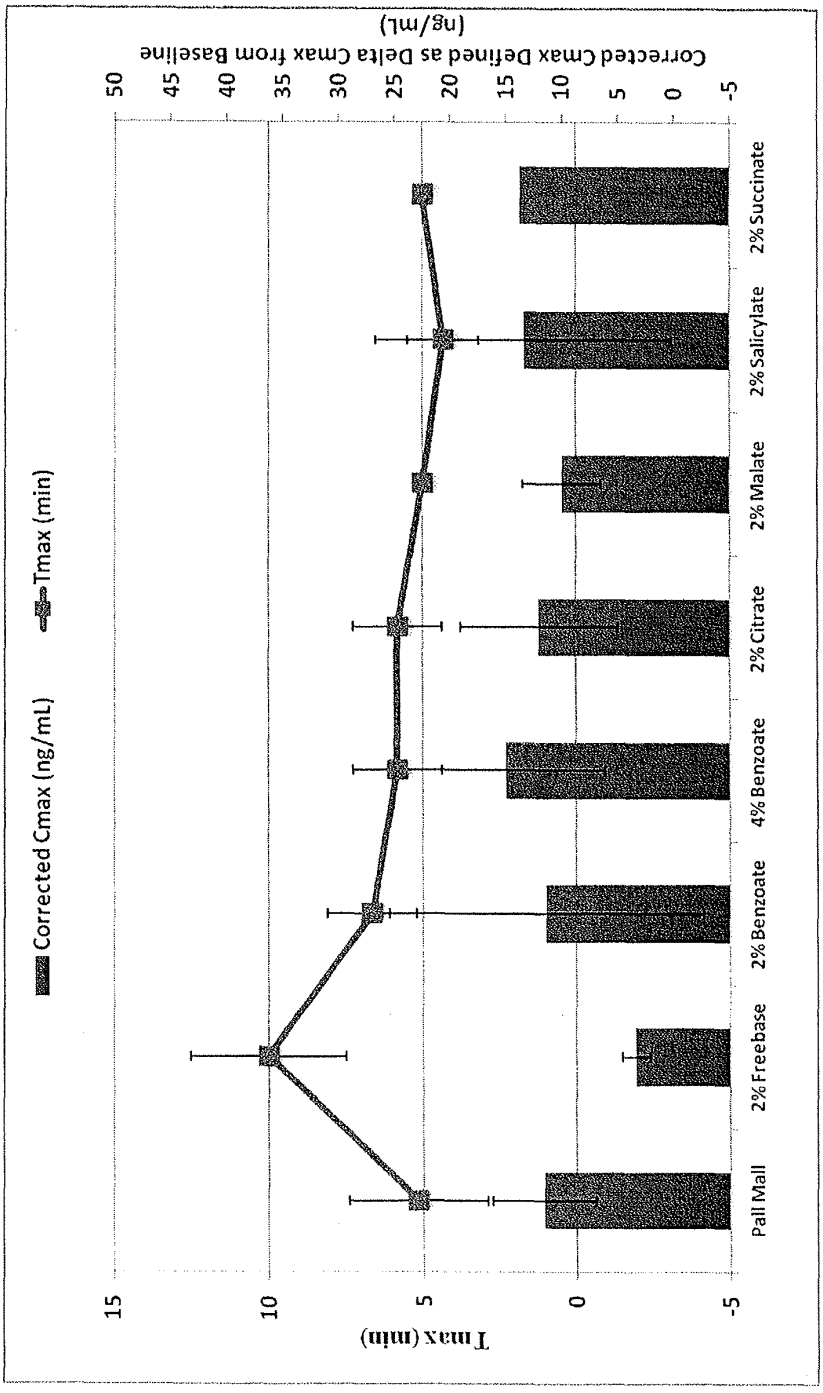

Corrected Cmax (ng/mL)
Tmax (min)
Corrected Cmax Defined as Delta Cmax from Baseline (ng/mL)
Tmax (min)
50
45
40
35
30
25
20
15
10
5
0
-5
15
10
5
0
-5
Pall Mall
2% Freebase
2% Benzoate
4% Benzoate
2% Citrate
2% Malate
2% Salicylate
2% Succinate

FIG. 6

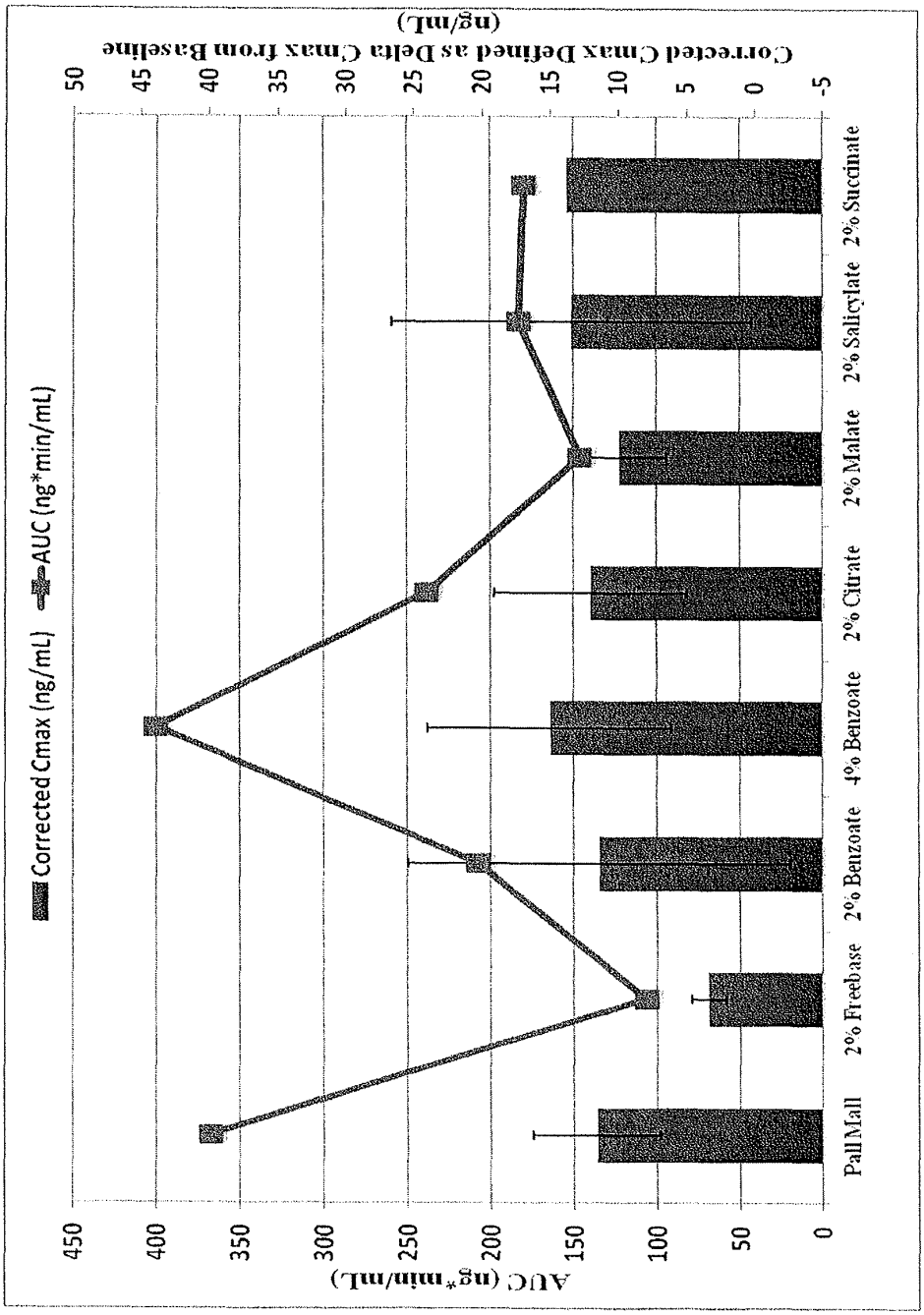

Corrected Cmax (ng/mL)
AUC (ng*min/mL)
AUC (ng*min/mL)
Corrected Cmax Defined as Delta Cmax from Baseline (ng/mL)
0
50
100
150
200
250
300
350
400
450
-5
0
5
10
15
20
25
30
35
40
45
50
PallMall
2% Freebase
2% Benzoate
4% Benzoate
2% Citrate
2% Malate
2% Salicylate
2% Succinate

FIG. 7

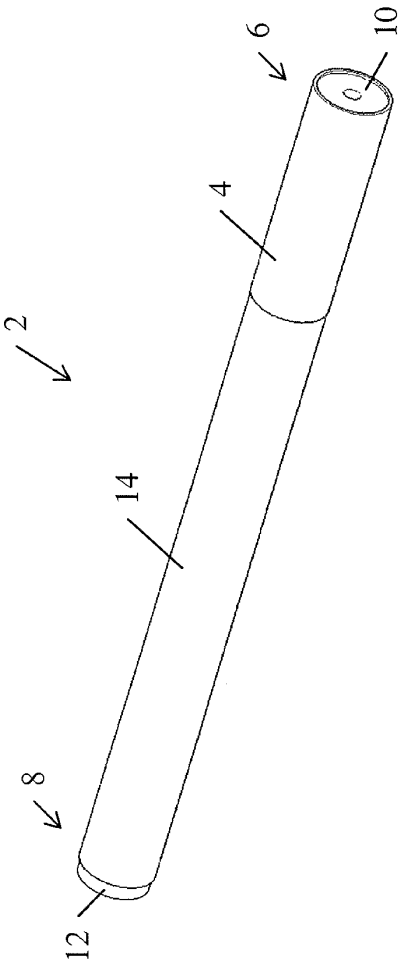
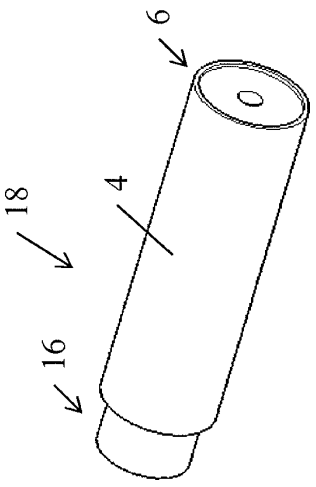


FIG. 8



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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13211-713.302
	Application Number	
Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

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For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13211-713.302
	Application Number	
Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	

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Application Information:

Title of the Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Attorney Docket Number	13211-713.302	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	8	**Suggested Figure for Publication (if any)**	

Filing By Reference :

Only compete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country i

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	66854		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13211-713.302
	Application Number	
Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14271071	2014-05-06
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14271071	Claims benefit of provisional	61820128	2013-05-06
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14271071	Claims benefit of provisional	61912507	2013-12-05

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13211-713.302
	Application Number	
Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13211-713.302
	Application Number	
Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee ◯ Legal Representative under 35 U.S.C. 117 ◯ Joint Inventor

◯ Person to whom the inventor is obligated to assign. ◯ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information:

Address 1			
Address 2			
City		**State/Province**	
Country [i]		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

PTO/AIA/14 (12-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13211-713.302
	Application Number	
Title of Invention	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Richard D. Shoop/			Date (YYYY-MM-DD)	2015-10-28
First Name	Richard D.	Last Name	Shoop	Registration Number	45763

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

EFS Web 2.2.10

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Richard Douglas Shoop/Jennifer Capizzi
Attorney Docket Number:	13211-713.302
Filed as Large Entity	
Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Claims in Excess of 20	1202	3	80	240
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**5980**

Electronic Acknowledgement Receipt	
EFS ID:	23924073
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Jennifer Capizzi
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	28-OCT-2015
Filing Date:	
Time Stamp:	23:09:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5980
RAM confirmation Number	9442
Deposit Account	504050
Authorized User	SHOOP, RICHARD D
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_Application.pdf	5729799 a0fafe23d46b05b7a4b344ecf6a40ed3f3561329	yes	108

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal of New Application	1	1
TrackOne Request	2	2
Fee Worksheet (SB06)	3	3
Oath or Declaration filed	4	5
Specification	6	95
Claims	96	99
Abstract	100	100
Drawings-only black and white line drawings	101	108

Warnings:

Information:

2	Application Data Sheet	13211-713-302_ADS.pdf	1561041 f3cdc5b4a2062fbbb263baa9c9ca414336b12797	no	7

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	42183 558233fc698b6b734efedcb88aa91b48e5c4a6b5	no	2

Warnings:

Information:

Total Files Size (in bytes):	7333023

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	23 minus 20 =	* 3			OR	x 80 =	240
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1840

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/925,961	10/28/2015	1629	1840	13211-713.302	23	3

CONFIRMATION NO. 1528

FILING RECEIPT

66854
SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403

OC000000078585888

Date Mailed: 11/12/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Adam BOWEN, San Francisco, CA;
Chenyue XING, San Francisco, CA;

Applicant(s)

Adam BOWEN, San Francisco, CA;
Chenyue XING, San Francisco, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 14/271,071 05/06/2014
which claims benefit of 61/820,128 05/06/2013
and claims benefit of 61/912,507 12/05/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 11/09/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/925,961**

Projected Publication Date: 02/18/2016

Non-Publication Request: No

Early Publication Request: No

Title

NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO CA 94403

MAILED
DEC 10 2015
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.:14/925,961

1. THE REQUEST FILED October 28, 2015 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Kimberly Inabinet at 571-272-4618.

/ Kimberly Inabinet/ Paralegal Specialist, Office of Petitions

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	13211-713.302	1528

66854 7590 01/20/2016

SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
01/20/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@shayglenn.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN ET AL.	
	Examiner DIONNE WALLS MAYES	Art Unit 1747	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/28/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-23* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-23* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of

activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

3. Claims 1-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-26 of Bowen ‘895 (U.S. Patent No. 9,215,895) in view of Gonda (US. Pat. App. Pub. 2014/0261474).

Regarding the instant independent claims 1, 10 and 18, the Hon ‘895 patent claims recite nearly all that is recited in the instant claims; but, it fails to recite that the nicotine formulation comprises a propylene glycol/glycerol liquid carrier. However, the Gonda reference teaches that a nicotine formulation, such as a nicotine lactate salt (based on lactic acid) in solution (i.e., glycerin/glycols), can be prepared so as to be inhaled which results in rapid delivery of nicotine (see abstract and paras.[0052],[0078]). Hence, it would have been obvious to one having ordinary skill in the art to have included the nicotine formulation of Gonda in the device of Hon ‘895 as such is already known in the art.

Regarding dependent claims 2-9, 11-17 and 19-23, the limitations of these claims are deemed to have been met by, or an obvious modification of, the claims of Hon ‘895.

4. Claims 1-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of copending Application No. 14/925,968. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims of said application generally encompass those of the instant application.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

5. Claims 1-7, 9-15, 17-21 and 23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 105-122 of copending Application No. 14/271,071.

While the claims of copending Application No. 14/271,071 are not identical to those of the instant application, they are not patentably distinct therefrom because, collectively, claims 105-122 of Application No. 14/271,071 generally encompass the above-referenced claims of the instant application.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

6. Claims 8, 16 and 22 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 105-122 of copending Application No. 14/271,071 in view of Gonda (US. Pat. No. 2014/0261474) and Bowen ‘717 et al (US. Pat. App. Pub. 2009/0151717).

Claims 105-122 of Application No. 14/271,071 fail to recite that inhalation of the aerosol into the user's lungs takes place over a period of about 5 minutes at a rate of about one inhalation per 30 seconds and results in a nicotine plasma T_{max} from about 3 min to about 8 min. However, Gonda states that adjustments in pH, in combination with changing the particle size of the aerosol, can be carried out to create a different experience for the user. By decreasing the pH of the nicotine formulation, the likelihood of airway irritation and cough is reduced. By decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels (see para. [0007],[0033]-[0036], [0052], [0064], [0086]). Further, Gonda states that, during inhalation of aerosolized nicotine formulations, a satisfactory dose of nicotine is achieved in a small number of breaths, spaced by short periods, preferably less than 2 minutes (see para. [0017]). (Note: To this point, the Bowen et al reference further discloses that, typically, when smokers “puff” on cigarettes they may take a puff every 30 seconds (i.e., in an intense smoking regime). Bowen et al then shows that aerosol devices used to inhale a nicotine substance can also be “smoked” in such manner (see para. [0107])). This collective disclosure indicates that the parameters of pH, aerosolized nicotine particle size, and even nicotine concentration in the liquid formulation and inhalation rate, are all “result-effective variables”. Note: Once a particular parameter is recognized as a result-effective variable, i.e., a variable which achieves a recognized result, the determination of the optimum or workable ranges of said variable can be characterized by routine experimentation. See *In re Boesch*, 617

F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy). MPEP 2144.05. Hence, it would have been obvious to one having ordinary skill in the art at the time of the invention to have undergone routine experimentation and arrived at the claimed inhalation rate which result in the claimed T_{max} parameters, after determining that these values provided, as close as possible, the same nicotine blood levels achieved by smoking a conventional cigarette - which is the goal of Gonda and Bowen et al.

This is a provisional nonstatutory double patenting rejection.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was

commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

10. Claims 1-7, 10-15, and 18-21 are rejected under 35 U.S.C. 103 as being unpatentable over Hon (US. Pat. App. Pub. 2006/0196518) in view of Gonda (US. Pat. No. 2014/0261474).

Regarding independent claims 1, 10 and 18, Hon discloses a flameless, battery-operated electronic atomizing cigarette, and a method of using the same, designed to help a smoker wean himself from the tobacco-smoking habit - while still enjoying the nicotine delivery. The cigarette is designed to dispense a liquid nicotine formulation contained in a storage container in aerosolized/vaporized form upon being heated by an electric heater, for inhalation by a user. The nicotine formulation may include anywhere from 0.1-6% nicotine by weight and tobacco essence (see abstract; paras. [0006],[0021],[0028]-[0032])(corresponding to the claimed "a method of delivering nicotine to a user…comprising: deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine…and a biologically acceptable liquid carrier, wherein…the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w)…heating at least a portion of the nicotine formulation to generate an inhalable aerosol”(claims 1,7); the “wherein the nicotine formulation further comprises at least one

flavorant" recitation of claims 6, 14, and 20; the "wherein the nicotine concentration is from about 4.5%" recitation of claims 7, 15 and 21).

Hon is silent as to whether the nicotine, in its liquid formulation, may be combined with a carboxylic acid; however, the Gonda reference teaches that administering an aerosolized, liquid nicotine-containing formulation via inhalation (i.e., pulmonary administration) in order to effectuate a peak level of nicotine in the blood plasma after a very short period of time - mimicking that which is typically achieved during actual cigarette smoking - is known. Specifically, Gonda teaches that a nicotine formulation, such as a nicotine lactate, pyruvate or benzoate salt (based on lactic, pyruvic and benzoic acids, respectively) in solution (i.e., glycerin and glycols), can be prepared so as to be inhaled which results in rapid delivery of nicotine (see abstract and paras.[0052],[0078]). Hence, it would have been obvious to one having ordinary skill in the art to have included the nicotine formulation of Gonda in the device of Hon for the benefits described above (corresponding to the claimed "nicotine, a carboxylic acid/lactic acid, and a biologically acceptable liquid carrier comprises propylene glycol and glycerol"; the "wherein the nicotine salt formulation comprises nicotine lactate" recitation of claim 2, 11 and 18; the "wherein the carboxylic acid comprises one or more of: pyruvic acid…or benzoic acid" recitation of claim 3) Hence, the modified Hon/Gonda invention meets all the limitations of the above-referenced claims.

Regarding claims 5, 13 and 19, Gonda doesn't specifically state the molar ratio of nicotine to carboxylic acid, for example; however, one of ordinary skill in the art would have optimized said nicotine/acid amounts in order to provide the optimal stoichiometric

amounts for nicotine salt formation and, in doing so, undergone routine experimentation and arrived at the claimed ratios (corresponding to the claimed “wherein the molar ratio of nicotine or organic acid is between about 1:1 and 1:3”).

Regarding claims 4 and 12, upon implementing the method of independent claims 1 and 10 by deploying the claimed electronic cigarette, it follows to reason that an increased heart rate would occur, naturally, as a result of its use (corresponding to the claimed “wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco”).

11. Claims 8-9, 16-17 and 22-23 are rejected under 35 U.S.C. 103 as being unpatentable over Hon (US. Pat. App. Pub. 2006/0196518) in view of Gonda (US. Pat. No. 2014/0261474) and Bowen ‘717 et al (US. Pat. App. Pub. 2009/0151717).

The modified Hon/Gonda invention fails to disclose anything about nicotine plasma concentrations; the time period at which the maximum concentration is reached after inhaling nicotine from the electronic cigarette; and micron size of the aerosol generated therefrom, to result in the claimed time period for peak nicotine concentration; however, it does disclose that each of these parameters impact nicotine delivery and absorption in the bloodstream (see paras. [0043],[0092]). Specifically, Gonda states that adjustments in pH, in combination with changing the particle size of the aerosol, can be carried out to create a different experience for the user. By decreasing the pH of the nicotine formulation, the likelihood of airway irritation and cough is reduced. By decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine

and leads to an increase in peak nicotine plasma levels (see para. [0007],[0033]-[0036], [0052], [0064], [0086]). Further, Gonda states that, during inhalation of aerosolized nicotine formulations, a satisfactory dose of nicotine is achieved in a small number of breaths, spaced by short periods, preferably less than 2 minutes (see para. [0017]). (Note: To this point, the Bowen et al reference further discloses that, typically, when smokers "puff" on cigarettes they may take a puff every 30 seconds (i.e., in an intense smoking regime). Bowen et al then shows that aerosol devices used to inhale a nicotine substance can also be "smoked" in such manner (see para. [0107])). This collective disclosure indicates that the parameters of pH, aerosolized nicotine particle size, and even nicotine concentration in the liquid formulation and inhalation rate, are all "result-effective variables". Note: Once a particular parameter is recognized as a result-effective variable, i.e., a variable which achieves a recognized result, the determination of the optimum or workable ranges of said variable can be characterized by routine experimentation. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy). MPEP 2144.05. Hence, it would have been obvious to one having ordinary skill in the art at the time of the invention to have undergone routine experimentation and fabricated the nicotine formulation of Hon in the form of a liquid nicotine lactate salt solution and, in so doing, arrived at the claimed particle size, and inhalation rate which result in the claimed T_{max} parameters, after determining that these values provided, as close as possible, the same nicotine blood levels achieved by smoking a conventional cigarette - which is the goal of Hon, Gonda and Bowen et al (corresponding to the

claimed “wherein inhalation of the aerosol into the user’s lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 min to about 8 min” recitation of claims 8, 16 and 22; the “wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns” recitation of claim 9, 17 and 23).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE WALLS MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Tuesday and Thursday, 8:00A - 6:30P EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Michael H. Wilson can be reached on 571-270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE WALLS MAYES/
Examiner, Art Unit 1747

Notice of References Cited	Application/Control No. 14/925,961	Applicant(s)/Patent Under Reexamination BOWEN ET AL.	
	Examiner DIONNE WALLS MAYES	Art Unit 1747	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2014/0261474 A1	09-2014	Gonda; Igor	A61M15/06	131/270
*	B	US-2006/0196518 A1	09-2006	Hon; Lik	A24F47/002	131/360
*	C	US-9,215,895 B2	12-2015	Bowen; Adam	A24F47/008	1/1
*	D	US-2009/0151717 A1	06-2009	Bowen; Adam	A61M11/041	128/200.23
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2015/01/20 15:51

			EPO; JPO; DERWENT; IBM_TDB			
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48
S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR;	ADJ	ON	2015/01/20 16:59

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08

S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31

		(plasma or blood) and (ph near5 "7") and heat$4 and lung				
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48

		(plasma or blood)				
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S66	723	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2015/09/17 14:46
S67	246	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB	ADJ	ON	2015/09/17 14:47
S68	196	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB	ADJ	ON	2015/09/17 14:49

1/ 11/ 2016 11:27:13 PM
C:\ Users\ dmayes\ Documents\ EAST\ Workspaces\ 14925961.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14925961	BOWEN ET AL.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC- SEARCHED		
Symbol	Date	Examiner
A24F47/008	1/11/2016	DWM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/925,961	10/28/2015	Adam BOWEN	13211-713.302

CONFIRMATION NO. 1528

PUBLICATION NOTICE

66854
SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403

OC000000080704213

Title:NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

Publication No.US-2016-0044967-A1
Publication Date:02/18/2016

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Mayes, Dionne

From:	Rick Shoop <rick@shayglenn.com>
Sent:	Tuesday, March 08, 2016 6:36 PM
To:	Mayes, Dionne
Cc:	Rick Shoop; Mary Buggie
Subject:	RE: 14/925,968 and 14/925,961 Telephone Interview of 3.10.2016
Attachments:	Apps. no 14.925968 and 14.925961 (Telephone Interview of 3.10.2016).docx

RE: 14/925,968 and 14/925,961

Dear Examiner Mayes:

Looking forward to talking with you on Thursday at 2 pm ET (11 am PT). We will call you in your office then (571-272-5836). I will be joined by one of the inventors, Adam Bowen. I'm also attaching a draft set of proposed claim amendments for discussion purposes. During the would like to discuss the cited art, in in particular the Hon (US 2006196518) and Gonda (US 20140261474) references, as well as the attached claim language.

Thank you again for all of your help, and please don't hesitate to contact me by phone or email.

AUTHORIZATION FOR ELECTRONIC COMMUNICATIONS

Applicants hereby authorized the use of electronic correspondence in this case. Applicants recognize that electronic (e.g., Internet) communications may not be secure, and hereby authorize the USPTO to communicate concerning any subject matter of this application by electronic mail and teleconference. Applicants understand that a copy of electronic communications will be made of record in the application file.

Best,
Rick Shoop

Rick Shoop, JD, PhD | Partner | ShayGlenn LLP
2755 Campus Dr. Suite 210 | San Mateo, CA 94403
☎ 650.287.2164 | 🖷 650 283.2092 | 🖷 650 212.7962
✉ rick@shayglenn.com | www.shayglenn.com

This electronic transmission and any attached document(s) are for the sole use of the individual or entity to whom it is addressed. It is confidential and may be attorney/client privileged. Any further distribution or copying of this message is strictly prohibited. If you received this message in error, please notify the sender, and destroy the attached message (and all attached documents), immediately.

1

EMAIL COVER SHEET

EMAIL: Dionne.Mayes@uspto.gov

ATTN: Examiner Mayes

Date: March 8, 2016

Number of pages (including cover sheet): 4

RE: Telephone Interview of March 10, 2016

From: Rick Shoop

Return Fax: 1-650-212-7562

Direct Dial: 1-650-283-2092 (cell)

NOTES

See attached

March 8, 2016

RE: 14/925,968 and 14/925,961

Dear Examiner Mayes:

We are looking forward to talking with you on Thursday at 2 pm ET (11 am PT). We will call you in your office then (571-272-5836). I will be joined by one of the inventors, Adam Bowen. I'm also attaching a drafi set of proposed claim amendments for discussion purposes. During the would like to discuss the cited art, in in particular the Hon (US 20061965l8) and Gonda (US 20140261474) references, as well as the attached claim language.

Thank you again for all of your help, and please don't hesitate to contact me by phone or email.

Best,

Rick Shoop
Reg. No. 45,763

POSSIBLE CLAIM AMENDMENTS
FOR DISCUSSION ONLY --- DO NOT ENTER

14/925,968 (Atty Docket No. 13211-713.303)

1. (Potential Claim Amendments for Discussion --- DO NOT ENTER) A method of delivering nicotine to a user comprising:

deploying ~~an electronic cigarette~~ a low-temperature vaporizer comprising a nicotine formulation that comprises nicotine, [[an organic acid]]lactic acid, and a biologically acceptable liquid carrier, wherein:

the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w);

the nicotine formulation comprises nicotine lactate as an acid-base reaction product of nicotine and lactic acid;

the biologically acceptable liquid carrier comprises propylene glycol and 90%-30% vegetable glycerol ; and

operation of the ~~electronic cigarette~~ low-temperature vaporizer comprises heating at least a portion of the nicotine formulation to generate an inhalable aerosol between about 100°C and 300°C;

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min and further wherein the user may modify the amount of nicotine delivered by adjusting inhalation strength.

1. (Potential Claim Amendments for Discussion --- DO NOT ENTER) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w);

b. the nicotine is protonated;

c. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation to generate an inhalable aerosol comprising protonated nicotine;

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min, and further

wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	13211-713.302	1528

66854 7590 03/16/2016

SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
03/16/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@shayglenn.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/925,961	BOWEN ET AL.	
	Examiner	Art Unit	
	DIONNE WALLS MAYES	1747	

All participants (applicant, applicant's representative, PTO personnel):

(1) *DIONNE WALLS MAYES*. (3)*ADAM BOWEN*.

(2) *RICHARD SHOOP*. (4)_____.

Date of Interview: *10 March 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *Those of Record*.

Identification of prior art discussed: *Hon (2006/0196518) and Gonda (2014/0261474)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants Representative, Mr. Shoop, and Inventor, Mr. Bowen, presented proposed amendments to the instant claims along with arguments supporting their position that the claims now clearly define over the prior art of record, sepcifically Hon and Gonda. Examiner Mayes indicated that while she could not definitively indicate that the proposed claims would be allowable, she did believe Applicant's arguments to be strong and would consider them favorably, in addition to performing an updated prior art search. Applicant indicated a quick response to the outstanding Office Action would be filed .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/DIONNE WALLS MAYES/ Examiner, Art Unit 1747	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Doc Code: PA..
Document Description: Power of Attorney

Attorney No.: 13211-713.302

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/925,961	October 28, 2015

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 66854

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

PAX LABS, INC.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	3-30-2016
Name	Adam Bowen		
Title	Chief Technology Officer and Co-Founder		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of one forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: PAX LABS, INC.

Application No./Patent No.: 14/925,961 Filed/Issue Date: October 28, 2015

Titled: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

PAX LABS, INC., a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Adam BOWEN and Chenyue XING To: PLOOM, INC.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 037990, Frame 0840, or for which a copy thereof is attached.

2. From: PLOOM, INC. To: PAX LABS, INC.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 037990, Frame 0859, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	3-36-2016 Date
Adam Bowen Printed or Typed Name	CTO and Co-Founder Title or Registration Number

[Page 2 of 2]

Supplemental Application Data Sheet

Application Information

Application number::	14/925,961
Filing Date::	October 28, 2015
Title::	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
Attorney Docket Number::	13211-713.302

- Please update the Applicant Information as follows:

Applicant Information

Assignee?::	YES
Organization name::	PAX Labs, Inc.
Street of mailing address::	660 Alabama Street, Second Floor
City of mailing address::	San Francisco
State or Province of mailing address::	CA
Postal or Zip Code of mailing address::	94110
Country of mailing address::	US

- Please update the Assignee Information as follows:

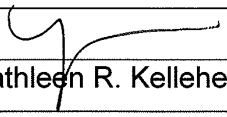
Assignee Information

Assignee name::	PAX Labs, Inc.
Street of mailing address::	660 Alabama Street, Second Floor
City of mailing address::	San Francisco
State or Province of mailing address::	CA
Postal or Zip Code of	

mailing address:: 94110

Country of mailing address:: US

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.			
Signature		**Date**	March 30, 2016
Name	Kathleen R. Kelleher	**Registration No.**	62,230

Electronic Acknowledgement Receipt

EFS ID:	25351232
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Kathleen R. Kelleher/Jennifer Capizzi
Filer Authorized By:	Kathleen R. Kelleher
Attorney Docket Number:	13211-713.302
Receipt Date:	30-MAR-2016
Filing Date:	28-OCT-2015
Time Stamp:	17:35:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_POA_Stmnt3-7 3c_SupplADS_03-30-16.pdf	286196 269a5ec1db2fc0a0cb3f24b9928319180dd 1fc31	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	1
	Assignee showing of ownership per 37 CFR 3.73	2	3
	Application Data Sheet	4	5
Warnings:			
Information:			
	Total Files Size (in bytes):	286196	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/925,961	10/28/2015	Adam BOWEN	13211-713.302

CONFIRMATION NO. 1528

66854
SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403

POA ACCEPTANCE LETTER

OC000000082128083

Date Mailed: 04/13/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/30/2016.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zmoguss/

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/925,961	10/28/2015	1747	1840	13211-713.302	23	3

CONFIRMATION NO. 1528

CORRECTED FILING RECEIPT

66854
SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403



Date Mailed: 04/13/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Adam BOWEN, San Francisco, CA;
Chenyue XING, San Francisco, CA;

Applicant(s)

PAX Labs, Inc., San Francisco, CA;

Assignment For Published Patent Application

PAX Labs, Inc., San Francisco, CA

Power of Attorney: The patent practitioners associated with Customer Number 66854

Domestic Priority data as claimed by applicant

This application is a CON of 14/271,071 05/06/2014
which claims benefit of 61/820,128 05/06/2013
and claims benefit of 61/912,507 12/05/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/09/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/925,961**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

Preliminary Class

131

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US- 374,584	12/13/1887	Cook	
	2	US- 576,653	2/9/1897	Bowlby	
	3	US- 595,070	12/7/1897	Oldenbusch	
	4	US- 720,007	2/10/1903	Dexter	
	5	US- 799,844	9/19/1905	Fuller	
	6	US- 968,160	8/23/1910	Johnson	
	7	US- 969,076	8/30/1910	Pender	
	8	US- 1,067,531	7/15/1913	MacGregor	
	9	US- 1,163,183	12/7/1915	Stoll	
	10	US- 1,299,162	4/1/1919	Fisher	
	11	US- 1,505,748	8/19/1924	Louis	
	12	US- 1,552,877	9/8/1925	Phillipps et al.	
	13	US- 1,632,335	6/14/1927	Hiering	
	14	US- 1,706,244	3/19/1929	Louis	
	15	US- 1,845,340	2/16/1932	Ritz	
	16	US- 1,972,118	9/4/1934	McDill	
	17	US- 1,998,683	4/23/1935	Montgomery	
	18	US- 2,031,363	2/18/1936	Elof	
	19	US- 2,039,559	5/5/1936	Segal	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	374	CA2641869A1	5/6/2010	Xia, Hao Ran		
	375	CN101869356A(w/EngTrans)	10/27/2010	Liu Zheqi		
	376	CN102754924A(w/EngTrans)	10/31/2012	Long		
	377	CN1122213A(w/EngAbs)	5/15/1996	Philip Morris Prod Inc		
	378	CN85106876A(w/EngCorres)	9/3/1986	M. J. Luinoziancaogose		
	379	DE19854005A1(w/EngAbs)	5/18/2000	Reemtsma Gmbh		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	20	US- 2,104,266	1/4/1938	McCormick	
	21	US- 2,231,909	2/18/1941	Hempel	
	22	US- 2,327,120	8/17/1943	McCoon	
	23	US- 2,460,427	2/1/1949	Musselman et al.	
	24	US- 2,483,304	9/27/1949	Rudolf	
	25	US- 2,502,561	4/4/1950	Ludwig	
	26	US- 2,765,949	10/9/1956	Swan	
	27	US- 2,830,597	4/15/1958	Jakob	
	28	US- 2,860,638	11/18/1958	Frank	
	29	US- 2,897,958	8/4/1959	Tarleton et al.	
	30	US- 2,935,987	5/10/1960	Ackerbauer	
	31	US- 3,146,937	9/1/1964	Joseph	
	32	US- 3,258,015	6/28/1966	Ellis et al.	
	33	US- 3,292,634	12/20/1966	Beucler	
	34	US- 3,373,915	3/19/1968	Anderson et al.	
	35	US- 3,420,360	1/7/1969	Young	
	36	US- 3,479,561	11/18/1969	Janning	
	37	US- 3,567,014	3/2/1971	Feigelman	
	38	US- 3,707,017	12/26/1972	Paquette	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	380	DE19854012A1(w/EngTrans)	5/18/2000	Reemtsma Gmbh		
	381	DE4200639A1(w/EngEquiv)	7/23/1992	Brown & Williamson Tob.		
	382	EP0532194A1	3/17/1993	Philip Morris Prod Inc		
	383	EP0535695A2	4/7/1993	Phillips Petroleum Co		
	384	EP1458388A(asWO03/055486)	9/22/2004	McNeil AB		
	385	EP2325093B1	6/20/2012	Imperial Tobacco Ltd		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	39	US- 3,792,704	2/19/1974	Parker	
	40	US- 3,861,523	1/21/1975	Fountain et al.	
	41	US- 3,941,300	3/2/1976	Troth	
	42	US- 4,020,853	5/3/1977	Nuttall	
	43	US- 4,049,005	9/20/1977	Hernandez et al.	
	44	US- 4,066,088	1/3/1978	Ensor	
	45	US- 4,207,976	6/17/1980	Herman	
	46	US- 4,215,708	8/5/1980	Bron	
	47	US- 4,219,032	8/26/1980	Tabatznik et al.	
	48	US- 4,506,683	3/26/1985	Cantrell et al.	
	49	US- 4,519,319	5/28/1985	Howlett	
	50	US- 4,595,024	6/17/1986	Greene et al.	
	579	US- 4,648,393	3/10/1987	Landis et al.	
	51	US- 4,708,151	11/24/1987	Shelar	
	52	US- 4,735,217	4/5/1988	Gerth et al.	
	53	US- 4,771,796	9/20/1988	Myer	
	54	US- 4,793,365	12/27/1988	Sensabaugh Jr. et al.	
	55	US- 4,794,323	12/27/1988	Zhou et al.	
	56	US- 4,798,310	1/17/1989	Kasai et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	386	EP2609821A1	7/3/2013	Philip Morris Prod S.A		
	390	ES2118034A1(w/EngAbs)	9/1/1998	Nugar Bobinajes Sl		
	391	GB1025630A	4/14/1966	British American Tobacco		
	392	GB1065678A	4/19/1967	Super Temp Corp		
	393	IE-S2005-0051	2/2/2005	Oglesby & Butler R&D Ltd		
	394	IE-S2005-0563	8/24/2005	Oglesby & Butler R&D Ltd		

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Sheet 4 of 20

Complete if Known	
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Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	57	US- 4,813,536	3/21/1989	Willis	
	58	US- 4,819,665	4/11/1989	Roberts et al.	
	59	US- 4,830,028	5/16/1989	Lawson et al.	
	60	US- 4,836,224	6/6/1989	Lawson et al.	
	61	US- 4,846,199	7/11/1989	Rose	
	62	US- 4,848,374	7/18/1989	Chard et al.	
	63	US- 4,848,563	7/18/1989	Robbins	
	64	US- 4,893,639	1/16/1990	White	
	65	US- 4,907,606	3/13/1990	Lilja et al.	
	66	US- 4,941,483	7/17/1990	Ridings et al.	
	67	US- 4,944,317	7/31/1990	Thal	
	68	US- 4,947,874	8/14/1990	Brooks et al.	
	69	US- 4,947,875	8/14/1990	Brooks et al.	
	70	US- 5,005,759	4/9/1991	Bouche	
	71	US- 5,020,548	6/4/1991	Farrier et al.	
	72	US- 5,027,836	7/2/1991	Shannon et al.	
	73	US- 5,050,621	9/24/1991	Creighton et al.	
	74	US- 5,060,671	10/29/1991	Counts et al.	
	75	US- 5,065,776	11/19/1991	Lawson et al.	

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	395	IE-S2005-0615	9/19/2005	Oglesby & Butler R&D Ltd		
	396	JP02-145179A(w/EngEquiv)	6/4/1990	Hercules Inc		
	397	JP03-049671(w/EngEquiv)	3/4/1991	Brown & Williamson Tob.		
	398	JP03-180166(w/EngEquiv)	8/6/1991	R J Reynolds Tobacco Co		
	399	JP09-075058(w/EngAbs)	3/25/1997	Nagai, Masaya		
	400	JP11-178563(w/EngAbs)	7/6/1999	Japan Tobacco Inc		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	76	US- 5,076,297	12/31/1991	Farrier et al.	
	77	US- 5,105,831	4/21/1992	Banerjee et al.	
	78	US- 5,105,838	4/21/1992	White et al.	
	79	US- 5,123,530	6/23/1992	Lee	
	80	US- 5,144,962	9/8/1992	Counts et al.	
	81	US- 5,183,062	2/2/1993	Clearman et al.	
	82	US- 5,224,498	7/6/1993	Deevi et al.	
	83	US- 5,249,586	10/5/1993	Morgan et al.	
	84	US- 5,261,424	11/16/1993	Sprinkel Jr.	
	85	US- 5,269,237	12/14/1993	Baker et al.	
	86	US- 5,269,327	12/14/1993	Counts et al.	
	87	US- 5,322,075	6/21/1994	Deevi et al.	
	88	US- 5,324,498	6/28/1994	Streusand et al.	
	89	US- 5,372,148	12/13/1994	McCafferty et al.	
	90	US- 5,388,574	2/14/1995	Ingebrethsen	
	91	US- 5,591,368	1/7/1997	Fleischhauer et al.	
	92	US- 5,605,226	2/25/1997	Hernlein	
	93	US- 5,641,064	6/24/1997	Goserud	
	94	US- 5,649,552	7/22/1997	Cho et al.	

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	401	JP2000-203639(w/EngAbs)	7/25/2000	S & B Foods Inc		
	402	JP2000-236865A(w/EngAbs)	9/5/2000	Seiko Kogyo KK		
	403	JP2001-165437A(wEngAbs)	6/22/2001	Tsubota Pearl Co Ltd		
	404	JP2005-034021A(w/EngCorres)	2/10/2005	Seiko Epson Corp		
	405	JP2006-504430A(w/EngEquiv)	2/9/2006	R J Reynolds Tobacco Co		
	406	JP62-278975(w/EngAbs)	12/3/1987	Watabe, Isamu		

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Sheet 6 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	95	US- 5,666,977	9/16/1997	Higgins et al.	
	96	US- 5,666,978	9/16/1997	Counts et al.	
	97	US- 5,708,258	1/13/1998	Counts et al.	
	98	US- 5,730,118	3/24/1998	Hermanson	
	99	US- 5,730,158	3/24/1998	Collins et al.	
	100	US- 5,746,587	5/5/1998	Racine et al.	
	101	US- 5,810,164	9/22/1998	Rennecamp	
	102	US- 5,819,756	10/13/1998	Mielordt	
	103	US- 5,845,649	12/8/1998	Saito et al.	
	104	US- 5,865,185	2/2/1999	Collins et al.	
	105	US- 5,881,884	3/16/1999	Podosek	
	106	US- 5,931,828	8/3/1999	Durkee	
	107	US- 5,934,289	8/10/1999	Watkins et al.	
	108	US- 5,938,018	8/17/1999	Keaveney et al.	
	109	US- 5,944,025	8/31/1999	Cook et al.	
	110	US- 5,954,979	9/21/1999	Counts et al.	
	111	US- 5,967,310	10/19/1999	Hill	
	112	US- 5,975,415	11/2/1999	Zehnal	
	113	US- 5,979,460	11/9/1999	Matsumura	

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	407	JP64-37276A(w/EngEquiv)	2/7/1989	R J Reynolds Tobacco Co		
	408	KR0193885B1(w/EngEquiv)	6/15/1999	Philip Morris Prod Inc		
	409	WO95/01137A1	1/12/1995	Voges Innovation Pty Ltd.		
	410	WO97/12639A1	4/10/1997	Slutsky, Arthur		
	411	WO00/28842A1(EngAbs)	5/25/2000	Reemtsma Gmbh		
	412	WO03/056948A1(EngAbs)	7/17/2003	Japan Tobacco Inc.		

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Sheet 7 of 20

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Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	114	US- 5,994,025	11/30/1999	Iwasa et al.	
	115	US- 5,996,589	12/7/1999	St. Charles	
	116	US- 6,053,176	4/25/2000	Adams et al.	
	118	US- 6,095,153	8/1/2000	Kessler et al.	
	119	US- 6,102,036	8/15/2000	Slutsky et al.	
	120	US- 6,125,853	10/3/2000	Susa et al.	
	121	US- 6,155,268	12/5/2000	Takeuchi	
	122	US- 6,164,287	12/26/2000	White	
	123	US- 6,234,169	5/22/2001	Bulbrook et al.	
	124	US- 6,269,966	8/7/2001	Pallo et al.	
	125	US- 6,349,728	2/26/2002	Pham	
	126	US- 6,381,739	4/30/2002	Breternitz Jr. et al.	
	127	US- 6,386,371	5/14/2002	Parsons	
	128	US- 6,431,363	8/13/2002	Hacker	
	129	US- 6,446,793	9/10/2002	Layshock	
	130	US- 6,510,982	1/28/2003	White et al.	
	131	US- 6,532,965	3/18/2003	Abhulimen et al.	
	132	US- 6,536,442	3/25/2003	St. Charles et al.	
	133	US- 6,557,708	5/6/2003	Polacco	

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	413	WO03/082031A1	10/9/2003	Steinberg, Dan A.		
	414	WO03/094900A1	11/20/2003	Alexza Molecular Delivery		
	415	WO2004/064548A1	8/5/2004	Netzer, Omry		
	417	WO2005/020726A1	3/10/2005	Lee, Seunghyun		
	418	WO2006/015070A1	2/9/2006	Brown & Williamson Tob.		
	419	WO2007/026131A1	3/8/2007	Acetate Products Ltd		

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	135	US- 6,606,998	8/19/2003	Gold	
	136	US- 6,615,840	9/9/2003	Fournier et al.	
	137	US- 6,622,867	9/23/2003	Menceles	
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	143	US- 6,799,576	10/5/2004	Farr	
	144	US- 6,803,545	10/12/2004	Blake et al.	
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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	421	WO2010/023561A1	3/4/2010	Actavis Group Ptc		
	422	WO2011/033396A2	3/24/2011	Minilogic Device Corp Ltd		
	423	WO2011/117580A2	9/29/2011	Kind Consumer Ltd		
	424	WO2012/021972A1	2/23/2012	Cogestor Inc.		
	425	WO2012/027350A2	3/1/2012	Alelov, Eli		
	426	WO2012/085207A1	6/28/2012	Philip Morris Prod S.A		

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 9 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

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	154	US- 7,644,823	1/12/2010	Gelardi et al.	
	155	US- 7,767,698	8/3/2010	Warchol et al.	
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	428	WO2013/050934A1	4/11/2013	SIS Resources Ltd.		
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	434	WO2014/093127A2	6/19/2014	Fuisz, Richard C.		
	436	WO2014/118286A2	8/7/2014	Philip Morris Prod S.A		

Examiner Signature		Date Considered	

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Sheet 10 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	175	US- 8,915,254	12/23/2014	Monsees et al.	
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	180	US- D590990	4/21/2009	Hon	
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	437	WO2014/139611A1	9/18/2014	Philip Morris Prod S.A		
	438	WO2014/140087A1	9/18/2014	Philip Morris Prod S.A		
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Sheet 11 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	197	US- 2004/0031495	2/19/2004	Steinberg	
	198	US- 2004/0099266	5/27/2004	Cross et al.	
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	448	WO2015/082652A1	6/11/2015	Philip Morris Prod S.A		
	449	WO2015/084544A1	6/11/2015	Pax Labs, Inc.		
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Sheet 12 of 20

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Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	217	US- 2006/0150991	7/13/2006	Lee	
	218	US- 2006/0191546	8/31/2006	Takano et al.	
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	235	US- 2007/0283972**	12/13/2007	Monsees et al.	

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	240	US- 2008/0216828	9/11/2008	Wensley et al.	
	241	US- 2008/0241255	10/2/2008	Rose et al.	
	242	US- 2008/0257367	10/23/2008	Paterno et al.	
	243	US- 2008/0276947	11/13/2008	Martzel	
	244	US- 2009/0004249	1/1/2009	Gonda	
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Sheet 14 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	255	US- 2009/0293895	12/3/2009	Axelsson et al.	
	256	US- 2010/0000672	1/7/2010	Fogle	
	257	US- 2010/0006092	1/14/2010	Hale et al.	
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	484	MONSEES, J.; U.S. Pat. App. # 12/115,400 entitled "Method And System For Vaporization Of A Substance", filed 5/5/2008	
	485	BOWEN et al.; U.S. Pat. App. # 14/960,259 entitled "Calibrated Dose Control", filed 12/4/2015	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Patent Application Fee Transmittal					
Application Number:	14925961				
Filing Date:	28-Oct-2015				
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF				
First Named Inventor/Applicant Name:	Adam BOWEN				
Filer:	Richard Douglas Shoop/Brian Flick				
Attorney Docket Number:	13211-713.302				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	25542971
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	20-APR-2016
Filing Date:	28-OCT-2015
Time Stamp:	12:24:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	9909
Deposit Account	504050
Authorized User	SHOOP, RICHARD D
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_4-20-2016.pdf	1952692 271cab16e3df391ad513991dc5797e616686a08f	yes	23
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	23	
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60	Fee Worksheet (SB06)	fee-info.pdf	30801 8bf450ed1bb9075ea149eca7bf5241ae68c76212	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	194113781

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on 4-20-2016.

Brian Flick
Name

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☐ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☐ **4).** Before the mailing of a first Office Action after filing a request for continued examination under § 1.114.
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☒ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☒ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☒ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☒ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s): 484 and 485

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☒ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☒ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☒ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☒ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s): 375-381, 390, 396-408, 411, 412, and 453

--AND/OR--

☒ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s): 375, 376, 378, 380, 381, 396-398, 404, 405, 407, and 408

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. Cite no(s):

☐ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement. Cite no(s):

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $180.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: 4/20/16

By: _____
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

Electronic Acknowledgement Receipt

EFS ID:	25543238
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	20-APR-2016
Filing Date:	28-OCT-2015
Time Stamp:	12:39:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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11	Non Patent Literature	Bombick_et_al-Part3ChemicalAndBiological.pdf	392773 5fa2131a60b3a540bbc3e44e70466aec6b1d8385	no	7
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12	Non Patent Literature	Bombick_et_al-Part2ChemicalAndBiological.pdf	478386 14ab76e4ed74bdec4d3e3071a6ad5df4c6421cdc	no	8
Warnings:					
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13	Non Patent Literature	Borgerding_et_al-Part1ChemicalAndBiological.pdf	1370908 fd584d757c9d92460d2fcddde06d50b5a8a34ca	no	13
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14	Non Patent Literature	ECF-AnyInterestInDeterminingNicotine.pdf	945899 f45d4738ac20cd0f4cfda305be518eb16c4556ce	no	8
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Information:					
15	Non Patent Literature	Flouris_et_al-AcuteImpactOfActive.pdf	1250365 0edc97cbd42bb7257ff660febd681ff100c9d6dc	no	12
Warnings:					
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16	Non Patent Literature	FoodAndDrugAdministration-TheCompoundingPharmacy.pdf	279626 415c15ba5cefff8c9d29ccf15e295ff317e5f752	no	3
Warnings:					
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17	Non Patent Literature	Goniewicz_et_al-NicotineLevelsInElectronic.pdf	785815 93f15bd1715bdf7fc9a2652cca5774ec1e9ff715	no	9
Warnings:					
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18	Non Patent Literature	HarvestVapour-AmericanBlendTobacco.pdf	192959 aa2d2ce86dbb83eaaeb0de6e2b01175fc928da9e	no	2
Warnings:					
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19	Non Patent Literature	INCHEM-BenzoicAcid-May2005.pdf	73915 e2fb66054fa0822703fa47b589f6ac3442871681	no	2
Warnings:					
Information:					

20	Non Patent Literature	INCHEM-LevulinicAcid-Mar2003.pdf	38840 696c8649b74fe2ad08053b5ad55ed838a8a081cb	no	1
Warnings:					
Information:					
21	Non Patent Literature	INCHEM-PyruvicAcid-Jan2003.pdf	33530 7371b9d02c93cafe786924332b0f6ee89b7a6475	no	1
Warnings:					
Information:					
22	Non Patent Literature	INCHEM-SorbicAcid-May2005.pdf	53872 57875ff939c0f0bf06c9f35643f5c751691e2d16	no	1
Warnings:					
Information:					
23	Non Patent Literature	Ingebrethsen_et_al-ElectronicCigaretteAerosol.pdf	878285 9adfa01d50eceb11167a85a8d4a1358640f3d752	no	9
Warnings:					
Information:					
24	Non Patent Literature	Kuo_et_al-AppendixDParticleSize.pdf	118553 bd6edf7f6957d7459bbfb02198723c3f321c8596	no	3
Warnings:					
Information:					
25	Non Patent Literature	McCann_et_al-DetectionOfCarcinogens.pdf	589865 2c765bee4e459ebc6a924f04ff346bd9923c85f5	no	5
Warnings:					
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26	Non Patent Literature	Mirriam-Webster_Lighter.pdf	217877 f7c501314ae49e09f1fbf39a5ba2e80245b35dc6	no	2
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Information:					
27	Non Patent Literature	Nicoli_et_al-MammalianTumorXenografts.pdf	1881086 01dec3636aa89952d4adaf56f48082fea27ec89a	no	5
Warnings:					
Information:					
28	Non Patent Literature	Perfetti_StructuralStudyNicotineSalts_1983.pdf	1995767 2c689cfbc458ce980fd57948bada4be583c1e834	no	12
Warnings:					
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29	Non Patent Literature	Seeman_et_al-TheFormOfNicotine.pdf	1326537 b591d90db200c24ab2b64f48266210d4da82fc58	no	13
Warnings:					
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30	Non Patent Literature	Torikai_et_al-EffectOfTemperature.pdf	711044 6bdde6d5e43171f769eed5db35224f150206102e	no	9
Warnings:					
Information:					
31	Non Patent Literature	Vansickel_et_al-AClinicalLaboratory.pdf	759955 df7d5b89aecd44cdc34a84ccc7a3b315de4aae75	no	9
Warnings:					
Information:					
32	Non Patent Literature	Ward-GreenLeafThreshing.pdf	1277487 b28df6ab57bb5892d621fa45fb6d06e65361d3a0	no	7
Warnings:					
Information:					
33	Non Patent Literature	Wells-GlycerinAsAConstituent.pdf	400896 55e15a965e5197a0ada0588565d1024ad9fd2e01	no	7
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Information:					
34	Non Patent Literature	YouTube-FireflyVaporizorReview.pdf	128746 19ccc5a77bdfaca405e07ddee58a341f6fb28ec7	no	1
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35	Non Patent Literature	Zhang_et_al-InVitroParticleSize.pdf	625228 e1cbf9ec3cb441b965b7a2fb3424a796b2b5c4a9	no	8
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		Total Files Size (in bytes):	39288763		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on April 20, 2016.
/Mary Buggie/ 4/20/2016
Mary Buggie Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	14/925,961	Confirmation No.	: 1528
First Named Inventor	:	Adam BOWEN		
Filing Date	:	October 28, 2015		
Art Unit	:	1747		
Examiner	:	Mayes, Dionne Walls		
Title	:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Customer No.	:	66854		

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

This reply is in response to the non-final Office Action mailed January 20, 2016 for which a response is due April 20, 2016, and is therefore timely filed. The Commissioner is hereby authorized to charge any fees to make this filing timely to Deposit Account No. 50-4050 and to credit any overpayments to Deposit Account No. 50-4050.

Amendments to the Claims are shown in the listing of claims that begins on page 2.
Interview Summary begins on page 6.
Remarks begin on page 7.

Reconsideration and allowance of the pending claims, in light of the amendments and remarks presented herein is respectfully requested.

SG Docket No.: 13211-713.302

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w);

b. the nicotine is protonated;

c. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine,

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min, and further

wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength.

2. (Original) The method of claim 1, wherein the nicotine salt formulation comprises nicotine lactate.

3. (Original) The method of claim 1, wherein the carboxylic acid comprises one or more of: pyruvic acid, salicylic acid, sorbic acid, lauric acid or benzoic acid.

4. (Original) The method of claim 1, wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

5. (Original) The method of claim 1, wherein a molar ratio of nicotine to carboxylic acid is between 1:1 and 1:3.

6. (Original) The method of claim 1, wherein the nicotine salt formulation further comprises at least one flavorant.

7. (Original) The method of claim 1, wherein the nicotine concentration is about 4.5%.

8. (Cancelled)

9. (Original) The method of claim 1, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

10. (Currently amended) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid comprising lactic acid, pyruvic acid, salicylic acid, sorbic acid, lauric acid or benzoic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w);

b. the nicotine is protonated;

c. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine,

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min, and further

wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength.

11. (Original) The method of claim 10, wherein the nicotine salt formulation comprises nicotine lactate.

12. (Original) The method of claim 10, wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

13. (Original) The method of claim 10, wherein a molar ratio of nicotine to carboxylic acid is between 1:1 and 1:3.

14. (Original) The method of claim 10, wherein the nicotine salt formulation further comprises at least one flavorant.

15. (Original) The method of claim 10, wherein the nicotine concentration is about 4.5%.

16. (Cancelled)

17. (Original) The method of claim 10, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

18. (Currently amended) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising:

deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, lactic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about .05% (w/w) to about 20% (w/w);
b. the nicotine formulation comprises protonated nicotine;
c. the nicotine salt formulation comprises nicotine lactate;

d. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising nicotine lactate,

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min, and further

wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength.

19. (Original) The method of claim 18, wherein a molar ratio of nicotine to organic acid is between 1:1 and 1:3.

20. (Original) The method of claim 18, wherein the nicotine salt formulation further comprises at least one flavorant.

21. (Original) The method of claim 18, wherein the nicotine concentration is about 4.5%.

22. (Cancelled)

23. (Original) The method of claim 18, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

INTERVIEW SUMMARY

Applicants thank the Examiner for the courtesies extended during the telephone interview of March 10, 2016. During the interview Applicants discussed the amendments made herein in light of the cited prior art, as discussed below. Agreement was reached that these amendments would overcome the cited art, although the Examiner indicated that further searching would need to be performed.

REMARKS

Claims 1-23 were pending. By this response, claims 1, 10 and 18 have been amended, claims 8, 16 and 22 have been cancelled, and no claims have been added. Support for these amendments, and for any new claims, may be found throughout the specification, but especially in paragraphs [110], [112]-[115], and [132]. Cancellation or amendment of any claim is not to be considered a dedication to the public of any subject matter.

Thus, claims 1-7, 9-15, 17-21 and 23 are currently under consideration.

DOUBLE PATENTING

Claims 1-23

Claims 1-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 9,215,895 ("Bowen '895") in view of U.S. Patent Application Publication No. 2014/0261474 to Igor Gonda ("Gonda").

By this response, all of the pending claims have been amended. Upon an indication that the claims are otherwise allowable, should the Examiner maintain the rejection of claims 1-23 for double patenting over Bowen '895 an Gonda, Applicants will likely file a terminal disclaimer, as suggested by the Examiner. In light of the amendments to the claims, a terminal disclaimer at this point would be premature.

Claims 1-23

Claims 1-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of co-pending Application No. 14/925,968.

By this response, all of the pending claims have been amended. Upon an indication that the claims are otherwise allowable, should the Examiner maintain the rejection of claims 1-23 for double patenting over co-pending U.S. Patent Application No. 14/925,968, Applicants will

likely file a terminal disclaimer, as suggested by the Examiner. In light of the amendments to the claims, a terminal disclaimer at this point would be premature.

Claims 1-7, 9-15, 17-21 and 23

Claims 1-7, 9-15, 17-21 and 23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 105-122 of co-pending Application No. 14/271,071.

By this response, claims 1-7, 9-15, 17-21 and 23 have been amended. Upon an indication that the claims are otherwise allowable, should the Examiner maintain the rejection of claims 1-7, 9-15, 17-21 and 23 for double patenting over co-pending U.S. Patent Application No. 14/271,071, Applicants will likely file a terminal disclaimer, as suggested by the Examiner. In light of the amendments to the claims, a terminal disclaimer at this point would be premature.

Claims 8, 16 and 22

Claims 8, 16 and 22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 105-122 of co-pending Application No. 14/271,071 in view of Gonda and U.S. Patent Application Publication No. 2009/0151717 to Bowen et al. ("Bowen '717").

By this response, claims 8, 16 and 22 have been cancelled, though their subject matter has been incorporated into the independent claims. Upon an indication that the claims are otherwise allowable, should the Examiner maintain the rejection of the claims for double patenting over Application no. 14/271,071, Gonda and Bowen '717, Applicants will likely file a terminal disclaimer, as suggested by the Examiner. In light of the amendments to the claims, a terminal disclaimer at this point would be premature.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-7, 10-15 and 18-21

Claims 1-7, 10-15 and 18-21 currently stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent Application Publication No. 2006/0196518 to Lik Hon ("Hon") in view of Gonda.

The Applicants respectfully disagree.

The combination of Hon and Gonda does not suggest all of the features of claims 1-7, 10-15 and 18-21. In addition, the combination of Hon with Gonda in the manner suggested by the Office Action of December 16, 2016 is improper because it relies on impermissible hindsight.

As described in the Applicants' specification and discussed during the telephone interview of March 10, 2016, the claimed invention solves a long standing problem in the field electronic cigarettes --- that is, how to convincingly mimic the experience of a traditional cigarette using a nicotine vaporizer --- by applying previously unrecognized discoveries. Specifically, the Applicants have discovered that some, but not all, nicotine salts, when properly formulated, may produce a nicotine plasma concentration (Cmax) and time course (Tmax) that most closely resembles that of traditional cigarettes.

The Applicants' instant claims are directed in particular, to method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette in which the nicotine salt used in the method is one particular class of nicotine salts, present in a solution of nicotine (e.g., freebase nicotine) and a carboxylic acid in a biologically acceptable liquid carrier and resistively heating this composition. This nicotine salt formulation, when vaporized at a temperature between about 100°C and 300°C, results in a user experience that closely mimics a traditional cigarette even within the first 3-8 minutes of inhaling. The combination of nicotine and the carboxylic acid (e.g., lactic acid) in the carrier and heating between 100°C and 300°C is based, in part, on the Applicants' discovery that only certain nicotine salts (e.g., and therefore only certain organic acids forming these salts) have a nicotine Cmax and Tmax in blood plasma of a user inhaling the vapor that is similar to that of inhaling smoke from a traditional cigarette. For example, the Applicants' disclosure (see, e.g.,

figures 1-5 and accompanying description) describes for the first time the plasma Tmax and Cmax of a variety of nicotine formulations, and teaches which formulations (and specifically which nicotine salts) do and do not have this desired effect.

Without the Applicant's teachings, one of skill in the art would not be motivated to provide a nicotine formulation and method of using it as described herein, and therefore it would not be obvious to combine references, including the Hon and Gonda references raised by the Office Action of December 16, 2015.

A. The combination of Hon and Gonda does not suggest all of the features of the claims.

The combination of Hon and Gonda does not suggest all of the features recited by the pending claims including claims 1-7, 10-15 and 18-21. Specifically, the combination of Hon and Gonda does not suggest a method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette, the method comprising: (1) *resistively heating a nicotine salt formulation including nicotine, a carboxylic acid, and a biologically acceptable liquid carrier to between about 100°C and about 300°C*; (2) wherein *inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min*, and further (3) wherein the *user may modify the amount of nicotine delivered by adjusting an inhalation strength.*

First, the combination of Hon and Gonda does not suggest a method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 minutes to about 8 min. Hon and Gonda are silent as to the Tmax profiles of any of the nicotine formulations described in either Hon or Gonda. Further, it would not be obvious to modify the combination of Hon and Gonda to include this feature. Applicants note that this limitation was originally present in dependent claims 8, 16 and 22, but has now been included in each of the independent claims. In the Office Action of December 16, 2015, the Hon and Gonda were combined with Bowen et al. (US patent App. Pub. 2009/0151717, hereafter

"Bowen '717"). The Office Action argues that this feature would be obvious, because the "collective disclosure [of Hon, Gonda and Bowen '717] indicates that the parameter of pH, aerosolized nicotine particle size and even nicotine concentration in the liquid formulation and inhalation rate are all 'results-effective variables'..." As such, only "routine experimentation" would be needed to optimize these variables to achieve the "recognized result" (see. Office Action, page 10), and therefore it would be obvious to one of ordinary skill "to have undergone routine experimentation and fabricated the nicotine formulation of Hon in the form of a liquid nicotine lactate salt solution and, in so doing, arrived at the claimed particle size and inhalation rate which result in the claimed Tmax parameters..."

Applicants disagree. In order to be obvious for optimization, a variable must be first recognized as a results-effective variable in the prior art. See, e.g., *In re Antonie,* 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In this case, neither the result (e.g., that the Tmax of nicotine in the plasma was between 3 and 8 minutes) nor the variables that Applicants have shown critically effect this result (in particular, the type of nicotine salt), are known in the prior art, and therefore it could not be obvious to optimize. Applicant point out that, as described in the Applicants' specification for the first time, the type of nicotine salt and therefore the organic acid used to form the salt in the formulation, is critical to achieving the recited Tmax. The variables cited by the Office Action in reference to Gonda (e.g., pH, particle size, nicotine concentration) are irrelevant if the wrong acid and therefore salt is generated, as described in the Applicants' specification (e.g., see paragraph [115] "... not all nicotine salts perform similarly to each other or to a traditional cigarette with respect to the rate of nicotine uptake in the blood at early time periods (0-1.5 minutes). These results are unexpected."). Without knowing what variables must be optimized (e.g., which acid and therefore nicotine salt to use), it could not be obvious to optimize the combination of Hon and Gonda, which each described a laundry list of acids and nicotine salts, including many that could not be optimized as recited in the claims.

Second, the combination of Hon and Gonda does not suggest a using a resistive heater to heat a nicotine formulation between about 100°C and about 300°C to generate an inhalable aerosol. Hon describes only "high temperature vaporization." See, e.g., Hon, abstract ("high temperature vaporization nozzle", [006] ("a high temperature vaporization nozzle"), [021] ("the nicotine solution is then vaporized into high temperature vapor"), and [025] ("vaporized and

condensed subsequently to form a puff of smoke at high temperature"). Gonda does not apply heat to form the vapor, but describes instead the use of a filter. Thus, the combination of Hon and Gonda does not suggest a low-temperature vaporizer or a method of using one.

Finally, the combination of Hon and Gonda does not suggest a method of delivering nicotine from an inhalable aerosol wherein the user may modify the amount of nicotine delivered by adjusting inhalation strength. Both Hon and Gonda are metered delivery devices in which the amount of material applied per puff is metered or determined by the device. In Hon, the dose of nicotine vapor is applied by spraying the high-temperature vapor that is actively pumped out of the electronic cigarette. See, e.g., Hon, paragraph [006] ("...an electronic pump or a valve connected with a metering cavity…"). Similarly in Gonda, the device partitions the volume inhaled into parts, so that vapor including nicotine is delivered as a bolus only during a portion of the inhalation. See, e.g., Gonda paragraph [021] and [094], which is taught as being important in controlling the rate of entry of nicotine to the blood and/or brain. Gonda, paragraph [025]. Neither Hon nor Gonda, nor the combination of the two, are configured to modify the amount of nicotine delivered by adjusting the inhalation strength.

B. Impermissible Hindsight is required to modify Hon (or Gonda) to obviate the pending claims.

It would not be obvious to modify Hon, Gonda, or the combination of Hon and Gonda to include all of the features recited in the claims, at least because this modification would require the knowledge found only in the Applicant's disclosure, which is impermissible hindsight. Specifically, the Applicants' instant claims are directed to particular nicotine salt formulations, present in a solution of nicotine (e.g., freebase nicotine) and carboxylic acid in a biologically acceptable liquid carrier. It was Applicant's discovery that only certain nicotine salt formulations (including carboxylic acids) when vaporized between about 100°C and 300°C, results in a user experience that closely mimics a traditional cigarette and produces a nicotine Tmax within the first 3-8 minutes of inhaling. Thus, combination of nicotine and lactic acid in the carrier for use in a vaporization device operating between 100°C and 300°C is based, in part, on the Applicants' unique discovery that only certain nicotine salts (e.g., and therefore only

certain organic acids forming these salts) have a nicotine Tmax in blood plasma of that is similar to that of inhaling smoke from a traditional cigarette.

Applicants respectfully submit that the combination of Hon and Gonda is improper because the Office Action relies on information gleaned solely from Applicant's specification. In this case, The Office Action is incorrect in suggesting that it would be obvious to modify Hon to include lactic acid from Gonda. Hon mentions only the use of a nicotine mixture "including an organic acid" and describes only citric acid. Gonda mentions a long list of organic acids that may be combined with nicotine, including lactic acid, but also include many others, in including many (such as citric acid) that do not produce a nicotine Tmax within the first 3-8 minutes of inhaling. It is only the Applicant's teaching of which acids and resulting nicotine salts which result in the recited features, including the unexpected result of producing a plasma nicotine Tmax of between 3 and 8 minutes. It is only the Applicants' own teaching that suggests the use of lactic acid with a solution of nicotine having a concentration from about 0.5% (w/w) to about 20% (w/w) in a carrier of propylene glycol and glycerol to produce a nicotine Tmax of 3-8 minutes.

MPEP § 2142 states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art" Any judgment on obviousness "is, in a sense, necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper" (MPEP § 2145(X)(A), quoting *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

In the present case, the Office Action argues that it would be obvious to modify Hon to include lactic acid because "the Gonda reference teaches that administering an aerosolized, liquid nicotine-containing formulation via inhalation (i.e., pulmonary administration) in order to effectuate a peak level of nicotine in the blood plasma after a very short time period – mimicking that which is typically achieve during actual cigarette smoking – is known." However, this is is not accurate. The prior art, Gonda included, did not realize that the some, but not all, nicotine salt formulations result in a peak (Tmax) blood plasma level within 3-8 minutes. This

information was known only to the Applicants. Instead, Gonda taught that peak nicotine concentration was set only by the concentration, particle size, and pH which effect the deposition profile in the user's airway. Gonda, as indeed all of the prior art, was not aware that the type of nicotine salt (and therefore the included acid) was important, and therefore could provide no guidance suggesting which acid and resulting salt from those known in the art (including those listed by Gonda) would work, or what formulation of this acid and nicotine would work. It was only the Applicant's teaching that provides this suggestion.

As discussed in detail in the Applicants' specification, some, but not all, nicotine nicotine salts and formulations of nicotine salts have the recited property of producing a nicotine Tmax within 3-8 minutes, and providing a user experience that mimic's traditional cigarettes. See, e.g., paragraphs [111], [114], and Example 6. Due to the lack of suggestion in the prior art to this effect, and the fact that this discovery is only present on the record in Applicant's specification, it follows that this suggestion has been improperly gleaned from Applicant's own specification and that the combination of Hon and Gonda (with or without Bowen'717) to teach this feature is an exercise of impermissible hindsight. Accordingly, it is respectfully submitted that the combination is improper and respectfully requested that the rejection be withdrawn.

Since the combination of Hon and Gonda does not suggest all of the features of claims 1-7, 10-15 and 18-21, and since the combination of Hon and Gonda to include even some of these features requires the use of impermissible hindsight, these claims cannot be obvious in light of these references. Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejection of claims 1-7, 10-15 and 18-21 and allowance of all of the currently pending claims.

Claims 8-9, 16-17 and 22-23

Claims 8-9, 16-17 and 22-23 currently stand rejected under 35 U.S.C. § 103 as being unpatentable over Hon in view of Gonda and Bowen '717.

The Applicants respectfully disagree.

Bowen '717 cannot cure the deficiencies discussed above. As already discussed, the combination of Hon, Gonda and Bowen '717 does not suggest the recited formulation, and

specifically does not suggest, without the use of hindsight based on the Applicant's disclosure: (1) *resistively heating a nicotine salt formulation including nicotine, a carboxylic acid, and a biologically acceptable liquid carrier to between about 100°C and about 300°C*; (2) wherein *inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min*, and further (3) wherein the *user may modify the amount of nicotine delivered by adjusting an inhalation strength.*

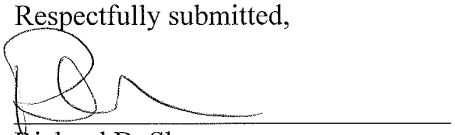
Since the combination of Hon, Gonda and Bowen '717 does not suggest all of the features recited in the claims, these claims cannot be obvious in light of these references. The Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejection of claims 8-9, 16-17 and 22-23, and allowance of the currently pending claims.

CONCLUSION

Applicants respectfully request that the Examiner expedite the prosecution of this patent application to issuance. If the Patent Office determines that an extension of time and/or other relief is required, Applicants petition for any required relief including extension of time, and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-4050**, referencing 13211-713.302. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: 4/20/16



Richard D. Shoop
Reg. No. 45,763

SHAY GLENN LLP
2755 CAMPUS DRIVE, SUITE 210
SAN MATEO, CA 94403
TELEPHONE: 650.287.2164
FACSIMILE: 650.212.7562

Electronic Acknowledgement Receipt

EFS ID:	25544371
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Mary Buggie
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	20-APR-2016
Filing Date:	28-OCT-2015
Time Stamp:	13:41:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_ResponseNFOA_4-20-2016.pdf	728852 f6ae259bdf99f6501a98ad4ced24b143969dd278	yes	16

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant summary of interview with examiner	6	6
	Applicant Arguments/Remarks Made in an Amendment	7	16
Warnings:			
Information:			
	Total Files Size (in bytes):	728852	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/20/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 23	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
/SHARONE MOORE/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	581	US- 2015/0128967	5/14/2015	Robinson et al.	
		US-			
		US-			
		US-			
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		US-			
		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	25762529
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Kathleen R. Kelleher/Brian Flick
Filer Authorized By:	Kathleen R. Kelleher
Attorney Docket Number:	13211-713.302
Receipt Date:	12-MAY-2016
Filing Date:	28-OCT-2015
Time Stamp:	15:40:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_5-12-2016.pdf	270921 cf23d5f3e08bdcd03fb347e8bc195e6469faf b49	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	270921	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on 5-12-2016.

Brian Flair
Name

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☐ **37 CFR §1.97(b)**
This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☐ **4).** Before the mailing of a first Office Action after filing a request for continued examination under § 1.114.
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☒ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☒ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☒ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☐ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☐ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☐ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☐ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s):

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.

☒ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: 5/12/16

By: _____
Kathleen R. Kelleher, Reg. No. 62,230

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	584	E-CIGARETTE FORUM; pg-gv-peg (discussion/posting); retrieved from the internet: https://e-cigarette-forum.com/forum/threads/pg-vg-peg.177551; 7 pgs.; April 8, 2011	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	25938766
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Kathleen R. Kelleher/Brian Flick
Filer Authorized By:	Kathleen R. Kelleher
Attorney Docket Number:	13211-713.302
Receipt Date:	01-JUN-2016
Filing Date:	28-OCT-2015
Time Stamp:	15:25:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_6-1-2016.pdf	253425 97495cc54acc9ba2442a38cb3e0a7af873b7f93a	yes	4

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
2	Non Patent Literature	E-Cigarette-Forum_PG-VG-PEG.pdf	503075 08272f3c84e30dbfdacb81fa2f4a81ca484066cd	no	7
Warnings:					
Information:					
		Total Files Size (in bytes):	756500		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on 6-17-2016.

Brian Tice
Name

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☐ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☐ **4).** Before the mailing of a first Office Action after filing a request for continued examination under § 1.114.
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☒ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☒ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☒ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☐ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☐ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☒ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☐ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☐ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☐ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s):

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.

☒ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

STATEMENT UNDER 37 CFR § 1.704(d)

☒ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: 6/1/10

By: _____
Kathleen R. Kelleher, Reg. No. 62,230

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	13211-713.302	1528

66854 7590 06/16/2016

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EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
06/16/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@shayglenn.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN ET AL.	
	Examiner DIONNE W. MAYES	Art Unit 1747	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 20, 2106*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-7,9-15,17-21 and 23* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7,9-15,17-21 and 23* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of

activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

3. Claims 1-7, 9-15, 17-21 and 23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of Bowen ‘895 (U.S. Patent No. 9,215,895) in view of Griffith, Jr. et al (US. Pat. App. Pub. 2013/0255702).

Regarding the instant independent claim 1, the Bowen ‘895 patent claims recite a method of delivering nicotine to a user comprising deploying an electronic cigarette comprising a nicotine formulation which comprises nicotine, a carboxylic acid and a biologically acceptable carrier (inherently creating an environment where a nicotine salt would be formed in solution), wherein inhalation of the aerosol is formed by heating the nicotine formulation and inhaling it into the user’s lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 min to about 8 min. Bowen ‘895 fails, however, to recite that the electronic cigarette operates by resistively heating the nicotine formulation to between about 100-300 degrees C, and that the specific biologically acceptable carrier is propylene glycol

and glycerol. However, the Griffith, Jr. et al reference teaches a low temperature electronic cigarette with a resistive heating element operating at the claimed temperature ranges to heat a nicotine formulation which also includes lactic acid, and a glycerin/vegetable glycerol solution (see paras.[0014],[0019],[0086]-[0088]). Hence, it would have been obvious to one having ordinary skill in the art to have included the nicotine formulation of Griffith, Jr. et al, operating at the designated temperatures, in the device of Bowen '895 as such is already known in the art.

Lastly, it follows that claimed "the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette" would naturally flow from the modified Bowen '895 invention as it meets all of the structural limitations as the instant claims.

Regarding claim 2, Griffith, Jr. et al discloses that its nicotine formulation can include lactic acid which would inherently form "nicotine lactate" in the solution. Hence, it would have been obvious to one having ordinary skill in the art to have used this acid in the modified claimed invention of Bowen '895 to form the resulting nicotine lactate salt in solution as such nicotine form is known.

Regarding claim 3, Bowen '895 discloses that its carboxylic acid can include "benzoic acid".

Regarding claim 4, it follows that "an increase of heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the modified claimed invention of Bowen '895 as it meets all of the structural limitations as the instant claims.

Regarding claim 5, Griffith, Jr. et al discloses that its aerosol precursor can include about 0.5 moles of lactic acid per 1:0 mole of nicotine.

Regarding claim 6, it would have been obvious to one having ordinary skill in the art to have added a flavorant to the modified nicotine formulation of Bowen '895 in order to enhance the organoleptic quality of the same for the benefit of the user.

Regarding claim 7, independent claim 1 of Bowen '895 recites a nicotine concentration of between 2% to 6% (w/w).

Regarding claim 9, Bowen '895 recites a nicotine formulation that generates an aerosol comprising particles sizes from about 0.1 microns to about 5 microns.

Regarding the instant independent claim 10, the Bowen '895 patent claims recite a method of delivering nicotine to a user comprising deploying an electronic cigarette comprising a nicotine formulation which comprises nicotine, a carboxylic acid and a biologically acceptable carrier (inherently creating an environment where a nicotine salt would be formed in solution), wherein inhalation of the aerosol is formed by heating the nicotine formulation and inhaling it into the user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 min to about 8 min. Bowen '895 fails, however, to recite that the electronic cigarette operates by resistively heating the nicotine formulation to between about 100-300 degrees C, and that the specific biologically acceptable carrier is propylene glycol and glycerol. However, the Griffith, Jr. et al reference teaches a low temperature electronic cigarette with a resistive heating element operating at the claimed temperature ranges to heat a nicotine formulation which also includes lactic acid, and a glycerin/vegetable glycerol solution (see paras.[0014],[0019],[0086]-[0088]). Hence, it would have been obvious to one having ordinary skill in the art to have included the

nicotine formulation of Griffith, Jr. et al, operating at the designated temperatures, in the device of Bowen '895 as such is already known in the art.

Lastly, it follows that claimed "the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the modified Bowen '895 invention as it meets all of the structural limitations as the instant claims.

Regarding claim 11, Griffith et al discloses lactic acid in its nicotine formulation - which would inherently form nicotine lactate in solution. Hence, it would have been obvious to one having ordinary skill in the art to have used this acid in the modified claimed invention of Bowen '895 to form the resulting nicotine lactate salt in solution as such nicotine form is known.

Regarding claim 12, it follows that "an increase of heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the claimed invention of Bowen '895 and Griffith, Jr. et al as it meets all of the structural limitations as the instant claims.

Regarding claim 13, Griffith, Jr. et al discloses that its aerosol precursor can include about 0.5 moles of lactic acid per 1:0 mole of nicotine.

Regarding claim 14, it would have been obvious to one having ordinary skill in the art to have added a flavorant to the modified nicotine formulation in order to enhance the organoleptic quality of the same for the benefit of the user.

Regarding claim 15, independent claim 1 of Bowen '925 recites a nicotine concentration of between 2% to 6% (w/w).

Regarding claim 17, Bowen '925 recites a nicotine formulation that generates an aerosol comprising particles sizes from about 0.1 microns to about 5 microns.

Regarding the instant independent claim 18, the Bowen '895 patent claims recite a method of delivering nicotine to a user comprising deploying an electronic cigarette comprising a nicotine formulation which comprises nicotine, a carboxylic acid and a biologically acceptable carrier (inherently creating an environment where a nicotine salt would be formed in solution), wherein inhalation of the aerosol is formed by heating the nicotine formulation and inhaling it into the user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 min to about 8 min. Bowen '895 fails, however, to recite that the electronic cigarette operates by resistively heating the nicotine formulation to between about 100-300 degrees C, and that the specific biologically acceptable carrier is propylene glycol and glycerol. However, the Griffith, Jr. et al reference teaches a low temperature electronic cigarette with a resistive heating element operating at the claimed temperature ranges to heat a nicotine formulation which also includes lactic acid, and a glycerin/vegetable glycerol solution (see paras.[0014],[0019],[0086]-[0088]). Hence, it would have been obvious to one having ordinary skill in the art to have included the nicotine formulation of Griffith, Jr. et al, operating at the designated temperatures, in the device of Bowen '895 as such is already known in the art.

Lastly, it follows that claimed "the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional

burned tobacco" would naturally flow from the modified Bowen '895 invention as it meets all of the structural limitations as the instant claims.

Regarding claim 19, Griffith, Jr. et al discloses that its nicotine formulation can include about 0.5 moles of lactic acid per one mole of nicotine.

Regarding claim 20, it would have been obvious to one having ordinary skill in the art to have added a flavorant to the modified nicotine formulation in order to enhance the organoleptic quality of the same for the benefit of the user.

Regarding claim 21, independent claim 1 of Bowen '925 recites a nicotine concentration of between 2% to 6% (w/w).

Regarding claim 23, independent claim 1, Bowen '925 recites a nicotine formulation that generates an aerosol comprising particles sizes from about 0.1 microns to about 5 microns.

4. Claims 1-2, 4-7, 9-15, 17-21 and 23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 6-10 and 12 of copending Application No. 14/925,968.

Although the claims at issue are not identical, they are not patentably distinct from each other because claims 1-4, 6-10 and 12 of co-pending Application No. 14/925,968 generally encompass the instant claims 1-2, 4-7, 9-15, 17-21 and 23.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

5. Claim 3 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 6-10 and 12 of copending Application No. 14/925,968 in view of Gonda (US. Pat. App. Pub. 2014/0261474).

Claims 1-4, 6-10 and 12 of co-pending Application No. 14/925,968 fails to disclose any acid other than “lactic acid” in its nicotine/propylene glycol/vegetable glycol formulation (serving to provide “nicotine lactate” in solution) and, as such, does not disclose “benzoic acid”; however, the Gonda reference shows that “nicotine benzoate” (formed form “benzoic acid”) is a known formulation to add in solution in an electronic cigarette-type device (see para. [0041],[0078]). Therefore, it would have been obvious to one having ordinary skill in the art to have provided a nicotine formulation that includes benzoic acid as such formulation is known.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

9. Claims 1-7, 9-15, 17-21 and 23 are rejected under 35 U.S.C. 103 as being unpatentable over Griffith, Jr. et al (US. Pat. App. Pub. 2013/0255702) - as evidenced by www.e-cigarette-forum.com's PG-VG-PEG Discussion Posting (hereinafter referred to as "the PG-VG-PEG Internet Posting") - in view of Gonda (US. Pat. No. 2014/0261474) and Bowen '717 et al (US. Pat. App. Pub. 2009/0151717).

Regarding independent claim 1, and claim 2, Griffith, Jr. et al discloses an aerosol delivery article, and its use, for yielding materials in an inhalable form. Specifically, Griffith, Jr. et al discloses the oral delivery of inhalable materials comprising a resistive heating element formed of a substrate wherein an electrically conductive material is integrally formed with a carrier material that can be coated or impregnated with materials that can be aerosolized for inhalation, i.e. aerosol precursor material. The

aerosol precursor can comprise any materials that are volatilizable at the disclosed working temperatures (ranging from 50-300 degrees C), an example of which is 75-80% by weight glycerol (Note: “The PG-VG-PEG Internet Posting” serves as evidence that the terms “glycerol” and “vegetable glycerol/glycerin” are synonymous), 1-10% by weight propylene glycol, 2-3% by weight nicotine and 0.1-0.5% by weight of one or more flavors. Griffith, Jr. et al also discloses that an organic acid (such as lactic acid) can be added as the “flavor” in said aerosol precursor - inherently creating an environment where a nicotine lactate salt would be formed from the nicotine and lactic acid (see paras.[0009], [0014],[0019],[0086]-[0088])(corresponding to the claimed “A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette, the method comprising: deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid, and a biologically acceptable liquid carrier, wherein: a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w); b. the nicotine is protonated; c. the biologically acceptable liquid carrier comprises propylene glycol and vegetable glycerol; and c. resistively heating at least a portion of the nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine”; and the “wherein the nicotine salt formulation comprises nicotine lactate” recitation of claim 2).

Griffith, Jr. et al is silent as to the peak amount and timeframe of nicotine delivery into a user's bloodstream upon inhalation of its aerosolized materials. However, the Gonda reference teaches that administering an aerosolized, liquid nicotine-containing

formulation via inhalation (i.e., pulmonary administration) in order to effectuate a peak level of nicotine in the blood plasma after a very short period of time - mimicking that which is typically achieved during actual cigarette smoking - can be accomplished. Specifically, Gonda teaches that a nicotine formulation in solution, can be prepared so as to be inhaled to emulate the effects of smoking wherein the aerosol is delivered in a relatively small volume at the beginning of a puff and a low puff rate to enhance deposition and rapid absorption in the lungs which results in rapid delivery of nicotine. (see paras. [0043], [0052], [0064], [0067], [0078], [0091]-[0092]). Also, Gonda states that adjustments in pH, in combination with changing the particle size of the aerosol, can be carried out to create a different experience for the user. For example, by decreasing the pH of the nicotine formulation, the likelihood of airway irritation and cough is reduced, and/or by decreasing the particle size of the inhaled material, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels (see para. [0007],[0033]-[0036], [0052], [0064], [0086]). Further, Gonda states that, during inhalation of aerosolized nicotine formulations, a satisfactory dose of nicotine is achieved in a small number of breaths, spaced by short periods, preferably less than 2 minutes (see para. [0017]). (Note: To this point, the Bowen ‘717 et al reference further discloses that, typically, when smokers “puff” on cigarettes they may take a puff every 30 seconds (i.e., in an intense smoking regime. Bowen ‘717 et al then shows that aerosol devices used to inhale a nicotine substance can also be “smoked” in such manner (see para. [0107])). The afore-mentioned *collective* disclosure indicates

that the parameters of pH, aerosolized nicotine particle size, nicotine concentration in the liquid formulation and even inhalation rate, are all “result-effective variables”. Once a particular parameter is recognized as a result-effective variable, i.e., a variable which achieves a recognized result, the determination of the optimum or workable ranges of said variable can be characterized by routine experimentation. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) MPEP 2144.05. Hence, it would have been obvious to one having ordinary skill in the art at the time of the invention to have undergone routine experimentation and fabricated the nicotine formulation of Griffith, Jr. et al in the form of a liquid nicotine solution and, in so doing, arrived at the claimed inhalation rate which result in the claimed T_{max} parameters, after determining that these values provided, as close as possible, the same nicotine blood levels achieved by smoking a conventional cigarette. Hence, it would have been obvious to one having ordinary skill in the art to have operated the device of Griffith, Jr. et al such that it delivers nicotine to a user per the teachings of Gonda in order to achieve the benefits described above (corresponding to the claimed “wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 minutes to about 8 min and further wherein the user may modify the amount of nicotine delivered by adjusting inhalation strength”).

Lastly, it follows that claimed “the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette” would naturally flow from the modified Griffith, Jr. et al invention as it meets all of the structural limitations as the instant claims.

Regarding claim 3, Griffith, Jr. et al fails to disclose any acid other than "lactic acid" in its nicotine/propylene glycol/vegetable glycol formulation (serving to provide "nicotine lactate" in solution) and, as such, does not disclose "benzoic acid"; however, the Gonda reference shows that "nicotine benzoate" (formed form "benzoic acid") is a known formulation to add in solution in an electronic cigarette-type device (see para. [0041],[0078]). Therefore, it would have been obvious to one having ordinary skill in the art to have provided a nicotine formulation that includes benzoic acid (corresponding to the claimed "wherein the carboxylic acid comprises one or more of: pyruvic acid, salicylic acid, sorbic acid, lauric acid or benzoic acid").

Regarding claim 4, it follows that "an increase of heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the modified Griffith, Jr. et al invention as it meets all of the structural limitations as the instant claims.

Regarding claim 5, Griffith, Jr. et al discloses that its aerosol precursor can include about 0.5 moles of lactic acid per one mole of nicotine (see para. [0086])(corresponding to the claimed "wherein a molar ratio of nicotine to organic acid is between about 1:1 and 1:3")

Regarding claim 6, Griffith, Jr. et al discloses that its aerosol precursor material can be combined with more than one flavorant (see para. [0049])(corresponding to the claimed "wherein the nicotine formulation further comprises at least one flavorant").

Regarding claim 7, Griffith, Jr. et al discloses that a specific non-limiting example of the nicotine content in its aerosol precursor may be about 2-3% by weight (see para. [00888]). However, it would have been obvious to one having ordinary skill in the art to

have adjusted this amount to be a bit higher - corresponding to the claimed amount - in order to satisfy the particular organoleptic preferences of the user (corresponding to the claimed “wherein the nicotine concentration is about 4.5%”).

Regarding claim 9, based on the disclosure of Gonda, as discussed above, that by decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels, it would have been obvious to one having ordinary skill in the art to have optimized the particle size of its aerosol to fall between 0.1 - 5 microns (corresponding to the claimed “wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns”).

Regarding independent claim 10, and claim 11, Griffith, Jr. et al discloses an aerosol delivery article, and its use, for yielding materials in an inhalable form. Specifically, Griffith, Jr. et al discloses the oral delivery of inhalable materials comprising a resistive heating element formed of a substrate wherein an electrically conductive material is integrally formed with a carrier material that can be coated or impregnated with materials that can be aerosolized for inhalation, i.e. aerosol precursor material. The aerosol precursor can comprise any materials that are volatilizable at the disclosed working temperatures (ranging from 50-300 degrees C), an example of which is 75-80% by weight glycerol (Note: “The PG-VG-PEG Internet Posting” serves as evidence that the terms “glycerol” and “vegetable glycerol/glycerin” are synonymous), 1-10% by weight propylene glycol, 2-3% by weight nicotine and 0.1-0.5% by weight of one or more flavors. Griffith, Jr. et al also discloses that an organic acid (such as lactic acid)

can be added as the “flavor” in said aerosol precursor - inherently creating an environment where a nicotine lactate salt would be formed from the nicotine and lactic acid (see paras.[0009], [0014],[0019],[0086]-[0088])(corresponding to the claimed “A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising: deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, a carboxylic acid comprising lactic acid…and a biologically acceptable liquid carrier, wherein: a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w); b. the nicotine is protonated; c. the biologically acceptable liquid carrier comprises propylene glycol and vegetable glycerol; and c. resistively heating at least a portion of the nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine”; and the “wherein the nicotine salt formulation comprises nicotine lactate” recitation of claim 11).

Griffith, Jr. et al is silent as to the peak amount and timeframe of nicotine delivery into a user's bloodstream upon inhalation of its aerosolized materials. However, the Gonda reference teaches that administering an aerosolized, liquid nicotine-containing formulation via inhalation (i.e., pulmonary administration) in order to effectuate a peak level of nicotine in the blood plasma after a very short period of time - mimicking that which is typically achieved during actual cigarette smoking - can be accomplished. Specifically, Gonda teaches that a nicotine formulation in solution, can be prepared so as to be inhaled to emulate the effects of smoking wherein the aerosol is delivered in a

relatively small volume at the beginning of a puff and a low puff rate to enhance deposition and rapid absorption in the lungs which results in rapid delivery of nicotine. (see paras. [0043], [0052], [0064], [0067], [0078], [0091]-[0092]). Also, Gonda states that adjustments in pH, in combination with changing the particle size of the aerosol, can be carried out to create a different experience for the user. For example, by decreasing the pH of the nicotine formulation, the likelihood of airway irritation and cough is reduced, and/or by decreasing the particle size of the inhaled material, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels (see para. [0007],[0033]-[0036], [0052], [0064], [0086]). Further, Gonda states that, during inhalation of aerosolized nicotine formulations, a satisfactory dose of nicotine is achieved in a small number of breaths, spaced by short periods, preferably less than 2 minutes (see para. [0017]). (Note: To this point, the Bowen '717 et al reference further discloses that, typically, when smokers "puff" on cigarettes they may take a puff every 30 seconds (i.e., in an intense smoking regime. Bowen '717 et al then shows that aerosol devices used to inhale a nicotine substance can also be "smoked" in such manner (see para. [0107])). The afore-mentioned *collective* disclosure indicates that the parameters of pH, aerosolized nicotine particle size, nicotine concentration in the liquid formulation and even inhalation rate, are all "result-effective variables". Once a particular parameter is recognized as a result-effective variable, i.e., a variable which achieves a recognized result, the determination of the optimum or workable ranges of said variable can be characterized by routine experimentation. See *In re Boesch*, 617

F.2d 272, 205 USPQ 215 (CCPA 1980) MPEP 2144.05. Hence, it would have been obvious to one having ordinary skill in the art at the time of the invention to have undergone routine experimentation and fabricated the nicotine formulation of Griffith, Jr. et al in the form of a liquid nicotine solution and, in so doing, arrived at the claimed inhalation rate which result in the claimed T_{max} parameters, after determining that these values provided, as close as possible, the same nicotine blood levels achieved by smoking a conventional cigarette. Hence, it would have been obvious to one having ordinary skill in the art to have operated the device of Griffith, Jr. et al such that it delivers nicotine to a user per the teachings of Gonda in order to achieve the benefits described above (corresponding to the claimed "wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 minutes to about 8 min and further wherein the user may modify the amount of nicotine delivered by adjusting inhalation strength").

Lastly, it follows that claimed "the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the modified Griffith, Jr. et al invention as it meets all of the structural limitations as the instant claims.

Regarding claim 12, it follows that "an increase of heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the modified Griffith, Jr. et al invention as it meets all of the structural limitations as the instant claims.

Regarding claim 13, Griffith, Jr. et al discloses that its aerosol precursor can include about 0.5 moles of lactic acid per one mole of nicotine (see para. [0086])(corresponding to the claimed “wherein a molar ratio of nicotine to organic acid is between about 1:1 and 1:3”)

Regarding claim 14, Griffith, Jr. et al discloses that its aerosol precursor material can be combined with more than one flavorant (see para. [0049])(corresponding to the claimed “wherein the nicotine formulation further comprises at least one flavorant”).

Regarding claim 15, Griffith, Jr. et al discloses that a specific non-limiting example of the nicotine content in its aerosol precursor may be about 2-3% by weight (see para. [00888]). However, it would have been obvious to one having ordinary skill in the art to have adjusted this amount to be a bit higher - corresponding to the claimed amount - in order to satisfy the particular organoleptic preferences of the user (corresponding to the claimed “wherein the nicotine concentration is about 4.5%”).

Regarding claim 17, based on the disclosure of Gonda, as discussed above, that by decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels, it would have been obvious to one having ordinary skill in the art to have optimized the particle size of its aerosol to fall between 0.1 - 5 microns (Corresponding to the claimed “wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns”).

Regarding independent claim 18, Griffith, Jr. et al discloses an aerosol delivery article, and its use, for yielding materials in an inhalable form. Specifically, Griffith, Jr. et

al discloses the oral delivery of inhalable materials comprising a resistive heating element formed of a substrate wherein an electrically conductive material is integrally formed with a carrier material that can be coated or impregnated with materials that can be aerosolized for inhalation, i.e. aerosol precursor material. The aerosol precursor can comprise any materials that are volatilizable at the disclosed working temperatures (ranging from 50-300 degrees C), an example of which is 75-80% by weight glycerol (Note: “The PG-VG-PEG Internet Posting” serves as evidence that the terms “glycerol” and “vegetable glycerol/glycerin” are synonymous), 1-10% by weight propylene glycol, 2-3% by weight nicotine and 0.1-0.5% by weight of one or more flavors. Griffith, Jr. et al also discloses that an organic acid (such as lactic acid) can be added as the “flavor” in said aerosol precursor - inherently creating an environment where a nicotine lactate salt would be formed from the nicotine and lactic acid (see paras.[0009], [0014],[0019],[0086]-[0088])(corresponding to the claimed “A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising: deploying an electronic cigarette comprising a nicotine salt formulation that includes nicotine, lactic acid, and a biologically acceptable liquid carrier, wherein: a. the nicotine concentration is from about 0.5% (w/w) to about 20% (w/w); b. the nicotine formulation comprises protonated nicotine; c. the nicotine salt formulation comprises nicotine lactate; d. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and resistively heating at least a portion of the

nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine").

Griffith, Jr. et al is silent as to the peak amount and timeframe of nicotine delivery into a user's bloodstream upon inhalation of its aerosolized materials. However, the Gonda reference teaches that administering an aerosolized, liquid nicotine-containing formulation via inhalation (i.e., pulmonary administration) in order to effectuate a peak level of nicotine in the blood plasma after a very short period of time - mimicking that which is typically achieved during actual cigarette smoking - can be accomplished. Specifically, Gonda teaches that a nicotine formulation in solution, can be prepared so as to be inhaled to emulate the effects of smoking wherein the aerosol is delivered in a relatively small volume at the beginning of a puff and a low puff rate to enhance deposition and rapid absorption in the lungs which results in rapid delivery of nicotine. (see paras. [0043], [0052], [0064], [0067], [0078], [0091]-[0092]). Also, Gonda states that adjustments in pH, in combination with changing the particle size of the aerosol, can be carried out to create a different experience for the user. For example, by decreasing the pH of the nicotine formulation, the likelihood of airway irritation and cough is reduced, and/or by decreasing the particle size of the inhaled material, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels (see para. [0007],[0033]-[0036], [0052], [0064], [0086]). Further, Gonda states that, during inhalation of aerosolized nicotine formulations, a satisfactory dose of nicotine is achieved in a small number of breaths, spaced by short periods, preferably

less than 2 minutes (see para. [0017]). (Note: To this point, the Bowen '717 et al reference further discloses that, typically, when smokers "puff" on cigarettes they may take a puff every 30 seconds (i.e., in an intense smoking regime. Bowen '717 et al then shows that aerosol devices used to inhale a nicotine substance can also be "smoked" in such manner (see para. [0107])). The afore-mentioned *collective* disclosure indicates that the parameters of pH, aerosolized nicotine particle size, nicotine concentration in the liquid formulation and even inhalation rate, are all "result-effective variables". Once a particular parameter is recognized as a result-effective variable, i.e., a variable which achieves a recognized result, the determination of the optimum or workable ranges of said variable can be characterized by routine experimentation. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) MPEP 2144.05. Hence, it would have been obvious to one having ordinary skill in the art at the time of the invention to have undergone routine experimentation and fabricated the nicotine formulation of Griffith, Jr. et al in the form of a liquid nicotine solution and, in so doing, arrived at the claimed inhalation rate which result in the claimed T_{max} parameters, after determining that these values provided, as close as possible, the same nicotine blood levels achieved by smoking a conventional cigarette. Hence, it would have been obvious to one having ordinary skill in the art to have operated the device of Griffith, Jr. et al such that it delivers nicotine to a user per the teachings of Gonda in order to achieve the benefits described above (corresponding to the claimed "wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma T_{max} from about 3 minutes to about 8 min and

further wherein the user may modify the amount of nicotine delivered by adjusting inhalation strength").

Lastly, it follows that claimed "the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco" would naturally flow from the modified Griffith, Jr. et al invention as it meets all of the structural limitations as the instant claims.

Regarding claim 19, Griffith, Jr. et al discloses that its aerosol precursor can include about 0.5 moles of lactic acid per one mole of nicotine (see para. [0086])(corresponding to the claimed "wherein a molar ratio of nicotine to organic acid is between about 1:1 and 1:3")

Regarding claim 20, Griffith, Jr. et al discloses that its aerosol precursor material can be combined with more than one flavorant (see para. [0049])(corresponding to the claimed "wherein the nicotine formulation further comprises at least one flavorant").

Regarding claim 21, Griffith, Jr. et al discloses that a specific non-limiting example of the nicotine content in its aerosol precursor may be about 2-3% by weight (see para. [00888]). However, it would have been obvious to one having ordinary skill in the art to have adjusted this amount to be a bit higher - corresponding to the claimed amount - in order to satisfy the particular organoleptic preferences of the user (corresponding to the claimed "wherein the nicotine concentration is about 4.5%").

Regarding claim 23, based on the disclosure of Gonda, as discussed above, that by decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an

increase in peak nicotine plasma levels, it would have been obvious to one having ordinary skill in the art to have optimized the particle size of its aerosol to fall between 0.1 - 5 microns (Corresponding to the claimed "wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns").

Response to Arguments

10. Applicant's arguments with respect to the claims have been considered but are moot in view of the new grounds for rejection, presented above, involving a new combination of prior art references, which were necessitated because of the amendments made to the claims, filed on April 20, 2016.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE WALLS MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Tuesday and Thursday, 8:00A - 6:30P EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael H. Wilson can be reached on 571-270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE WALLS MAYES/
Examiner, Art Unit 1747

/MICHAEL H WILSON/
Supervisory Patent Examiner, Art Unit 1747

PTO/SB/08A (04-07)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	581	US- 2015/0128967	5/14/2015	Robinson et al.	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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Sheet 1 of 20

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First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	1	US- 374,584	12/13/1887	Cook	
	2	US- 576,653	2/9/1897	Bowlby	
	3	US- 595,070	12/7/1897	Oldenbusch	
	4	US- 720,007	2/10/1903	Dexter	
	5	US- 799,844	9/19/1905	Fuller	
	6	US- 968,160	8/23/1910	Johnson	
	7	US- 969,076	8/30/1910	Pender	
	8	US- 1,067,531	7/15/1913	MacGregor	
	9	US- 1,163,183	12/7/1915	Stoll	
	10	US- 1,299,162	4/1/1919	Fisher	
	11	US- 1,505,748	8/19/1924	Louis	
	12	US- 1,552,877	9/8/1925	Phillipps et al.	
	13	US- 1,632,335	6/14/1927	Hiering	
	14	US- 1,706,244	3/19/1929	Louis	
	15	US- 1,845,340	2/16/1932	Ritz	
	16	US- 1,972,118	9/4/1934	McDill	
	17	US- 1,998,683	4/23/1935	Montgomery	
	18	US- 2,031,363	2/18/1936	Elof	
	19	US- 2,039,559	5/5/1936	Segal	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	374	CA2641869A1	5/6/2010	Xia, Hao Ran		
	375	CN101869356A(w/EngTrans)	10/27/2010	Liu Zheqi		
	376	CN102754924A(w/EngTrans)	10/31/2012	Long		
	377	CN1122213A(w/EngAbs)	5/15/1996	Philip Morris Prod Inc		
	378	CN85106876A(w/EngCorres)	9/3/1986	M. J. Luinoziancaogose		
	379	DE19854005A1(w/EngAbs)	5/18/2000	Reemtsma Gmbh		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	20	US- 2,104,266	1/4/1938	McCormick	
	21	US- 2,231,909	2/18/1941	Hempel	
	22	US- 2,327,120	8/17/1943	McCoon	
	23	US- 2,460,427	2/1/1949	Musselman et al.	
	24	US- 2,483,304	9/27/1949	Rudolf	
	25	US- 2,502,561	4/4/1950	Ludwig	
	26	US- 2,765,949	10/9/1956	Swan	
	27	US- 2,830,597	4/15/1958	Jakob	
	28	US- 2,860,638	11/18/1958	Frank	
	29	US- 2,897,958	8/4/1959	Tarleton et al.	
	30	US- 2,935,987	5/10/1960	Ackerbauer	
	31	US- 3,146,937	9/1/1964	Joseph	
	32	US- 3,258,015	6/28/1966	Ellis et al.	
	33	US- 3,292,634	12/20/1966	Beucler	
	34	US- 3,373,915	3/19/1968	Anderson et al.	
	35	US- 3,420,360	1/7/1969	Young	
	36	US- 3,479,561	11/18/1969	Janning	
	37	US- 3,567,014	3/2/1971	Feigelman	
	38	US- 3,707,017	12/26/1972	Paquette	

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	380	DE19854012A1(w/EngTrans)	5/18/2000	Reemtsma Gmbh		
	381	DE4200639A1(w/EngEquiv)	7/23/1992	Brown & Williamson Tob.		
	382	EP0532194A1	3/17/1993	Philip Morris Prod Inc		
	383	EP0535695A2	4/7/1993	Phillips Petroleum Co		
	384	EP1458388A(asWO03/055486)	9/22/2004	McNeil AB		
	385	EP2325093B1	6/20/2012	Imperial Tobacco Ltd		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	39	US- 3,792,704	2/19/1974	Parker	
	40	US- 3,861,523	1/21/1975	Fountain et al.	
	41	US- 3,941,300	3/2/1976	Troth	
	42	US- 4,020,853	5/3/1977	Nuttall	
	43	US- 4,049,005	9/20/1977	Hernandez et al.	
	44	US- 4,066,088	1/3/1978	Ensor	
	45	US- 4,207,976	6/17/1980	Herman	
	46	US- 4,215,708	8/5/1980	Bron	
	47	US- 4,219,032	8/26/1980	Tabatznik et al.	
	48	US- 4,506,683	3/26/1985	Cantrell et al.	
	49	US- 4,519,319	5/28/1985	Howlett	
	50	US- 4,595,024	6/17/1986	Greene et al.	
	579	US- 4,648,393	3/10/1987	Landis et al.	
	51	US- 4,708,151	11/24/1987	Shelar	
	52	US- 4,735,217	4/5/1988	Gerth et al.	
	53	US- 4,771,796	9/20/1988	Myer	
	54	US- 4,793,365	12/27/1988	Sensabaugh Jr. et al.	
	55	US- 4,794,323	12/27/1988	Zhou et al.	
	56	US- 4,798,310	1/17/1989	Kasai et al.	

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	386	EP2609821A1	7/3/2013	Philip Morris Prod S.A		
	390	ES2118034A1(w/EngAbs)	9/1/1998	*Nugar Bobinajes Sl*		
	391	GB1025630A	4/14/1966	British American Tobacco		
	392	GB1065678A	4/19/1967	Super Temp Corp		
	393	IE-S2005-0051	2/2/2005	Oglesby & Butler R&D Ltd		
	394	IE-S2005-0563	8/24/2005	Oglesby & Butler R&D Ltd		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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Sheet 4 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	57	US- 4,813,536	3/21/1989	Willis	
	58	US- 4,819,665	4/11/1989	Roberts et al.	
	59	US- 4,830,028	5/16/1989	Lawson et al.	
	60	US- 4,836,224	6/6/1989	Lawson et al.	
	61	US- 4,846,199	7/11/1989	Rose	
	62	US- 4,848,374	7/18/1989	Chard et al.	
	63	US- 4,848,563	7/18/1989	Robbins	
	64	US- 4,893,639	1/16/1990	White	
	65	US- 4,907,606	3/13/1990	Lilja et al.	
	66	US- 4,941,483	7/17/1990	Ridings et al.	
	67	US- 4,944,317	7/31/1990	Thal	
	68	US- 4,947,874	8/14/1990	Brooks et al.	
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	70	US- 5,005,759	4/9/1991	Bouche	
	71	US- 5,020,548	6/4/1991	Farrier et al.	
	72	US- 5,027,836	7/2/1991	Shannon et al.	
	73	US- 5,050,621	9/24/1991	Creighton et al.	
	74	US- 5,060,671	10/29/1991	Counts et al.	
	75	US- 5,065,776	11/19/1991	Lawson et al.	

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	395	IE-S2005-0615	9/19/2005	Oglesby & Butler R&D Ltd		
	396	JP02-145179A(w/EngEquiv)	6/4/1990	Hercules Inc		
	397	JP03-049671(w/EngEquiv)	3/4/1991	Brown & Williamson Tob.		
	398	JP03-180166(w/EngEquiv)	8/6/1991	R J Reynolds Tobacco Co		
	399	JP09-075058(w/EngAbs)	3/25/1997	Nagai, Masaya		
	400	JP11-178563(w/EngAbs)	7/6/1999	Japan Tobacco Inc		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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Sheet 5 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	76	US- 5,076,297	12/31/1991	Farrier et al.	
	77	US- 5,105,831	4/21/1992	Banerjee et al.	
	78	US- 5,105,838	4/21/1992	White et al.	
	79	US- 5,123,530	6/23/1992	Lee	
	80	US- 5,144,962	9/8/1992	Counts et al.	
	81	US- 5,183,062	2/2/1993	Clearman et al.	
	82	US- 5,224,498	7/6/1993	Deevi et al.	
	83	US- 5,249,586	10/5/1993	Morgan et al.	
	84	US- 5,261,424	11/16/1993	Sprinkel Jr.	
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	87	US- 5,322,075	6/21/1994	Deevi et al.	
	88	US- 5,324,498	6/28/1994	Streusand et al.	
	89	US- 5,372,148	12/13/1994	McCafferty et al.	
	90	US- 5,388,574	2/14/1995	Ingebrethsen	
	91	US- 5,591,368	1/7/1997	Fleischhauer et al.	
	92	US- 5,605,226	2/25/1997	Hernlein	
	93	US- 5,641,064	6/24/1997	Goserud	
	94	US- 5,649,552	7/22/1997	Cho et al.	

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	401	JP2000-203639(w/EngAbs)	7/25/2000	S & B Foods Inc		
	402	JP2000-236865A(w/EngAbs)	9/5/2000	Seiko Kogyo KK		
	403	JP2001-165437A(wEngAbs)	6/22/2001	Tsubota Pearl Co Ltd		
	404	JP2005-034021A(w/EngCorres)	2/10/2005	Seiko Epson Corp		
	405	JP2006-504430A(w/EngEquiv)	2/9/2006	R J Reynolds Tobacco Co		
	406	JP62-278975(w/EngAbs)	12/3/1987	Watabe, Isamu		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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Sheet 6 of 20

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Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	95	US- 5,666,977	9/16/1997	Higgins et al.	
	96	US- 5,666,978	9/16/1997	Counts et al.	
	97	US- 5,708,258	1/13/1998	Counts et al.	
	98	US- 5,730,118	3/24/1998	Hermanson	
	99	US- 5,730,158	3/24/1998	Collins et al.	
	100	US- 5,746,587	5/5/1998	Racine et al.	
	101	US- 5,810,164	9/22/1998	Rennecamp	
	102	US- 5,819,756	10/13/1998	Mielordt	
	103	US- 5,845,649	12/8/1998	Saito et al.	
	104	US- 5,865,185	2/2/1999	Collins et al.	
	105	US- 5,881,884	3/16/1999	Podosek	
	106	US- 5,931,828	8/3/1999	Durkee	
	107	US- 5,934,289	8/10/1999	Watkins et al.	
	108	US- 5,938,018	8/17/1999	Keaveney et al.	
	109	US- 5,944,025	8/31/1999	Cook et al.	
	110	US- 5,954,979	9/21/1999	Counts et al.	
	111	US- 5,967,310	10/19/1999	Hill	
	112	US- 5,975,415	11/2/1999	Zehnal	
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	407	JP64-37276A(w/EngEquiv)	2/7/1989	R J Reynolds Tobacco Co		
	408	KR0193885B1(w/EngEquiv)	6/15/1999	Philip Morris Prod Inc		
	409	WO95/01137A1	1/12/1995	Voges Innovation Pty Ltd.		
	410	WO97/12639A1	4/10/1997	Slutsky, Arthur		
	411	WO00/28842A1(EngAbs)	5/25/2000	Reemtsma Gmbh		
	412	WO03/056948A1(EngAbs)	7/17/2003	Japan Tobacco Inc.		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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Attorney Docket Number	13211-713.302

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	114	US- 5,994,025	11/30/1999	Iwasa et al.	
	115	US- 5,996,589	12/7/1999	St. Charles	
	116	US- 6,053,176	4/25/2000	Adams et al.	
	118	US- 6,095,153	8/1/2000	Kessler et al.	
	119	US- 6,102,036	8/15/2000	Slutsky et al.	
	120	US- 6,125,853	10/3/2000	Susa et al.	
	121	US- 6,155,268	12/5/2000	Takeuchi	
	122	US- 6,164,287	12/26/2000	White	
	123	US- 6,234,169	5/22/2001	Bulbrook et al.	
	124	US- 6,269,966	8/7/2001	Pallo et al.	
	125	US- 6,349,728	2/26/2002	Pham	
	126	US- 6,381,739	4/30/2002	Breternitz Jr. et al.	
	127	US- 6,386,371	5/14/2002	Parsons	
	128	US- 6,431,363	8/13/2002	Hacker	
	129	US- 6,446,793	9/10/2002	Layshock	
	130	US- 6,510,982	1/28/2003	White et al.	
	131	US- 6,532,965	3/18/2003	Abhulimen et al.	
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Examiner Initials*	Cite No.[1]	Foreign Patent Document / Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	413	WO03/082031A1	10/9/2003	Steinberg, Dan A.		
	414	WO03/094900A1	11/20/2003	Alexza Molecular Delivery		
	415	WO2004/064548A1	8/5/2004	Netzer, Omry		
	417	WO2005/020726A1	3/10/2005	Lee, Seunghyun		
	418	WO2006/015070A1	2/9/2006	Brown & Williamson Tob.		
	419	WO2007/026131A1	3/8/2007	Acetate Products Ltd		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 8 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	134	US- 6,598,607	7/29/2003	Adiga et al.	
	135	US- 6,606,998	8/19/2003	Gold	
	136	US- 6,615,840	9/9/2003	Fournier et al.	
	137	US- 6,622,867	9/23/2003	Menceles	
	138	US- 6,655,379	12/2/2003	Clark et al.	
	139	US- 6,672,762	1/6/2004	Faircloth et al.	
	140	US- 6,688,313	2/10/2004	Wrenn et al.	
	141	US- 6,726,006	4/27/2004	Funderburk et al.	
	142	US- 6,772,756	8/10/2004	Shayan	
	143	US- 6,799,576	10/5/2004	Farr	
	144	US- 6,803,545	10/12/2004	Blake et al.	
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	421	WO2010/023561A1	3/4/2010	Actavis Group Ptc		
	422	WO2011/033396A2	3/24/2011	Minilogic Device Corp Ltd		
	423	WO2011/117580A2	9/29/2011	Kind Consumer Ltd		
	424	WO2012/021972A1	2/23/2012	Cogestor Inc.		
	425	WO2012/027350A2	3/1/2012	Alelov, Eli		
	426	WO2012/085207A1	6/28/2012	Philip Morris Prod S.A		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 9 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

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	155	US- 7,767,698	8/3/2010	Warchol et al.	
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	158	US- 7,886,507	2/15/2011	McGuinness Jr.	
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	160	US- 8,141,701	3/27/2012	Hodges	
	161	US- 8,156,944	4/17/2012	Hon	
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	428	WO2013/050934A1	4/11/2013	SIS Resources Ltd.		
	429	WO2013/083635A1	6/13/2013	Philip Morris Prod S.A		
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	434	WO2014/093127A2	6/19/2014	Fuisz, Richard C.		
	436	WO2014/118286A2	8/7/2014	Philip Morris Prod S.A		

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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Sheet 10 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	184	US- D644375	8/30/2011	Zhou	
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	192	US- 2001/0052480	12/20/2001	Kawaguchi et al.	
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	437	WO2014/139611A1	9/18/2014	Philip Morris Prod S.A		
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Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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Sheet 11 of 20

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Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	198	US- 2004/0099266	5/27/2004	Cross et al.	
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	207	US- 2005/0034723	2/17/2005	Bennett et al.	
	208	US- 2005/0061759	3/24/2005	Doucette	
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	213	US- 2005/0268911	12/8/2005	Cross et al.	
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	448	WO2015/082652A1	6/11/2015	Philip Morris Prod S.A		
	449	WO2015/084544A1	6/11/2015	Pax Labs, Inc.		
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	453	WO2015/124878A1(EngAbs)	8/27/2015	Smokio		
	454	WO2015/148547A1	10/1/2015	Nicotech LLC		
	455	WO2015/175979A1	11/19/2015	Pax Labs, Inc.		

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	223	US- 2007/0006889	1/11/2007	Kobal et al.	
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Sheet 13 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	236	US- 2008/0023003	1/31/2008	Rosenthal	
	237	US- 2008/0029095	2/7/2008	Esser	
	238	US- 2008/0092912	4/24/2008	Robinson et al.	
	239	US- 2008/0149118	6/26/2008	Oglesby et al.	
	240	US- 2008/0216828	9/11/2008	Wensley et al.	
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Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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	256	US- 2010/0000672	1/7/2010	Fogle	
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Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	295	US- 2012/0260927	10/18/2012	Liu	
	296	US- 2012/0267383	10/25/2012	Van Rooyen	
	298	US- 2012/0325227	12/27/2012	Robinson et al.	
	299	US- 2013/0042865**	2/21/2013	Monsees et al.	
	300	US- 2013/0068239	3/21/2013	Youn	
	301	US- 2013/0140200	6/6/2013	Scatterday	
	302	US- 2013/0152922	6/20/2013	Benassayag et al.	
	303	US- 2013/0186416	7/25/2013	Gao et al.	
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	334	US- 2014/0345631**	11/27/2014	Bowen et al.	
	335	US- 2014/0345635	11/27/2014	Rabinowitz et al.	
	337	US- 2014/0366898**	12/18/2014	Monsees et al.	
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	342	US- 2015/0027468	1/29/2015	Li et al.	
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	474	FLOURIS et al.; Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function; Inhal. Toxicol.; 25(2); pp. 91-101; Feb 2013	
	471	FOOD & DRUG ADMINISTRATION; Warning letter to The Compounding Pharmacy; retrieved 10/10/2014 from http://www.fda.gov/ICECI/EnfocementActions/WarningLetters/2002/ucm144843.htm; 3 pgs.; April 9, 2002	
	475	GONIEWICZ et al.; Nicotine levels in electronic cigarettes; Nicotine Tobacco Research; 15(1); pp. 158-166; Jan 2013	
	468	HARVEST VAPOR; American Blend Tobacco (product info.); retrieved from the internet (http://harvestvapor.com/); 2 pgs.; print/retrieval date: 10/10/2014	
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Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	469	INCHEM; Levulinic Acid; JECFA Evaluation Summary; retrieved 10/10/2014 from http://www.inchem.org/documents/jecfa/feceval/jec_1266.htm; 1 pg.; March 10, 2003	
	472	INCHEM; Pyruvic Acid; JECFA Evaluation Summary; retrieved 10/10/2014 from http://www.inchem.org/documents/jecfa/feceval/jec_2072.htm; 1 pg.; January 29, 2003	
	473	INCHEM; Sorbic Acid; JECFA Evaluation Summary; retrieved 10/10/2014 from http://www.inchem.org/documents/jecfa/feceval/jec_2181.htm; 1 pg.; May 29, 2005	
	464	INGEBRETHSEN et al.; Electronic cigarette aerosol particle size distribution measurements; Inhalation Toxicology; 24(14); pp. 976-984; December 2012	
	467	KUO et al.; Appendix D: Particle size-U.S. sieve size and tyler screen mesh equivalents; Applications of Turbulent and Multiphase Combustion; John Wiley & Sons, Inc.; pp. 541-543; May 1, 2012	
	465	McCANN et al.; Detection of carcinogens as mutagens in the salmonella/microsome test: Assay of 300 chemicals: Discussion; Proc. Nat. Acad. Sci.; 73(3); pp. 950-954; March 1976	
	460	MIRRIAM-WEBSTER Online Dictionary; Lighter; retrieved 1/4/2013 from the internet: (http://www.merriam-webster.com/dictionary/lighter?show=0&t=1357320593); 2 pgs.; print date: 1/4/2013	
	479	NICOLI et al.; Mammalian tumor xenografts induce neovascularization in Zebrafish embryos; Cancer Research; 67(7); pp. 2927-2931; April 1, 2007	
	483	PERFETTI; Structural study of nicotine salts; Beitrage zur Tabakforschung International; Contributions to Tobacco Research; 12(2); pp. 43-54; June 1983	
	476	SEEMAN et al.; The form of nicotine in tobacco. Thermal transfer of nicotine and nicotine acid salts to nicotine in the gas phase; J Aric Food Chem.; 47(12); pp. 5133-5145; Dec 1999	

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden. should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/08b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 20 of 20

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	462	TORIKAI et al.; Effects of temperature, atmosphere and pH on the generation of smoke compounds duriung tobacco pyrolysis; Food and Chemical Toxicology; 42(9); pp. 1409-1417; September 2004	
	477	VANSICKEL et al.; A clinical laboratory model for evaluating the acute effects of electronic cigarettes: Nicotine delivery profile and cardiovascular and subjective effects; Cancer Epidemiology Biomarkers Prevention; 19(8); pp. 1945-1953; (online) July 20, 2010	
	463	WARD; Green leaf threshing and redrying tobacco; Section 10B; in TOBACCO Production, Chemistry and Technology; Davis and Nielsen (Eds.); Blackwell Science Ltd.; pp. 330-333; July 15, 1999	
	466	WELLS; Glycerin as a constituent of cosmetics and toilet preparations; Journal of the Society of Cosmetic Chemists; 9(1); pp. 19-25; January 1958	
	480	YouTube; Firefly Vaporizor Review w/ Usage Tips by The Vape Critic; retrieved from the internet (http://www.youtube.com/watch?v=1J38N0AV7wI); 1 pg.; published 12/10/2013; download/print date: 2/18/2015	
	478	ZHANG et al.; In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns; Nicotine Tobacco Research; 15(2); pp. 501-508; Feb 2013	
	484	MONSEES, J.; U.S. Pat. App. # 12/115,400 entitled "Method And System For Vaporization Of A Substance", filed 5/5/2008	
	485	BOWEN et al.; U.S. Pat. App. # 14/960,259 entitled "Calibrated Dose Control", filed 12/4/2015	

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	584	E-CIGARETTE FORUM; pg-gv-peg (discussion/posting); retrieved from the internet: https://e-cigarette-forum.com/forum/threads/pg-vg-peg.177551; 7 pgs.; April 8, 2011	

Examiner Signature	/Dionne Walls Mayes/	Date Considered	06/07/2016

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2015/01/20 15:51

			EPO; JPO; DERWENT; IBM_TDB			
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48
S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR;	ADJ	ON	2015/01/20 16:59

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08

S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31
S49	1	("20060196518").PN.	US-PGPUB;	OR	OFF	2015/05/14

			USPAT			19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09

S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	(14/925961).APP.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30
S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S66	723	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2015/09/17 14:46
S67	246	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB	ADJ	ON	2015/09/17 14:47
S68	196	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB	ADJ	ON	2015/09/17 14:49
S72	833	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2016/01/11 23:26

6/11/2016 11:53:02 AM
C:\Users\dmayes\Documents\EAST\Workspaces\14925961.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14925961	BOWEN ET AL.
	Examiner	Art Unit
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U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	590	US- 2013/0199528	8/8/2013	Goodman et al.	
	591	US- 2014/0144429	5/29/2014	Wensley et al.	
	592	US- 2015/0272220	10/1/2015	Spinka et al.	
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	585	JP10-501999A(w/EngEquiv)	2/24/1998	Boehringer Ingelheim		

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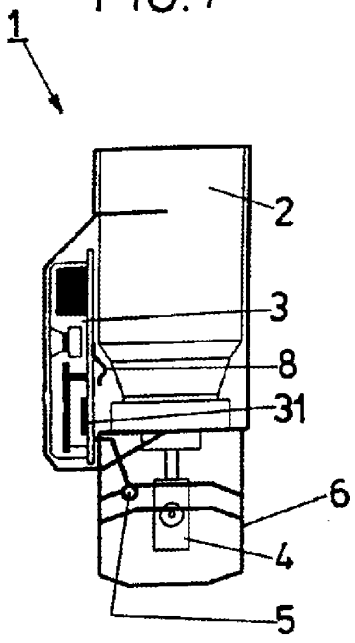
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(54)【発明の名称】　エーロゾル吸入器

(57)【要約】
温度センサ（５）が霧化ノズル（４）の領域に配置されているエーロゾル吸入器であって、前記センサが、作動要素が作動させられて吸入動作が引き起こされた後、引き続いて起こる推進剤の膨張による冷却を検知する。作動および冷却は、電子モジュール（３）によって、電子的に検出される。技術および治療用のデータを信号から得ることができ、このデータが、ディスプレユニット及び／或いはアラーム装置を介してユーザに伝えられ、所望の方法による治療に影響を及ぼす。

FIG.1



【特許請求の範囲】
１．推進剤と該推進剤内に散らされた吸入すべき医薬品とからなるエーロゾルのため供給容器を備え、かつ、作動要素を備え、さらに、内部に空気通路を有するマウスピースを備えた吸入器であって、作動要素の作動に引き続いて、エーロゾルが供給容器からノズルを通ってマウスピースの空気通路に入り、医薬品の能動的な吸入が可能になる吸入器において、電子モジュール（３）を備え、該電子モジュール（３）が、モニタ機能用電子ユニット（３１）を有し、該電子ユニット（３１）が、ノズル（４）の流れ領域に配置された少なくとも一つの温度センサ（５）からの信号と作動を認識する装置（８）からの信号とを供給され、前記吸入器が、更に、前記評価電子ユニット（３１）による評価結果の出力用表示装置（３４）を備えていることを特徴とする吸入器。
２．評価電子ユニット（３１）が、霧化が起こらないときに、警告信号を発生させることを特徴とする請求の範囲第１項に記載の吸入器。
３．前記温度センサ（５）が、吸入開始時に、通過する空気を検知し、対応する信号を評価電子ユニット（３）に送り、評価電子ユニット（３）が、患者のための調和した助けとして、視覚的および／あるいは聴覚的に表わされる信号を生成することを特徴とする請求の範囲第１項または第２項のいずれか１項に記載の吸入器。
４．もう一つの温度センサをエーロゾルの流れ通路に配置し、前記もう一つのセンサが、電子評価ユニット（３１）に送られ第１の温度センサ（５）からの信号とリンクされる基準信号を生成し、このリンクの結果により、エーロゾルの放出用が導かれることを特徴とする請求の範囲第１項ないし第３項のいずれか１項に記載の吸入器。
５．霧化に先立って、温度センサ（５）の周囲温度が検出され、デジタル化され、評価電子ユニット（３１）に記憶され、霧化の間、温度変化の時間特性が検出され、温度プロファイルとしてデジタル化され、そして、エーロゾルの霧化量が、後者の信号と前に記憶されていた周囲温度との間の差の適当な極限値間における積分値から、導かれることを特徴とする請求の範囲第１項ないし第３項

のいずれか１項に記載の吸入器。
６．評価電子ユニット（３１）が、メモリと、これを通してデータを外部から前記メモリに入力し且つ前記メモリからデータを読みだすシリアルインターフェイスとを備えた、マイクロコントローラあるいは特注回路で構成されていることを特徴とする請求の範囲第１項ないし第５項のいずれか１項に記載の吸入器。
７．前記供給容器（２）が吸入器に着脱自在に挿入可能であり、その外側に光学的にコード化された表面を備え、前記電子モジュール（３）が前記コードが示す情報を解読できることを特徴とする請求の範囲第１項ないし第６項のいずれか１項に記載の吸入器。
８．交換可能な供給容器（２）が電子メモリを有し、該メモリに記憶されたデータを前記評価電子ユニット（３１）が読出し可能であり、かつ、前記評価電子ユニット（３１）がデータを前記メモリに入力可能であることを特徴とする請求の範囲第７項に記載の吸入器。
９．前記交換可能な供給容器（２）が、ＥＥＰＲＯＭモジュールを備えていることを特徴とする請求の範囲第８項に記載の吸入器。
10. 前記温度センサ（５）からの信号が、該信号が作動要素を作動させて自動的に吸入行程を引き起こすような方法で、評価されることを特徴とする請求の範囲第１項ないし第９項に記載の吸入器。
11. 請求の範囲第１項ないし第１０項に記載の吸入器の機能をモニタする電子モジュールであって、前記吸入器に着脱自在に取付け可能であり、それ自身から離れるように突出し、少なくとも一つの温度センサ（５）を備え、吸入器（１）に連結された後、前記センサ（５）が、前記ノズル（４）の開口に近接して当接することを特徴とする電子モジュール。
12. 第２の温度センサが配置されていることを特徴とする請求の範囲第１１項に記載の電子モジュール。
13. 温度センサ（５）が、ＮＴＣ抵抗器、サーミスタあるいは表面熱電対であることを特徴とする請求の範囲第１１項または第１２項のいずれか１項に記載の電子モジュール。

【発明の詳細な説明】

エーロゾル吸入器

本発明は、吸入すべき医療物質（医薬品）用のエーロゾル吸入器に関し、かつ、そのような吸入器に関連に使用される電子モジュールに関するものである。

エーロゾル吸入器は、吸入すべき所定量の医薬品を患者が能動的に吸い込むのを助ける器具である。このような器具の典型的な使用例は、急性の喘息発作である。対応する作動要素を作動させると、推進剤と、この推進剤の中に存在しかつその中に分散している医薬品とからなるエーロゾルが、供給容器から、ノズルを通って、マウスピース内のエアーチャネルにはいり、そこで、エーロゾルは患者によって能動的に吸入される。エーロゾルの放出および霧化を、電子的あるいは機械的に引起こすことができる。

以前は、作動要素の作動時に、実際に霧化が起こったか否かを検出することは不可能であった。例えば、ノズルの障害によって、霧化が起こらないことがある。エーロゾル供給容器が空のときにも、当然、霧化は起こらない。患者は、急性発作を抑えるのに必要な薬を吸入しているので、実際は、事実でないか或いは一部分だけが事実かもしれないが、このことにより余病が併発されることがある。所定量の一部のみの供給が、しばしば、行われると、患者は、更に吸引することによって医薬品の効果を増そうとする。これは危険な状況をもたらし、その結果、過量摂取が起こることがある。さらに、患者を治療している医師が、所定の時間間隔内に投与した投与回数の概略が分からなくなってしまい、確実な治療の妨げとなってしまう。

このような背景の下、本発明の目的は、少なくとも、作動要素を作動させた時、エーロゾルの霧化を確実に認識かつこれを評価即ち活用することができるタイプのエーロゾル吸入器をさらに改良することである。更に、本発明によれば、投与された回数、供給容器内に残っている投与量およびその表示のような処置パラメータに関連する一連の評価、更に、例えば、医師の処方箋に対応しているかどうかを決定するためのエーロゾルのチェックが可能である。更に、そのような吸入

器と関連して使用するために電子モジュールが設けられることになり、この電子モジュールは、本発明の目的の電子部品として満足のいくものであるが、原則として、公知の全てのエーロゾル吸入器に対しても、エーロゾル吸入器の付属品として使用できる。

この目的は、請求の範囲第１項の特徴部分の特徴を備えた吸入器、および、請求の範囲第８項による電子モジュールによって達成される。

有利な改良例が、関連する従属項に記載されている。

本発明によれば、電子モジュールを備えた吸入器が提供され、該電子モジュールは、ノズルの流れ領域に配置された少なくとも１つの温度センサからの信号および作動要素の作動を認識する装置からの信号を供給される、機能モニタ用評価電子ユニットを備えており、さらに、評価電子ユニットによって生成された評価結果の出力を表示する装置を備えている。

本発明の要点は、エーロゾルの霧化が起こるノズル内に温度センサを直接配置したことである。このことにより、推進剤の冷却が温度センサを冷却し、明確に規定された電気信号を生成できるので、作動の認識および霧化時におこる推進剤の冷却に基づいたエーロゾル霧化の能動的検出が可能となる。その結果、ノズル内に障害があったり、あるいは、エーロゾル供給容器が空であるといった機能不全を、確実に検出できる。

特別かつ簡単な実施態様では、評価電子ユニットが、霧化が起こらないときに警告信号を生成し、そして、供給容器内にまだ収容されている吸入投与量の数を示す信号を生成する。これらの信号は、適当な表示装置によって、警告の場合には、聴覚信号で、患者に伝えられる。霧化をモニタしているので、供給容器が空であったり、あるいは又、特に、ノズルに障害があったときに起こるように、霧化が起こらず医薬品を吸入しなかった場合には、使用者に警告を与えることができる。

さらに有利な態様では、温度センサが、吸入の開始時に、通過する空気流を検出し、これに対応する信号を発生させ、この信号が評価電子ユニットに送られ、評価電子ユニットが、吸入行程において患者を助けるために、光学的かつ／あるいは音声的に示される信号を生成する。

この更なる態様の背景は以下の通りである：

エーロゾルの正確な吸入は、理想的には、以下のようにおこなわれる、即ち、患者は、息を吐いてから、器具を口に当て、吸入を開始した後に、作動要素を押して、霧化を引き起こす。しかしながら、多くの使用者にとって、呼吸と霧化を引起こすことを調整することは難しい。しかしながら、呼吸と霧化引き起こしとのタイミングが合わないと、薬剤による治療の効果が減少し、治療効果が損なわれる。吸入開始の直後に、患者が、視覚的表示あるいは聴覚的表示によって霧化が差し迫っていることを知らされるという点で、上述した更なる実施態様は有効である。このようにして、処置の臨床的効果が、著しく向上する。

別の実施態様では、もう一つの温度センサがエーロゾル流路の外側に配置されており、このもう一つの温度センサが基準信号を生成し、この基準信号が、同様に、評価電子ユニットに送られ、第１の温度センサからの信号と関連付けられ、この結果により、放出されたエーロゾルの量が、導き出される。この関連付けは、例えば、ノズルに直接配置された第１の温度センサと周囲温度との間の相違の時間特性を形成することができる差動増幅器で行うことができる。次いで、下流側の評価電子ユニットが、この差の信号を受け、適当な極限値間での、この信号のインテグレイション（integration）すなわち積分値が、評価電子ユニットのメモリ内に記憶された関連する事項の助けで、エーロゾルの霧化量になる値を与える。量的な検出を行っているので、患者は、吸入を行う度に、更に吸入する必要があるか否かについての正確な情報を得ることができる。評価電子ユニットのプログラム内に設定されている特定量に届かない場合には、吸入された活性成分が少なすぎることを患者に知らせる警告信号を出してもよい。このようなモニタが可能であるということにより、吸入器を使用する際の信頼性が高くなり、治療がより効率的になる。

他の実施態様として、霧化に先立って、ノズルの領域に配置された温度センサの周囲温度を検出し、デジタル化し、評価電子ユニットに記憶できるので、エーロゾルの放出量を決定できる。吸入中に、エーロゾルを霧化させたとき、センサの温度変化の時間特性を、所謂温度プロファイルとして検出する。この温度プロファイルをデジタル化し、この値から、予め記憶しておいた周囲温度を除する。

適当な極限値間での差の積分値が、評価電子ユニットのメモリ内に記憶された関連事項の助けで、エーロゾルの霧化量となる値を与える。センサ信号増幅器の出力電圧とセンサの温度との関係を、評価電子ユニットのメモリ内に記憶させることができる。センサおよび信号増幅器の非線形性、および、周囲温度の変化によって生じる作動点のシフトの影響を、評価電子ユニット内で、計算により排除することができる。

他の実施態様において、もし評価電子ユニットがマイクロコントローラを備えているなら、データ記憶用のメモリおよび外部コンピュータとの接続用シリアルインターフェイスを備えているのが好ましい。

この実施態様により、担当の医師は、関連する分野では全く初めて、医師が決めた吸入投与回数を患者が本当に吸入した否かおよび吸入器が行われている時間間隔をモニタできることになる。多量のデータをメモリにインプットすること、及び、これに関連する機能が可能である。このように、例えば、医師は、次の吸入を行うまでの時間間隔を予め定めることができ、モジュール内の実時間（リアルタイム）のクロックにより、視覚的および／あるいは聴覚的な信号を出して、患者に次の吸入を思い出させることができる。

この機能をモニタすることができ、そして、この機能の実行あるいは不実行を同様にメモリに記憶させることができる。担当の医師が次に来たとき、このデータは、シリアルインタフェイスを介して読み出され、医師によって解読される。メモリへの入出力のために、電子モジュールは、上述したように、シリアルインターフェイスを介して、外部コンピュータに接続されるように構成されることになる。

本発明による吸入器の評価電子ユニットの存在により、別の機能を簡略化でき、もう一つの実施態様では、エーロゾル供給容器が、吸入器に着脱自在に挿入可能な、交換可能部品であるようにすることができる。着脱自在な供給容器の外側に、例えば、写真のフイルムカートリッジの所謂ＤＸ－コード(DX-coding)と関連して知られているような光学コード化面を設けることができる。評価電子ユニットが、このコードが示す情報を解読できるように設計されている。この情報は、例えば、エーロゾル内の医薬品の活性成分のタイプおよびその期限を表してい

る。

このデータは読み出されて、評価電子ユニットのマイクロコントローラ内で、例えば、医師が入力した活性成分のタイプに関連する情報と比較される。両者が異なっている場合には、警告信号を発するように構成することができる。上述した電子モジュール内のリアルタイムのクロックを、エーロゾル内の医薬品の期限データをチェックして、期限が過ぎたときに、警告を発するために使用できる。

この実施態様では、交換可能な供給容器は、それ自身が、電子メモリを備えており、このメモリも記憶されたデータを評価電子ユニットが読み出し、かつ、評価電子ユニットがデータをこのメモリに入力できるように構成してもよい。このメモリは、上述した光学コードに加えて設けても、或いは、メモリだけを設けても良い。吸入器と外部コンピュータの間のデータ交換のために、例えば、医師の前提で、電源無しでデータを保持する差し込み型ＥＥＰＲＯＭモジュールを使用してもよい。外部コンピュータは、これを介して、ＥＥＰＲＯＭモジュールにデータを入出力できるアダプタを有している。この記憶モジュールを介して、一方では、活性成分に関する情報及び処方された処置を器具に伝達することができ、他方では、器具それ自身に、実際の治療データを入力できる。

さらに別の実施態様として、センサ接触子を吸入器のマウスピースに配置してもよい。センサ接触子からの信号は、評価電子ユニットに送られる。このようにして、正しい霧化の場合に、患者が実際に医薬品を受入れているか否かをチェックできる。これにより、正しいが、空間に開放されて患者に到達しなかった霧化は、確実に、投与された投与量としてメモリに記録されない。

エーロゾルが霧化するノズルに直接設けられた温度センサを吸入器が備え、作動要素の作動を認識する装置を備え、かつ、センサからの信号および作動認識装置からの信号を評価する評価電子ユニットを備えていることによって、上述したモニタが可能であることを強調しておく。実際の吸入器とは独立して取扱われ、且つ、それ自身が商品である、導入部で言及した電子モジュールは、本発明によって、吸入器に着脱自在に固定できる別体のハウジングを備え、また、それ自身から離れて突出する少なくとも一つのセンサを備え、このセンサは、吸入器のノ

ズル開口のすぐ近傍に配置されている。

電子モジュールは、吸入器とは別に、製造し且つ試験することができる。電子モジュールは、製造の最終段階において初めて、吸入器に取付けられ、完成品が最終試験を受ける。しかしながら、電子モジュールを、具体的な吸入器とは別に独立して流通させ、付属品として提供することもできる。

さらに別の実施態様では、上述した第２の温度基準センサを電子モジュールに配置し、これによって、ユニット全体が、第２のセンサが、例えば吸入器に、つけられていないときと同じように、大変コンパクトになり、これは勿論、電気的接続を行うことを必要とすることになる。

温度センサは、ＮＴＣ抵抗器、サーミスタあるいは表面熱電対のような電気的特定が、温度変化によって、評価できるように変化する素子であるのが好ましい。

評価電子ユニットは、必要な全ての電子的機能が集積されたマイクロコントローラあるいは特注回路で構成するのがよい。この設計により、評価電子ユニットおよび電源要求のために必要なスペースの減少が可能になり、これは、バッテリの容積および電子モジュールの全体の容積が、関連して減少するからである。ＳＭＤ技術で回路板を構成するのがよい。スペースおよびコスト上の理由から、チップオンボード(chip-on-board:COB)あるいはテープ自動化接着(tape-automated bonding)技術によって、ＩＣハウジングを使用することなく、マイクロコントローラを組立てるのがよい。表示ユニットおよび必要なバッテリは、クリップ留め式プラスチックフレームを介して、回路板に固定され、導電性ラバーおよび接触バネを介して回路板に電気的に接続されている。

吸入器のキャップの脱着によって、追加の操作行程なしで、器具スイッチのオンオフを行うことができる。もしキャップが比較的長時間開いたままであるなら、電子ユニットは、所定時間経過後、自動的に所謂”スリープモード”に切り替わり、吸入を引き金にして、自動的に、”起こされる”。キャップが適所にあるときには、霧化が起こらないように機械的にロックされている。

表示ユニットは３ディジット７セグメントディスプレと、日常の投与量警告、

電源警告および故障表示のための符号とを備えたＬＣＤからなるのが好ましい。

新たに充填したエーロゾル供給容器を吸入器に挿入すると、電子モジュールのリセット用押しボタンを作動させ、残りの投与量を、満タンの容器に対応する値に設定する必要がある。この機能は、他の実施態様にしたがって、すなわち、作動要素が作動させられた時および容器が交換された時のいずれの場合にも、信号を評価電子ユニットに送る作動認識装置によって、実施することもできる。

本発明による吸入器の吸入工程が、電子的に起こるように構成してもよい。この目的のために必要な電子ユニットを、同様に、電子モジュール内に収容することができる。マウスピースに設けられたセンサ接触子によって、誤作動を防止する。

上述したように、ノズルの流れ領域に設けられた温度センサによって吸入過程を電子的に認識することを、呼吸によって完全に自動的に霧化を、起こすために利用することができる。この目的で、対応する信号を評価した後で、評価電子ユニットが、吸入器の作動要素に信号を送り、霧化を起こす。したがって、器具によって、調和が完全に確保される。患者は、ただ、器具を口にあて、息を吸うだけでよい。

センサからの信号の評価は、以下のようにして行われる、即ち、増幅後に、アナログ信号を直ちにデジタル化し、上述した比較器の機能は、評価電子ユニットのプログラムによって保証され、対応する切り換えレベルおよび遅延時間が、プログラムによって決定される。

以下、本発明による吸入器の実施態様を詳細に説明する。添付図面において、

図１は、横方向に取付けられた電子モジュールを備えた吸入器の正面図であり、

図２は、図１の吸入器の側面図であり、

図３は、図１および図２の器具の平面図であり、

図４は、評価電子ユニットの主要回路の線図であり、

図５ａないし図５ｃは、出力信号の時間特性を示し、

図６は、ノズル開口に設けられたセンサと基準センサの間の差信号の積分値の

時間特性を示し、

図７は、吸入行程を電子的に評価する場合の出力信号の時間特性を示している。

図１ないし図３は、本発明による吸入器の図面であり、これらの図面は、主要な線だけが示され、正確な断面には対応していない。

本発明による吸入器１は、エーロゾル用の供給容器２を備えている。本実施態様においては、供給容器２は、ハウジングに着脱自在に取付けられており、ハウジングは、空気通路７が内部に延びているマウスピース６を備えている。（図示しない）作動要素によって、投与量のエーロゾルが、供給容器２からノズル４に入り、そこで霧化される。患者は、空気通路７を通して、この霧化エーロゾルを吸う。

この行程中、供給容器２は動き、作動認識装置８を介して信号を発生させ、この信号が、評価電子ユニット３１に送られる。第１の温度センサ５が、ノズル４の開口に直接配置されている。ノズル４からの霧化が起こると、推進剤が膨張して、ノズル開口の領域の温度が下がる。この温度低下を温度センサ５が検知し、温度センサ５が、対応する信号を生成して、この信号が、同様に、評価電子ユニット３１に送られる。

上述したように、本実施態様では、電子モジュール３が、吸入器１にクリップ留めされ、独立して取り扱えるようになっている。これはコンパクトな構成のものであり、全ての必要な構成要素を収容しており、これらのうち、バッテリ３６および光学表示ユニット３４が、図１ないし図３に、参照番号を付されて示されている。この光学表示ユニットは、３ディジット７セグメントのＬＣＤ表示装置であるのが好ましい。評価電子ユニット３０の主要回路の線図を、図４に示す。

本実施態様においては、主要構成部品は、評価電子ユニット３１であり、このユニットに、作動認識装置８からの信号および温度センサ５からの信号が送られる。評価電子ユニットは、接点３３が閉じられるまで作動されず、これは、器具のキャップが外されたときに起こる。

この回路は、バッテリ３６から電気を供給される。本実施態様では、上述した

表示ユニット３４によって表示が行われる。

更に、リセットスイッチ３５が設けられており、これは新たに充填された供給容器が吸入器１に挿入されたとき作動させられ、残り投与量が、評価電子ユニット３１のメモリ内で、満タンの供給容器に対応する値に設定される。

信号処理を、図５および図６を参照して、簡単に説明する。

図５ａは、温度センサ５の電圧U_1の曲線を示す。ノズル４内で推進剤が膨張し、これに伴って、センサ５が冷却されると、電圧U_1は初めは、急激に上昇し、霧化行程の後、熱的な時定数に従って、その初期値まで落ちる。

図５ｂは、入口に図５ａの電圧U_1が与えられる周波数分離増幅器の出力電圧U_2の時間特性を示す。霧化の場合に、U_2が明確なパルスを有していることがわかる。

電圧U_2は、例えば、休止状態で一定の正の出力電圧を有し正しい霧化が行われてるときには、負のパルスを出し、そのとき、一時的に、電圧を確実に０にする比較器に供給される。電圧U_3は、評価電子ユニットに対するデジタル入力信号である。増幅器および比較器を、評価電子ユニットの一部分として形成してもよい。

図６は、周囲温度にさらされている基準センサとしてもう一つの温度センサ（図示せず）を設けたときの、電子的評価の可能性を示す。差動増幅器を使って、周囲温度と吸入器１のノズル４の温度との差の時間特性を導き、この時間特性を、マイクロコントローラ内に収容されたプロセッサのアナログ－デジタル変換器に送る。図６における適当な極限値t_1及びt_2の間の信号U_1の積分値が、変数

$$Q' = \int_{t_1}^{t_2} u_1 (t)\ dt$$

を与え、この変数が、プロセッサのＲＯＭ記憶装置モジュール内に記憶された明確に規定された関連する値の助けによって、実際のエーロゾル霧化量Ｑになる。

最後に、図７は、吸入行程の認識が電子的に評価される、他の実施態様による信号処理を示す。

霧化認識用に設けられた周波数分離増幅器を、信号処理のために使用するのが

好ましい。

図７ａは、温度センサの電圧U_1の時間特性を示し、図７ｂは、分離増幅器の出力における電圧U_2の特性を示し、図７ｃは、霧化認識用の比較器の出力における電圧U_3を示し、図７ｄは、吸い込みおよび正しい霧化を伴った吸入行程のためのもう一つの比較器の出力における電圧U_4の時間特性を示す。

温度センサの電圧U_1は、最初に、小さなパルスを有し、このパルスの前側が、

吸入の開始、即ち、最初の吸入空気が温度センサ５を通過したことを示す。しかしながら、周波数分離増幅器の出力電圧U_2は、すでに、極端に目立つパルスを有している。この電圧は比較器に送られ、比較器の出力電圧U_4が、評価電子Ｕ３１用のデジタル出力信号である。電圧U_4の前側面は、吸入（t_0）の開始と同時に起こる。評価電子ユニット３１のプログラム内で、この側面に対して自由規定された遅延時間の後、評価電子ユニット３１は、電気機械変換器（例えば圧電発振器）を介して聴覚信号を発する。

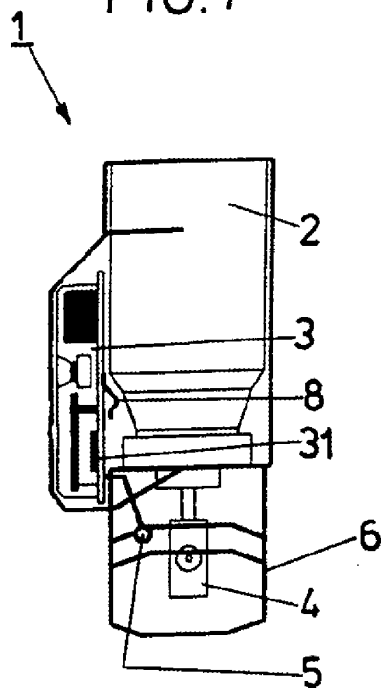
電圧U_1の、即ち、より強い正の上昇、および、強い負のパルスを備えた電圧U_2の連続推移は、引き起こしに続くエーロゾルの正しい霧化による、温度センサ５の冷却の結果である。対応する比較器の出力電圧U_3は、負のパルスを有しており、これが、評価電子ユニットに送られる。

口を吸入器につけてから吸入を行い、かつ、信号を聞くまでは、作動要素を作動させて霧化を引き起こさないので、患者にとって取扱いが簡単である。これは、患者が、例えば吸入器に口をつけ吸い込んだ直後に霧化を起こさないことを確実にし、あるいは、吸入行程が終わったときにはスイッチを入れないが、正しく吸入を伴っているときには霧化を引き起こすことを確実にする。これは、治療に好ましく影響する。

本発明は上述した実施例に限定されるものでなく、検出したデータの使用および評価に関連する上述した全ての可能性を含むものである。

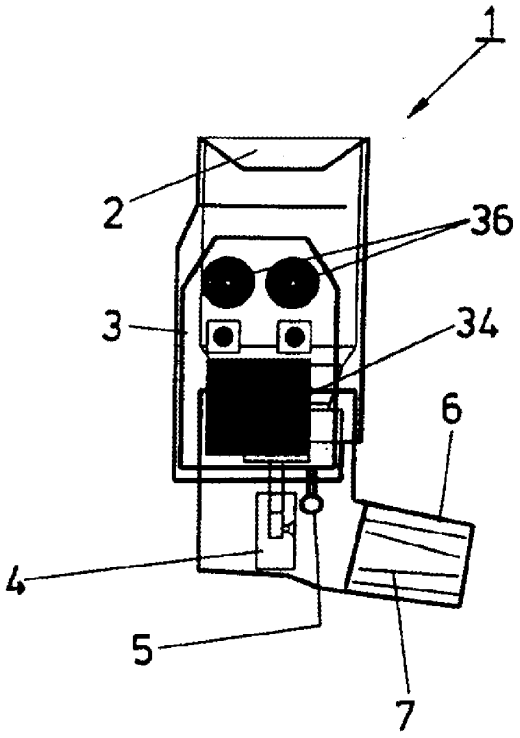
【図１】

FIG.1



【図２】

FIG.2



【図３】

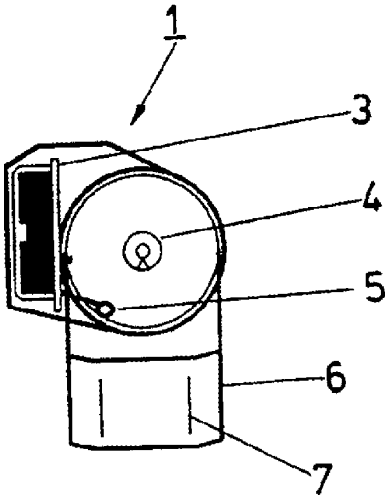


FIG.3

【図４】

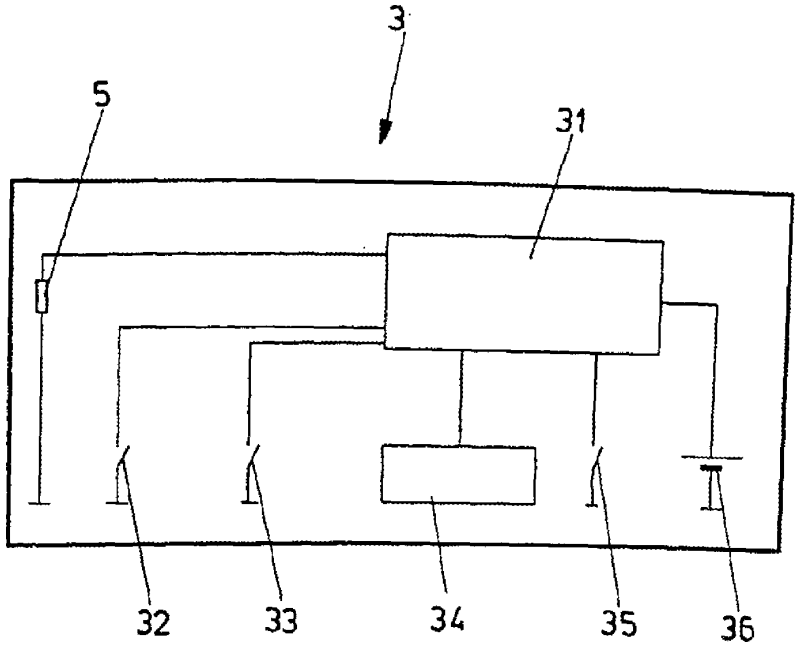


FIG. 4

【図５】

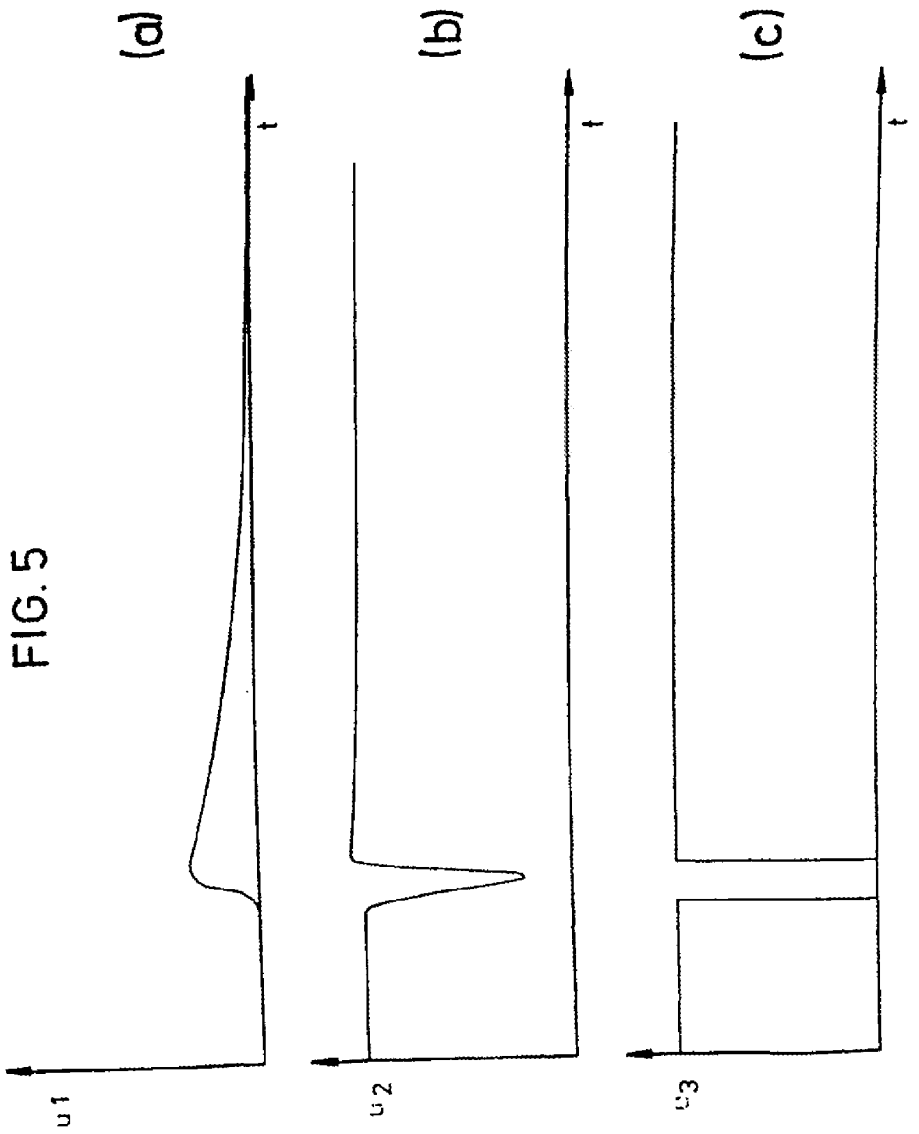
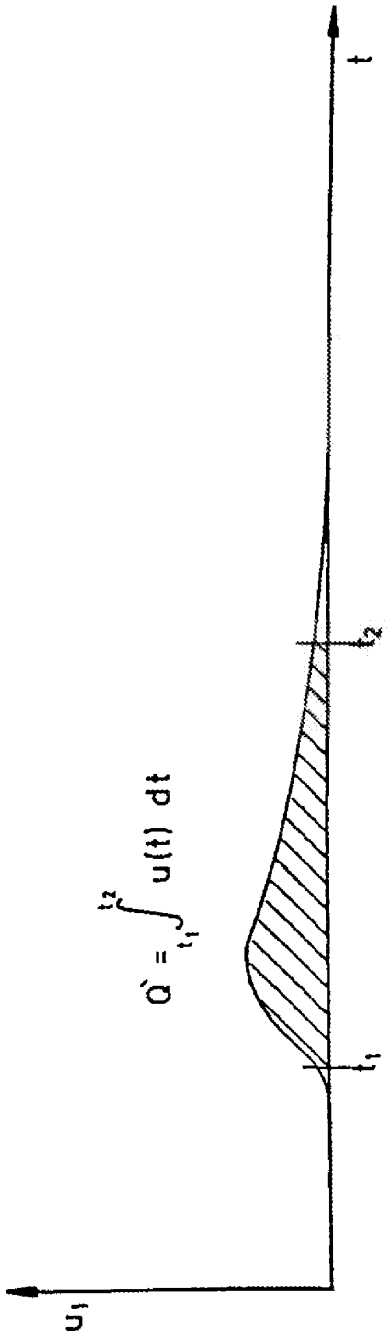


FIG.5

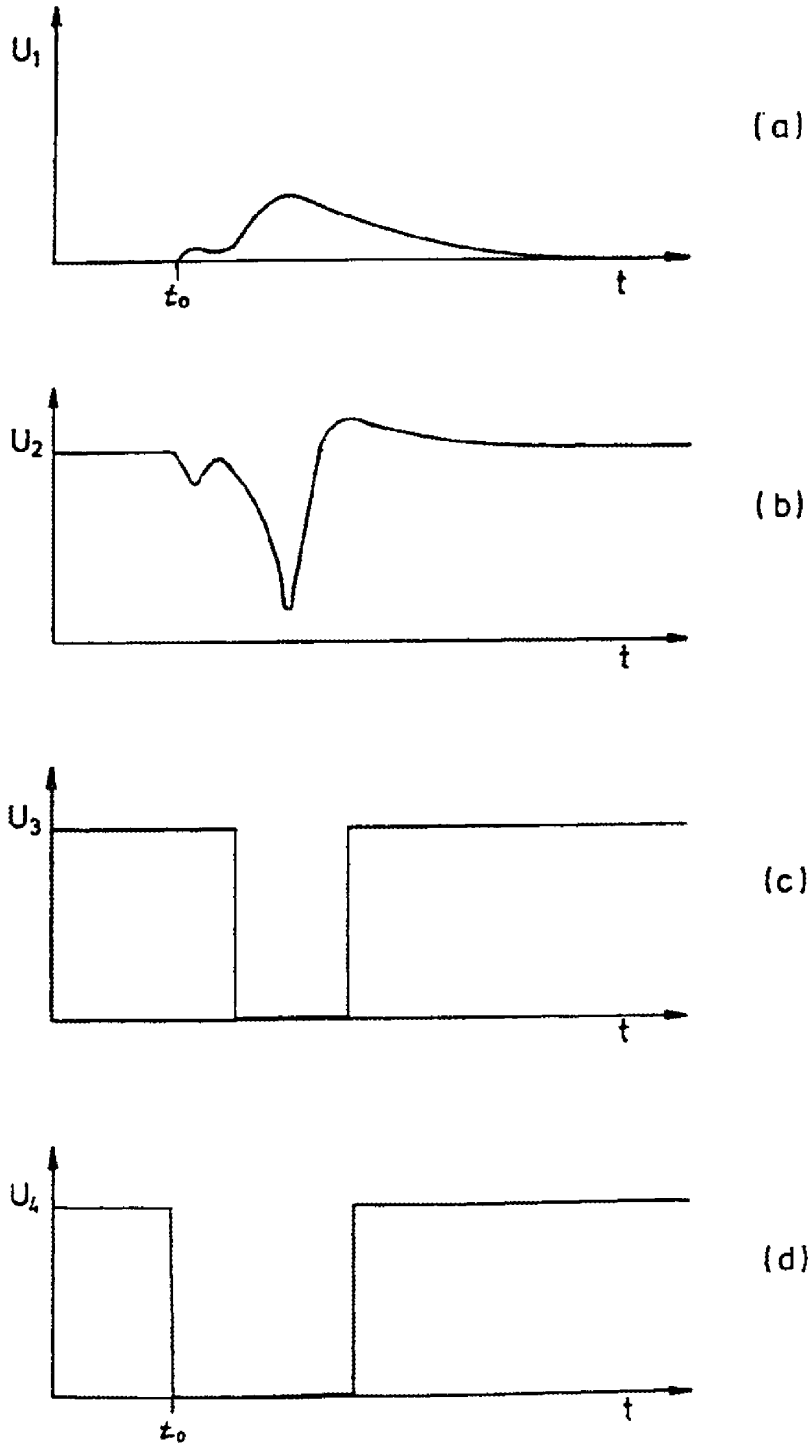
【図６】

FIG.6



【図7】

FIGUR 7



INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/EP 95/02410

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 07599 (MINNESOTA MINING & MFG) 14 May 1992 see abstract; figure 1 see page 13, line 1 - page 14, line 10 see page 19, line 6 - line 31	1-13
Y	US,A,5 284 133 (BURNS JAMES S ET AL) 8 February 1994 see abstract; figure 4A see column 7, line 51 - column 10, line 34 see column 12, line 3 - line 31	1-13
A	WO,A,92 15353 (MIRIS MEDICAL CORP) 17 September 1992 see abstract; figure 1 see page 29, line 6 - page 30, line 33	1,4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 1995	17. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Zeinstra, H

Form PCT/ISA/210 (second sheet) (July 1992)

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Inte. ional Application No
PCT/EP 95/02410

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 17231 (INNOMED INC) 15 October 1992 see abstract; figure 4 see page 5, line 20 - page 6, line 32 see page 10, line 22 - page 11, line 9	7

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. ..nal Application No
PCT/EP 95/02410

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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US-A-5284133	08-02-94	NONE		
WO-A-9215353	17-09-92	US-A-	5404871	11-04-95
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		US-A-	5392768	28-02-95
WO-A-9217231	15-10-92	NONE		

Form PCT/ISA/210 (patent family annex) (July 1992)

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United States Patent [19]

Nöhl et al.

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[45] Date of Patent: *Sep. 19, 2000

[54] **AEROSOL INHALER**

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[73] Assignee: **Boehringer Ingelheim KG**, Ingelheim, Germany

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

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PCT Pub. Date: **Jan. 11, 1996**

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[51] **Int. Cl.**[7] **A61M 11/00**

[52] **U.S. Cl.** **128/200.14**; 128/200.23; 128/204.23; 128/205.23

[58] **Field of Search** 128/200.24, 200.14, 128/200.23, 203.12, 204.21, 204.23, 205.23

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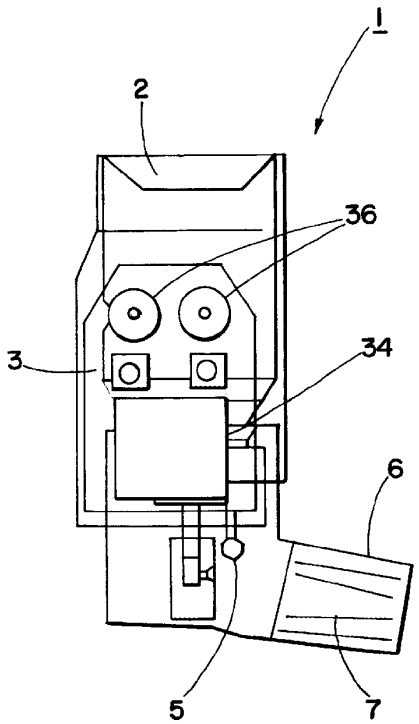
Primary Examiner—Aaron J. Lewis

Attorney, Agent, or Firm—Robert P. Raymond; Alan R. Stempel; Mary-Ellen M. Devlin

[57] **ABSTRACT**

In an aerosol inhaler it is proposed that a thermal sensor **5** be arranged in the region of the atomization nozzle **4**, which sensor, following the actuation of an actuating element and the triggering of an inhalation process, undergoes cooling as a result of the expansion of the propellant which then occurs. The actuation and cooling are electronically detected in an electronic module **3**. Technical and therapeutic data can be derived from the signal, which data are communicated to the user via the display unit and/or alarm devices and influence the therapy in the desired manner.

1 Claim, 5 Drawing Sheets



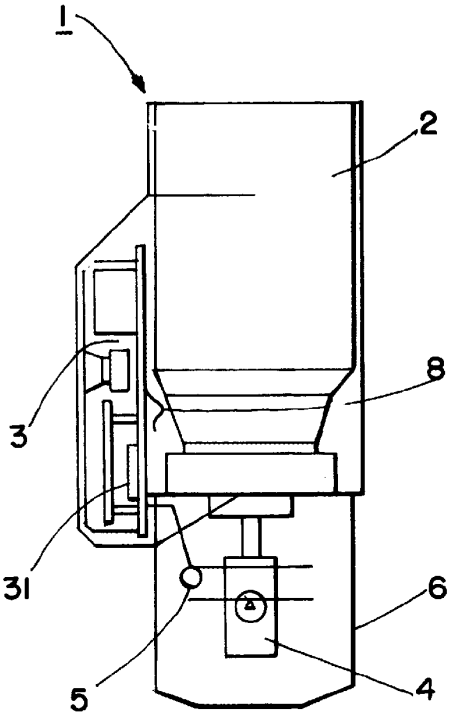


Fig. 1

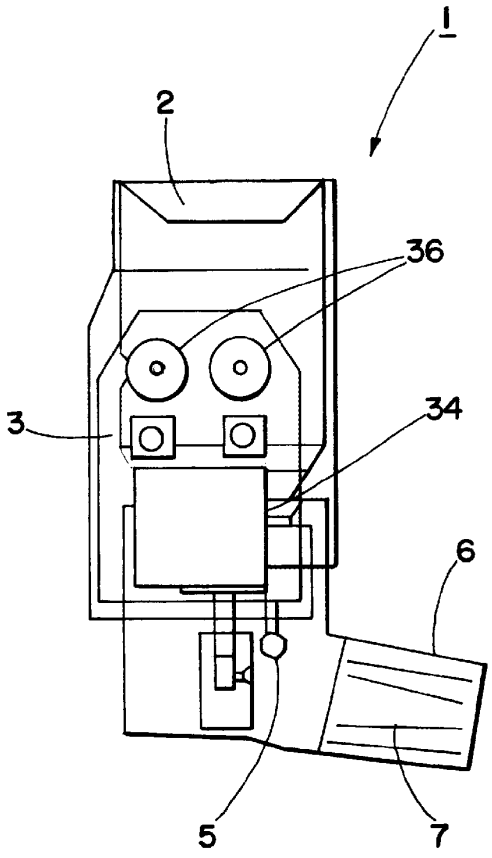


Fig. 2

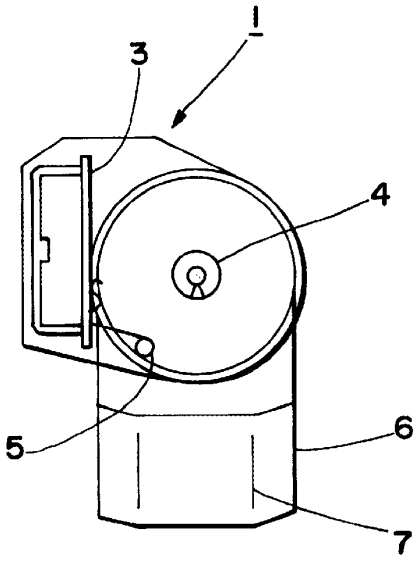


Fig. 3

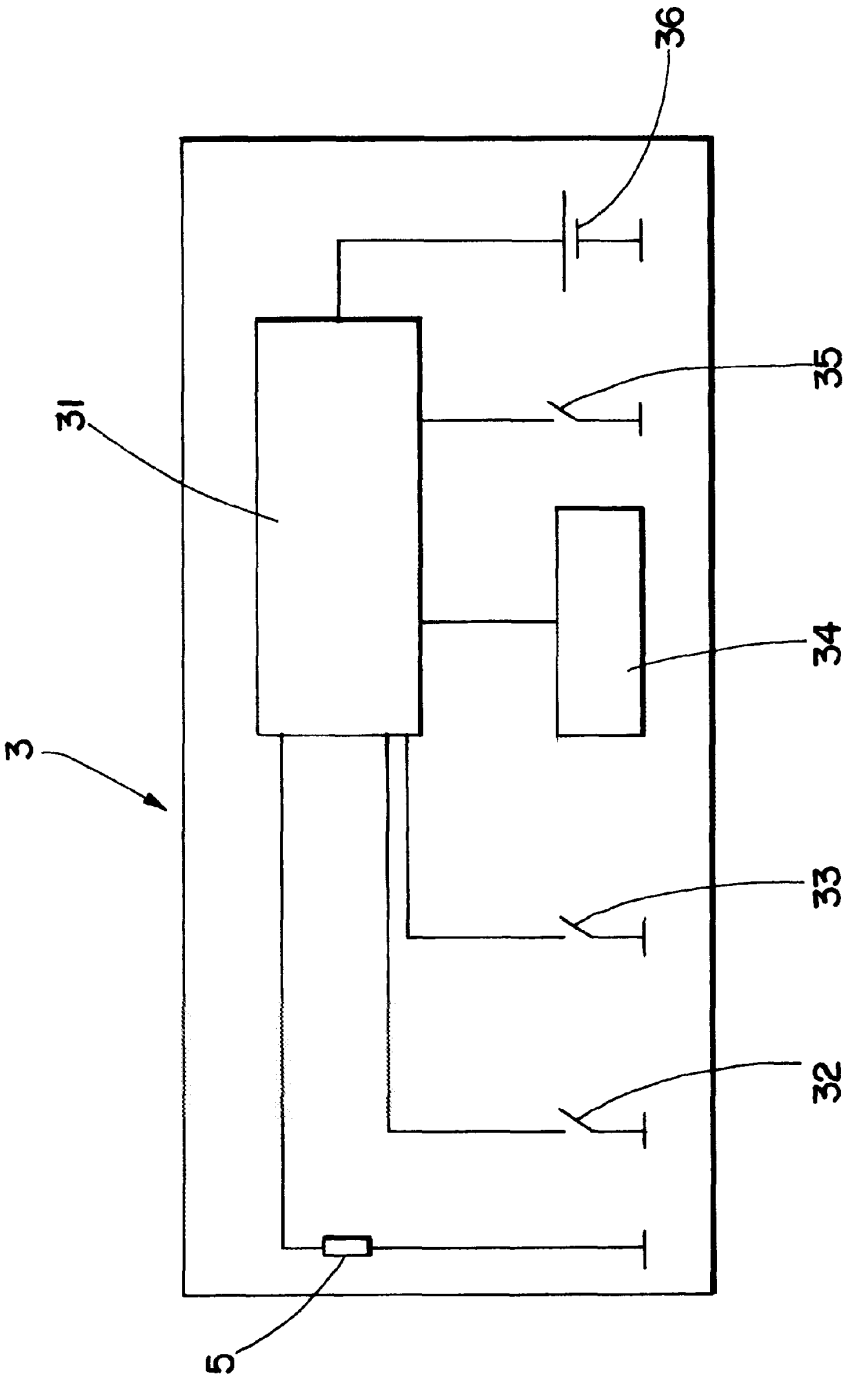
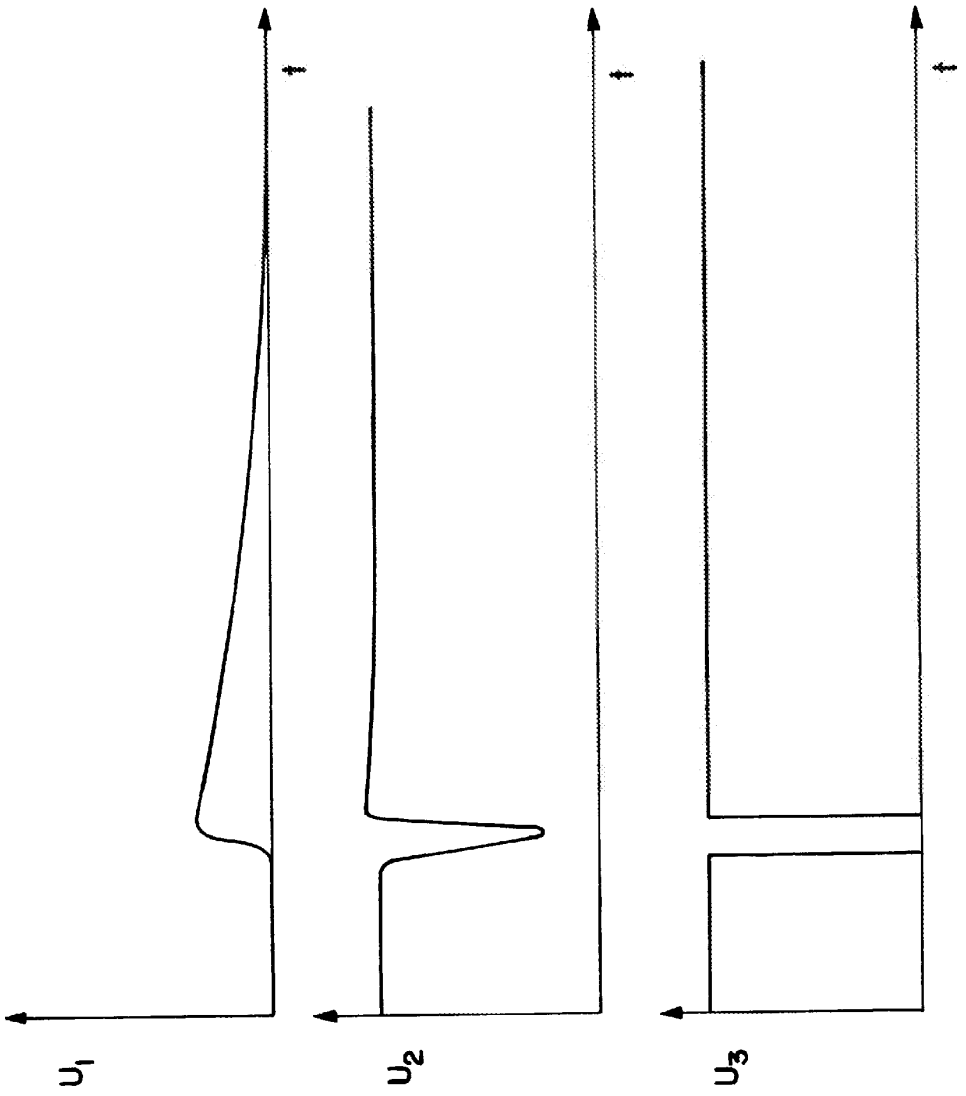


Fig. 4

Fig. 5(a)

Fig. 5(b)

Fig. 5(c)



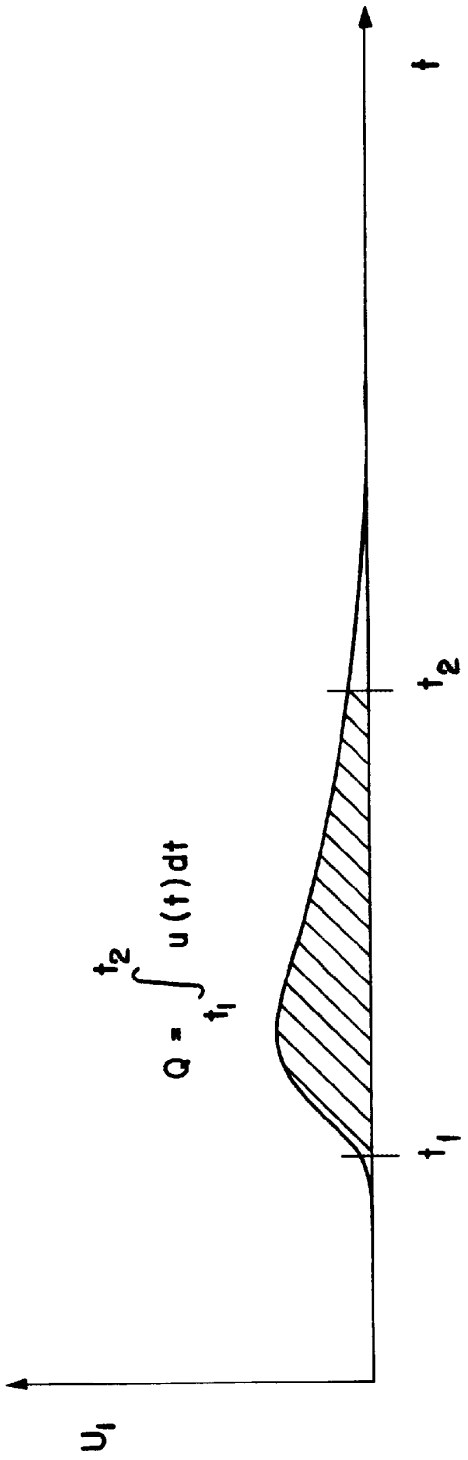


Fig. 6

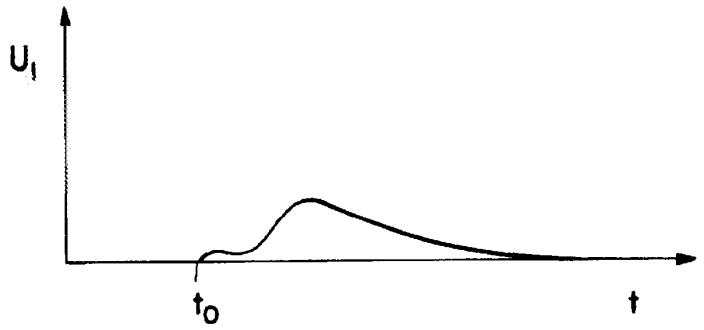


Fig. 7(a)

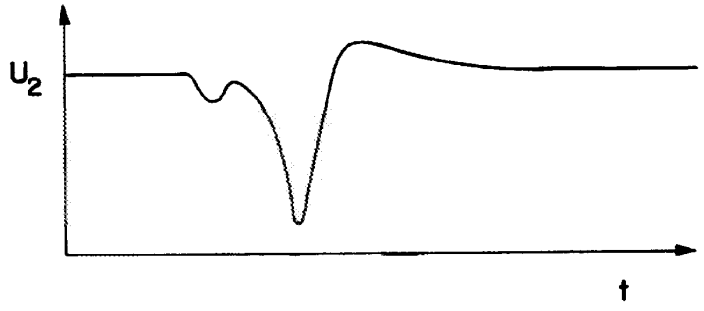


Fig. 7(b)

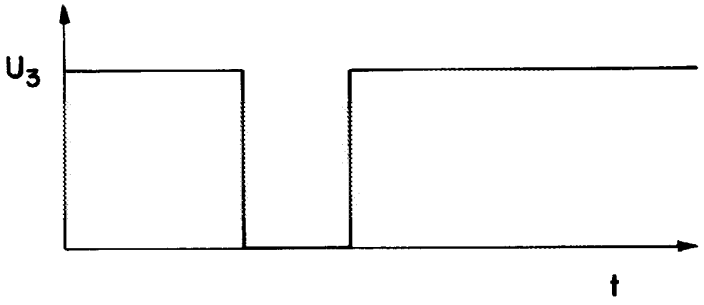


Fig. 7(c)

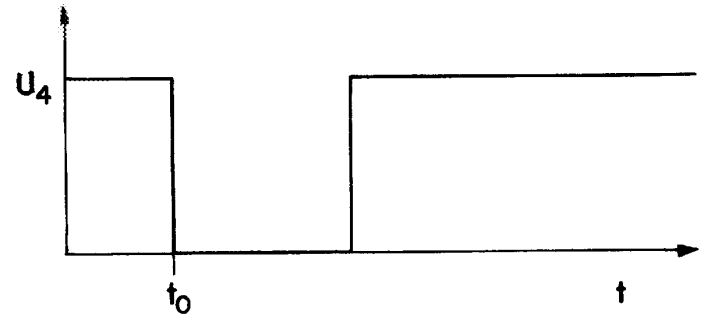


Fig. 7(d)

AEROSOL INHALER

The invention relates to an aerosol inhaler for a medicinal substance to be inhaled and to an electronic module for use in association with such an inhaler.

An aerosol inhaler is to be understood as a device with the aid of which a patient can actively breathe in a given dose of a medicinal substance to be inhaled. A typical application for such a device is an acute asthma attack. Upon the actuation of a corresponding actuating element, the aerosol, consisting of a propellant and of the medicinal substance present in said propellant and distributed therein, passes from the supply container provided therefor, through a nozzle, into the air channel of a mouthpiece from where it is actively inhaled by the patient. The aerosol emission and atomization can be triggered electronically or mechanically.

Previously it was not possible to detect whether, upon the actuation of the actuating element, atomization had actually taken place or not. For example, this can be prevented by obstruction of the nozzle. Naturally atomization also does not take place when the aerosol supply container is empty. This can lead to complications as the patient has supposedly inhaled the medicine necessary to combat an acute attack, whereas in fact this is not true or only partially true. An only partial supply of the given dose frequently gives rise to a desire on the part of the patient to augment the effect of the medicinal substance by further inhalation. This can lead to a dangerous situation as a result of overdosing. Furthermore, the doctor caring for the patient loses an overview of the number of doses administered within a predetermined time interval, which is an impediment to responsible medical treatment.

Therefore, with this background, the object of the present invention is to further develop an aerosol inhaler of the type defined in such manner that it is at least possible to reliably recognise and evaluate the atomization of the aerosol upon the actuation of the actuating element. In accordance with further aspects of the invention, a series of evaluations relating to some treatment parameters, such as the number of administered doses, the doses remaining in the supply container and the indication thereof, as well as for example the checking of the aerosol to determine whether it corresponds to the doctor's prescription, are to be possible. Furthermore, an electronic module is to be provided for use in association with such an inhaler, which electronic module fulfils the electronic part of the object of the invention but in principle can also be used in the case of all known aerosol inhalers, and thus as an accessory to an aerosol inhaler.

In accordance with the invention, it is thus provided that the inhaler be equipped with an electronic module which comprises an evaluating electronic unit for function monitoring which is supplied with signals from at least one thermal sensor arranged in the flow region of the nozzle and from a device for recognising the actuation of the actuating element, and comprises a display device for the output of the evaluation result produced by the evaluating electronic unit.

The crux of the invention thus consists in that a thermal sensor is arranged directly on the nozzle in which the atomization of the aerosol takes place. This permits a positive detection of the atomization of the aerosol on the basis of the recognition of the actuation and of the cooling of the propellant which occurs upon atomization, in that the cooling of the propellant leads to the cooling of the thermal sensor and a clearly defined electric signal can be generated. Malfunctions, such as obstructed nozzles or an empty aerosol supply container, can thus be reliably detected.

In a special and simple exemplary embodiment, the evaluating electronic unit generates a warning signal when

atomization does not take place, and a signal representing the number of inhalation doses still contained in the supply container. These signals are communicated to the patient by means of a suitable display or, in the case of the warning, with an acoustic signal. As a result of the monitoring of the atomization the user can be warned when no atomization has occurred and thus he has not inhaled any medicinal substance, as can happen when a supply container is empty or also in particular when a nozzle is obstructed.

In accordance with a further advantageous development, it is provided that the thermal sensor detects the air flowing past it at the start of the inhalation, generates a corresponding signal therefrom, and sends this signal to the evaluating electronic unit which itself generates a signal which is optically and/or acoustically displayed as a coordination aid for the patient in the inhalation process.

The background to this further development is as follows:

The correct inhalation of the aerosol ideally proceeds in such manner that, having exhaled, the patient applies the device to his mouth and after the start of the inhalation triggers the atomization by depressing the actuating element. Many users have problems however in coordinating their breathing and the triggering of the atomization. An incorrect timing sequence of inhalation and triggering diminishes the effect of the medicament however, and impairs the clinical result. It is here that the described further development comes into effect in that immediately following the start of the inhalation the patient is informed by means of the optical or acoustic display that atomization is imminent. In this way the clinical result of the treatment is distinctly improved.

In accordance with a further embodiment it is provided that a further thermal sensor is arranged outside of the flow path of the aerosol, which further thermal sensor generates a reference signal which is likewise fed to the evaluating electronic unit and is linked with the signal from the first thermal sensor in such manner that the result permits the emitted quantity of aerosol to be deduced. The linking can take place, for example, in a differential amplifier in which it is possible to form the time characteristic of the difference between the temperature of the first thermal sensor arranged directly on the nozzle and the environmental temperature. The downstream, evaluating electronic unit then receives this difference signal and the integration of said signal within suitable limits supplies a value which, with the aid of a relation stored in a memory of the evaluating electronic unit, leads to the atomized quantity of aerosol. As a result of the quantitative detection, after each inhalation the patient can be given precise information as to whether a further inhalation is necessary. In the event of the undershooting of a specified quantity, preset in the program of the evaluating electronic unit, a warning signal can be generated which informs the patient that too little active ingredient has been inhaled. This monitoring possibility leads to greater reliability in the use of inhalers and to a more efficient therapy.

Alternatively, the emitted quantity of aerosol can be determined in that prior to the atomization the environmental temperature of the thermal sensor, which is anyhow arranged in the region of the nozzle, can be detected, digitalized and stored in the evaluating electronic unit. When the aerosol is now atomized during inhalation, the time characteristic of the temperature changes of the sensor is detected as so-called temperature profile. This temperature profile is digitalized and the previously stored environmental temperature is subtracted therefrom. The integration of the difference within suitable limits supplies a value which, with the aid of a relation stored in the memory of the evaluating

electronic unit, leads to the atomized quantity of aerosol. The relation between the output voltage of the sensor signal amplifier and the temperature of the sensor can be stored in the memory of the evaluating electronic unit. Any non-linearities of the sensor and the signal amplifier, and thus also the influence of shifts in operating point, caused by changes in the environmental temperature, can be computationally eliminated in the evaluating electronic unit.

If, in accordance with a further embodiment, the evaluating electronic unit comprises a microcontroller, the latter is preferably assigned a memory for the storage of data as well as a serial interface for communication with an external computer.

This embodiment provides the doctor in charge with the possibility, entirely novel in the relevant field, of monitoring whether the patient has actually inhaled the number of inhalation doses prescribed by him, and the time interval within which this has taken place. An abundance of data to be input into the memory, and functions associated therewith, are possible. Thus for example the doctor can also predetermine a time interval after which a further inhalation is to take place, and by means of a real-time clock present in the module an optical and/or acoustic signal is generated to remind the patient of the further inhalation.

The functions can be monitored and the implementation or non-implementation thereof can likewise be stored in the memory. On the occasion of a further visit to the doctor in charge, this data can then be read out via the serial interface and interpreted by the doctor. For the input into and output from the memory, the electronic module is to be connected via the serial interface—as already mentioned—to an external computer.

The presence of the evaluating electronic unit in the inhaler according to the invention facilitates further functions; in accordance with another embodiment the aerosol supply container can consist of a replaceable part so that it is detachably insertable into the inhaler. The exterior of the detachable supply container can have optically coded surfaces, such as are known for example in connection with the so-called DX-coding of miniature film cartridges in photography. The evaluating electronic unit is then designed in such manner that it can decode the information contained in this code. This information can for example indicate the type of active ingredient of the medicinal substance in the aerosol and the expiry date thereof. This data can be read out and compared in the microcontroller of the evaluating electronic unit for example with the information relating to the type of active ingredient input by the doctor. In the event of differences, an alarm signal can be triggered. The aforementioned real-time clock in the electronic module can be used to check the expiry data of the medicinal substance in the aerosol and to trigger an alarm when the expiry date is exceeded.

In this embodiment the replaceable supply container can also itself comprise an electronic memory; the data stored in this memory can be read out by the evaluating electronic unit and the evaluating electronic unit can input data into this memory. This memory can be provided in addition to the aforesaid optical coding or also by itself. For the data exchange between the inhaler and an external computer located, for example, at the doctor's premises, a plug-in EEPROM module which retains its data without a power supply can be used. The external computer has an adapter via which data can be input into the EEPROM module and also read out from the latter. Via this storage module, on the one hand the information concerning the type of active ingredient and the prescribed treatment can be communicated to the device and on the other hand the device itself inputs the therapy actual data therein.

In another embodiment a sensor contact can be arranged on the mouthpiece of the inhaler. The signal from this sensor contact is fed to the evaluating electronic unit. It is thus possible to check whether, in the case of correct atomization, the patient has actually received the medicinal substance. This ensures that an atomization which, although correct, has been released into space and thus has not reached the patient, is not recorded in the memory as an administered dose.

Here it should again be emphasised that all the aforementioned monitoring possibilities are conditional upon the inhaler being provided with a thermal sensor directly on the nozzle where the aerosol is atomized, and with a device for recognising the actuation of the actuating element and with an evaluating electronic unit which evaluates the signals from this sensor and from the actuation-recognition device. The electronic module referred to in the introduction, as a part which is to be handled independently of the actual inhaler and which can itself constitute a commercial article, is provided in accordance with the invention with a separate housing which can be detachably secured to the inhaler and comprises, projecting away from itself, the at least one thermal sensor which is to be arranged in the direct vicinity of the nozzle opening in the inhaler.

The electronic module can be produced and tested independently of the inhaler. Only in the last production step is the electronic module clipped onto the device and the complete device subjected to final testing. However, it can also be marketed separately, independently of a concrete type of inhaler and serve as accessory.

In accordance with an advantageous further development the aforementioned second thermal reference sensor is also arranged on the electronic module, whereby the unit as a whole becomes very compact as this second sensor is not to be applied, for example, to the inhaler, which indeed would additionally require the establishment of an electric connection.

The thermal sensor or sensors is/are preferably NTC resistors, thermistors or surface thermoelements, i.e. elements whose electrical properties change in an evaluatable manner in the event of a change in temperature.

The evaluating electronic unit can be formed by a microcontroller or a customised circuit in which all the necessary electronic functions are integrated. This design allows a reduction in the space required for the evaluating electronic unit and the power requirement and—due to the associated reduction in the battery volume—in the overall volume of the electronic module. The circuit board of the electronic module advantageously can be constructed in accordance with SMD technology. For reasons of space and costs the microcontroller can be assembled without the use of an IC housing in accordance with chip-on-board (COB)—or tape-automated-bonding (TAB) technology. The display unit and necessary batteries are fixed on the circuit board via a clip-on plastics frame and electrically connected to the circuit board via conductive rubber and contact springs.

The switching on and off of the device can take place without an additional operating step by the removal and application of the inhaler cap. If the cap remains open for a relatively long time interval, after a specified time the electronic unit is automatically switched to a so-called "sleep mode" and is automatically "awoken" by the triggering of an inhalation. When the cap is in place, mechanical locking can be provided which prevents the triggering of the atomization.

The display unit can preferably consist of a LCD with a 3-digit, 7-segment display and a symbol for the daily dose warning, battery warning and display of a device fault.

When a newly filled aerosol supply container is inserted in the inhaler, it is necessary to actuate a reset pushbutton on the electronic module whereby the remaining dose is set at a value corresponding to a full container. This function can also be implemented, in accordance with another embodiment, by means of the actuation-recognition device which sends a signal to the evaluating electronic unit both when the actuating element is activated and when the container is changed. The reset pushbutton is then not required.

The inhalation process of the inhaler according to the invention can also be electronically triggered. The electronic unit required for this purpose can likewise be accommodated in the electronic module. Incorrect triggerings are substantially prevented by a sensor contact on the mouthpiece.

The electronic recognition of the inhalation phase, referred to in the foregoing, by means of the thermal sensor in the flow region of the nozzle can also be used to trigger the atomization fully automatically via the breath. For this purpose, after a corresponding signal evaluation, the evaluating electronic unit sends a signal to the actuating element of the inhaler and thus triggers the atomization. The coordination is then assumed in full by the device. The patient need only apply the device to his mouth and inhale.

The evaluation of the sensor signal can also take place in that, after amplification, the analogue signals are immediately digitalized, the function of the above described comparators is assumed by the program of the evaluating electronic unit, and the corresponding switching levels and delay times are determined by the program.

In the following the inhaler according to the invention will be explained in detail in the form of an exemplary embodiment. In the drawings:

FIG. **1** is a front view of the inhaler with electronic module clipped-on laterally;

FIG. **2** is a side view of the inhaler according to FIG. 1;

FIG. **3** is a plan view of the device according to FIGS. **1** and **2**;

FIG. **4** is a principal circuit diagram of the evaluating electronic unit;

FIGS. **5***a* to **5***c* show time characteristics of output signals and

FIG. **6** shows a time characteristic of the integration of the difference signal between the thermal sensor at the nozzle opening and the reference sensor, and

FIG. **7** illustrates further time characteristics of output signals in the case of which the inhalation phase is electronically evaluated.

FIGS. **1** to **3** are views of the inhaler according to the invention which represent only principal diagrams and do not correspond to actual sectional illustrations.

The inhaler **1** according to the invention comprises a supply container **2** for an aerosol. In the present case the supply container **2** is detachably connected to a housing which has a mouthpiece **6** with air channel **7** extending therein. By means of an actuating element (not shown here) a dose of the aerosol is inlet from the supply container **2** into the nozzle **4** where it is atomized. The patient breathes in this atomized aerosol through the air channel **7**.

During this process the supply container **2** moves and via the actuation-recognition device **8** releases a signal which is fed to the evaluating electronic unit **31**. The first thermal sensor **5** is arranged directly at the opening of the nozzle **4**. When an atomization from the nozzle **4** takes place, the propellant expands and the temperature in the region of the nozzle opening falls. This fall in temperature is detected by the thermal sensor **5**, which latter generates a corresponding signal which is likewise fed to the evaluating electronic unit **31**.

As already mentioned, in the present case the electronic module **3** is clipped onto the inhaler **1** and can be handled independently. It is of compact construction and contains all the necessary components, of which the batteries **36** and the optical display unit **34** have been provided with reference symbols in FIGS. **1** to **3**. The optical display unit preferably consists of a 3-digit, 7-segment LCD display. The principal circuit diagram of the evaluating electronic unit **30** is shown in FIG. **4**.

In the present case the main component is an evaluating electronic unit **31** which is supplied with the signal from the actuation-recognition device **8** and the signal from the thermal sensor **5**. The evaluating electronic unit is not activated until the contact **33** is closed, which occurs when the cap of the device has been removed.

The circuit is supplied by the battery **36**. In the present case the display takes place via the aforementioned display unit **34**.

Finally a reset switch **35** is also provided, which must be actuated when a newly filled supply container is inserted into the inhaler **1** so that the remaining dose is set, in the memory of the evaluating electronic unit **31**, at a value corresponding to a full supply container.

The signal processing will be briefly explained with reference to FIGS. **5** and **6**.

FIG. **5***a* illustrates the curve of the voltage U_1 across the thermal sensor **5**. Upon the expansion of the propellant in the nozzle **4** and the accompanying cooling of the sensor **5**, the voltage U_1 initially rises steeply and after the atomization process falls to its original value in accordance with the thermal time constant.

FIG. **5***b* shows the time characteristic of an output voltage U_2 of a frequency-selective amplifier, to the input of which the voltage U_1 from FIG. **5***a* is applied. It can be seen that U_2 has a pronounced pulse in the case of atomization (event).

The voltage U_2 is fed for example to a comparator which in the rest state has a constant positive output voltage and in the case of correct atomization emits a negative pulse and at the time of an event temporarily assumes the voltage zero. The voltage U_3 is the digital input signal for the evaluating electronic unit. Amplifier and comparator can form part of the evaluating electronic unit.

Finally FIG. **6** shows the possibilities of electronic evaluation when a further thermal sensor (not shown) is provided as reference sensor which is exposed to the environmental temperature. Thus with the aid of a differential amplifier it is possible to form the time characteristic of the difference between the environmental temperature and the temperature of the nozzle **4** in the inhaler **1** and to supply this time characteristic to an analogue-digital converter of a processor contained in the microcontroller. The integration of this signal U_1 from FIG. **6** within suitable limits t_1 and t_2 supplies a variable

$$Q' = \int_{t_1}^{t_2} u_1(t)dt$$

which, with the aid of a clearly defined relation stored in a ROM storage module of the processor, leads to the actually atomized quantity of aerosol Q.

Finally FIG. **7** shows the signal processing in the event that, in accordance with a further development, the recognition of the inhalation phase is electronically evaluated.

The frequency-selective amplifier provided for the atomization recognition is preferably used for the signal processing.

FIG. **7***a* shows the time characteristic of the voltage U_1 across the thermal sensor, FIG. **7***b* shows the characteristic of the voltage U_2 at the output of the selective amplifier, FIG. **7***c* shows the characteristic of the voltage U_3 at the output of the comparator for the atomization recognition and FIG. **7***d* shows the time characteristic of the voltage U_4 at the output of a further comparator for the duration of a breathing-in and inhalation phase with correct atomization.

The voltage U_1 across the thermal sensor firstly has a small pulse, the front flank of which represents the start of the inhalation, i.e. when the first inhalation air passes the thermal sensor **5**. The output voltage U_2 of the frequency-selective amplifier here already has an extremely marked pulse however. The voltage is fed to a comparator whose output voltage U_4 is the digital input signal for the evaluating electronic unit **31**. The front flank of the voltage U_4 coincides with the start of the inhalation (t_0). After a delay time, freely defined in the program of the evaluating electronic unit **31**, for this flank, the evaluating electronic unit **31** emits an acoustic signal via an electromechanical transducer (for example a piezoelectric oscillator).

The continued course of the voltage U_1, namely in a more strongly positive ascent, and of the voltage U_2 with the strongly negative pulse result from the cooling of the thermal sensor **5** due to the correct atomization of the aerosol which follows the triggering. The output voltage U_3 of the corresponding comparator then has a negative pulse which is fed to the evaluating electronic unit.

For the patient, handling is simplified in that he starts to inhale having applied the inhaler to his mouth, and not until he hears a signal does he trigger the atomization by actuating the actuating element. This ensures that the patient does not trigger the atomization for example immediately after having applied the inhaler to his mouth and then inhale, or does note trigger the atomization when the inhalation phase is over, but triggers the atomization correctly with the inhalation. This serves to favourably influence the effects of the medicament.

The invention is not limited to the concrete exemplary embodiment explained here but includes all the possibilities, described in the foregoing, relating to the use and evaluation of the detected data.

What is claimed is:

1. An improvement in an inhaler for the administration by inhalation of an aerosol consisting of a medicament an a propellant, said inhaler being of a known design comprising:

a) a supply container having propellant and medicament therein;

b) a nozzle for atomizing propellant and medicament conveyed thereto, to form an aerosol therefrom, having an opening from which the aerosol so formed is expelled;

c) means for conveying propellant from the supply container to the nozzle;

d) an actuating element for causing the conveyance of propellant and medicament from the supply container to the nozzle, upon actuation by a user of the inhaler; and,

e) a mouthpiece having a channel, through which the aerosol formed by the nozzle is expelled from the inhaler, so that it may be inhaled;

wherein the improvement comprises the addition of an an electronic means for sensing and reporting whether aerosol has been expelled from the inhaler upon actuation by the user, said electronic means comprising:

f) a first thermal sensor, located in the vicinity of the nozzle opening, which produces an electrical signal that varies in response to the temperature in the vicinity of the nozzle opening, including any decrease in temperature caused by the expuslion of aerosol from the nozzle opening;

g) a second thermal sensor, located away from the vicinity of the nozzle opening, for developing a reference signal which represents the ambient temperature and which is not influence by the expulsion of aerosol from the nozzle opening;

h) an actuation-recognition device for producing an electrical signal upon actuation of the actuating means;

i) an evaluating electronic unit, connected to the first thermal sensor, the second thermal sensor and the actuation recognition device, which evaluating electronic unit compares the signals of the two thermal sensors in order to determine whether there has been a decrease in temperature in the vicinity of the nozzle opening, and which uses the signal from the the actuation recognition device to evaluate whether a decrease in temperature in the vicinity of the nozzle opening has coincided with actuation of the actuating means, and which thereby determines whether aerosol has been expelled from the inhaler upon actuation by the user; and,

j) an electronic display, by means of which the determination of the evaluating electronic unit is reported.

* * * * *

Electronic Patent Application Fee Transmittal					
Application Number:	14925961				
Filing Date:	28-Oct-2015				
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF				
First Named Inventor/Applicant Name:	Adam BOWEN				
Filer:	Richard Douglas Shoop/Brian Flick				
Attorney Docket Number:	13211-713.302				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	26143028
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	22-JUN-2016
Filing Date:	28-OCT-2015
Time Stamp:	15:44:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	2360
Deposit Account	504050
Authorized User	SHOOP, RICHARD D
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_6-22-2016.pdf	273021 2b335ee5cb0e52591238a56bd9e140b255adcaac	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
2	Foreign Reference	JP10-501999AwEngEquiv.pdf	3881257 9f5f4be56c683c9397af0c0f9f521e95b21f35e6	no	32
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30801 1d5a3cd2df2bd48a1e559a8efd172cfb64625f45	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4185079		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on June 22, 2016.

/Brian Flick/
Name

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

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This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☐ **37 CFR §1.97(b)**
This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☐ **4).** Before the mailing of a first Office Action after filing a request for continued examination under § 1.114.
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

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☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

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☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement. or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☒ **37 CFR § 1.97(d)**

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--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☐ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☐ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☒ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☒ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language:

--AND/OR--

☒ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached:

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☒ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. Cite no(s): 585

☒ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement. Cite no(s): 590-592

STATEMENT UNDER 37 CFR § 1.704(d)

☒ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $180.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: June 22, 2016

By: _____
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	595	US- 9,220,302	12/29/2015	DePiano et al.	
	596	US- 9,226,526	1/5/2016	Liu	
	597	US- 9,271,525	3/1/2016	Liu	
	598	US- 9,271,529	3/1/2016	Alima	
	599	US- 9,272,103	3/1/2016	Storz	
	600	US- 9,277,769	3/8/2016	Liu	
	601	US- 9,282,772	3/15/2016	Tucker et al.	
	602	US- 9,282,773	3/15/2016	Greim et al.	
	603	US- 9,289,014	3/22/2016	Tucker et al.	
	604	US- 9,308,336	4/12/2016	Newton	
	605	US- 9,326,547	5/3/2016	Tucker et al.	
	606	US- 9,351,522	5/31/2016	Safari	
	608	US- 2015/0282525	10/8/2015	Plojoux et al.	
	609	US- 2015/0313275	11/5/2015	Andersonet al.	
	611	US- 2015/0351456	12/10/2015	Johnson et al.	
	614	US- 2016/0021931	1/28/2016	Haweset al.	
	607	US- 2016/0058071	3/3/2016	Hearn	
	618	US- 2016/0058072	3/3/2016	Liu	
	621	US- 2016/0081395	3/24/2016	Thorens et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	639	WO2015/149647A1(w/ Eng Abs)	10/8/2015	Kimree Hi-Tech Inc.		
	640	WO2015/168828A1(w/ Eng Abs)	11/12/2015	Kimree Hi-Tech Inc.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	623	US- 2016/0106154	4/21/2016	Lord	
	624	US- 2016/0106155	4/21/2016	Reevell	
	627	US- 2016/0120218	5/5/2016	Schennum et al.	
	630	US- 2016/0135503	5/19/2016	Liu	
	632	US- 2016/0143359	5/26/2016	Xiang	
	635	US- 2016/0143365	5/26/2016	Liu	
		US-			
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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Richard Douglas Shoop/Brian Flick
Attorney Docket Number:	13211-713.302

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	26323169
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	12-JUL-2016
Filing Date:	28-OCT-2015
Time Stamp:	13:14:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$180
RAM confirmation Number	071216INTEFSW00011644504050
Deposit Account	504050
Authorized User	Richard Shoop
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_7-12-2016.pdf	365697 f85211113c5a49c4ef01cad57a30c687e5b83592	yes	5
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	5	
Warnings:					
Information:					
2	Foreign Reference	WO2015149647A1wEngAbs.pdf	4126062 5befb950204f07116668f0505bde16b475a60b4c	no	30
Warnings:					
Information:					
3	Foreign Reference	WO2015168828A1wEngAbs.pdf	3569086 5ee87f51ce7ac3a070eabc7220a3d17100792211	no	30
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30800 6b9d6c80587e3746701832362f79779318775f36	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	8091645		

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CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on 7-12-2016.

Brian Flak
Name

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

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  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☐ **4).** Before the mailing of a first Office Action after filing a request for continued examination under § 1.114.
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

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☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☐ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☒ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☐ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☐ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☒ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☒ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s): 639 and 640

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.

☒ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $180.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: 7/12/16

By: _____

Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
14/925,961	10/28/2015	PAX Labs, Inc.	13211-713.302	23682

Acknowledgement of Change to Small Entity Status

The entity status change request below filed through Private PAIR on 08/22/2016 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant asserting small entity status. See 37 CFR 1.27.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Richard D. Shoop/
Name:	Richard D. Shoop
Registration Number:	45763

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on September 12, 2016.
/Mary Buggie/ 9/12/2016
Mary Buggie Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	14/925,961	Confirmation No.	: 1528
First Named Inventor	:	Adam BOWEN		
Filing Date	:	October 28, 2015		
Art Unit	:	1747		
Examiner	:	Mayes, Dionne Walls		
Title	:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Customer No.	:	66854		

Mail Stop 16
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REFUND UNDER 37 C.F.R. § 1.28

On June 22, 2016 and July 12, 2016, Applicants electronically filed Information Disclosure Statements via the Electronic Filing System (EFS). The undiscounted fees of $180 were paid via Deposit Account No. 50-4050. **Applicants hereby assert small entity status**, as shown in the copy of the Change Entity Status electronically submitted on August 22, 2016. Therefore, Applicants request a refund of $180 to Deposit Account No. 50-4050.

ITEMIZATION			
Fee Description	**Undiscounted Entity Amount Previously Paid**	**Current Small Entity Fees**	**Refund Requested**
Information Disclosure Statement	$180 on June 22, 2016	$90	$90
Information Disclosure Statement	$180 on July 12, 2016	$90	$90
Total Refund Requested to Deposit Account No. 50-4050:			**$180**

SG Docket No.: 13211-713.302

If it is determined that a telephone conference would expedite the processing of this Request, please contact the undersigned at the number given below.

Respectfully submitted,



Date: September 12, 2016

Richard D. Shoop
Reg. No. 45,763

SHAY GLENN LLP
2755 CAMPUS DRIVE, SUITE 210
SAN MATEO, CA 94403
TELEPHONE: 650.212.1700
FACSIMILE: 650.212.7562

Change Entity Status - Confirmation

Request ID	23682
Timestamp	Aug 22, 2016 8:51:57 PM EST
Status	Submitted

The Entity Status of the application has been successfully changed

Application Number	14/925,961
Attorney Docket Number	13211-713.302
Title	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
Updated Entity Status	Small
Micro certification statement	N/A

☑ I certify, in accordance with 37 CFR 1.4(d)(4):

◉ I am an attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Filed By	Richard D. Shoop
Registration Number	45763

Signatures

Signature	Name
/Richard D. Shoop/	Richard D. Shoop

Point of Contact Info

Name	Richard D. Shoop
Telephone	650-287-2164
Email	rick@shayglenn.com

Electronic Acknowledgement Receipt

EFS ID:	26900598
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Mary Buggie
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	12-SEP-2016
Filing Date:	28-OCT-2015
Time Stamp:	17:42:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Refund Request	13211-713-302_RequestRefund.pdf	83826 ec2fad555d79c3dee01bd6a02567e7edddf8a621	no	3

Warnings:

Information:	
Total Files Size (in bytes):	83826

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

USPTO
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DIVISION

2016 SEP 12 AM 9:14

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8 I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on September 12, 2016.	
/Mary Buggie/	9/12/2016
Mary Buggie	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 14/925,961	Confirmation No.	: 1528
First Named Inventor	: Adam BOWEN		
Filing Date	: October 28, 2015		
Art Unit	: 1747		
Examiner	: Mayes, Dionne Walls		
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Customer No.	: 66854		

Mail Stop 16
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REFUND UNDER 37 C.F.R. § 1.28

On June 22, 2016 and July 12, 2016, Applicants electronically filed Information Disclosure Statements via the Electronic Filing System (EFS). The undiscounted fees of $180 were paid via Deposit Account No. 50-4050. **Applicants hereby assert small entity status**, as shown in the copy of the Change Entity Status electronically submitted on August 22, 2016. Therefore, Applicants request a refund of $180 to Deposit Account No. 50-4050.

ITEMIZATION			
Fee Description	**Undiscounted Entity Amount Previously Paid**	**Current Small Entity Fees**	**Refund Requested**
Information Disclosure Statement	$180 on June 22, 2016	$90	$90
Information Disclosure Statement	$180 on July 12, 2016	$90	$90
Total Refund Requested to Deposit Account No. 50-4050:			**$180**

SG Docket No.: 13211-713.302

If it is determined that a telephone conference would expedite the processing of this Request, please contact the undersigned at the number given below.

Respectfully submitted,



Date: September 12, 2016

Richard D. Shoop
Reg. No. 45,763

SHAY GLENN LLP
2755 CAMPUS DRIVE, SUITE 210
SAN MATEO, CA 94403
TELEPHONE: 650.212.1700
FACSIMILE: 650.212.7562

Electronic Acknowledgement Receipt

EFS ID:	26323169
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF 09/20/2016 SSANDARA 00000001 504050 14925961 01 FC:2806 90.00 DA 09/20/2016 SSANDARA 00000002 504050 14925961 01 FC:2806 90.00 DA
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	12-JUL-2016
Filing Date:	28-OCT-2015
Time Stamp:	13:14:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$180
RAM confirmation Number	071216INTEFSW00011644504050
Deposit Account	504050
Authorized User	Richard Shoop

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Adjustment date: 09/20/2016 SSANDARA
06/23/2016 INTEFSW 00002360 504050 14925961
01 FC:1806 180.00 CR

Adjustment Date: 09/20/2016 SSANDARA
07/12/2016 INTEFSW 00011644 504050 14925961
01 FC:1806 180.00 CR
Adjustment date: 09/20/2016 SSANDARA

PTO/SB/30 (07-14)
Approved for use through 07/31/2016 OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam BOWEN
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not compy with the requirements of 35 U.S.C 371, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO on page 2.)

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☑ Other Certificate & Request for Prioritized Examination

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 50-4050.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☑ Other Track 1 Fee; Processing fee

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Richard D. Shoop/	Date	September 16, 2016
Name (Print/Type)	Richard D. Shoop	Registration No.	45,763

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature	/Mary Buggie/		
Name (Print/Type)	Mary Buggie via EFS	Date	September 16, 2016

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Adam BOWEN	Nonprovisional Application Number (if known):	14/925,961
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	Date September 16, 2016
Name (Print/Typed) Richard D. Shoop	Practitioner Registration Number 45,763

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on September 16, 2016.
/Mary Buggie/ 9/16/2016
Mary Buggie Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	14/925,961	Confirmation No.	: 1528
First Named Inventor:	:	Adam BOWEN		
Filing Date	:	October 28, 2015		
Art Unit	:	1747		
Examiner	:	Mayes, Dionne Walls		
Title	:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Customer No.	:	66854		

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.114

This communication is in response to the final Office Action dated June 16, 2016, for which a response is due September 16, 2016. Thus, this response is timely filed. A Request for Continued Examination (RCE) is filed herewith. Also filed herewith is a Certification and Request for Prioritized Examination.

The Commissioner is authorized to charge any fees to make this filing timely to Deposit Account No. 50-4050.

Amendments to the Claims are shown in the listing of claims that begins on page 2.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette, the method comprising:

deploying an electronic cigarette comprising a liquid solution consisting essentially of: a nicotine lactate salt formulation that includes nicotine, a ~~carboxylic~~ lactic acid, [[and]] a biologically acceptable liquid carrier, and at least one flavorant wherein:

a. the nicotine concentration is from about [[0.5%]] 4% (w/w) to about [[20%]] 12% (w/w);

b. the nicotine is protonated;

c. the biologically acceptable liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% glycerol;

d. the lactic acid concentration is sufficient to protonate most of the nicotine; and

resistively heating at least a portion of the liquid solution ~~nicotine salt formulation~~ between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine,

wherein inhalation of the aerosol into a user's lungs at a rate of 10 puffs over a period of about [[5]]3 minutes from a first puff ~~at a rate of about one inhalation per 30 seconds~~ results in an increase in heart rate that peaks within 3 minutes from the first puff when measured for 10 minutes from the start of puffing ~~a nicotine plasma Tmax from about 3 min to about 8 min, and further~~

~~wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength~~.

2. (Cancelled)

3. (Cancelled)

4. (Original) The method of claim 1, wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

5. (Currently amended) The method of claim 1, wherein a molar ratio of nicotine to ~~carboxylic~~ lactic acid is between 1:1 and 1:3.

6. (Cancelled)

7. (Original) The method of claim 1, wherein the nicotine concentration is about 4.5%.

8. (Cancelled)

9. (Original) The method of claim 1, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

10. (Currently amended) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising:

deploying an electronic cigarette comprising a liquid solution consisting essentially of a nicotine lactate salt formulation that includes nicotine, a ~~carboxylic acid comprising~~ lactic acid, ~~pyruvic acid, salicylic acid, sorbic acid, lauric acid or benzoic acid,~~ at least one flavorant, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about [[0.5%]] 4% (w/w) to about [[20%]] 12% (w/w);
b. the nicotine is protonated;
c. the biologically acceptable liquid carrier comprises propylene glycol and glycerol;

d. the lactic acid concentration is sufficient to protonate most of the nicotine; and

resistively heating at least a portion of the ~~nicotine salt formulation~~ liquid solution between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine,

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min, and further

wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength.

11. (Cancelled)

12. (Original) The method of claim 10, wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

13. (Currently amended) The method of claim 10, wherein a molar ratio of nicotine to ~~carboxylic~~ lactic acid is between 1:1 and 1:3.

14. (Cancelled)

15. (Original) The method of claim 10, wherein the nicotine concentration is about 4.5%.

16. (Cancelled)

17. (Original) The method of claim 10, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

18. (Currently amended) A method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco, the method comprising:

deploying an electronic cigarette comprising a nicotine lactate salt formulation that includes nicotine, lactic acid, and a biologically acceptable liquid carrier, wherein:

a. the nicotine concentration is from about [[0.5%]] 4% (w/w) to about [[20%]] 12% (w/w);

b. the nicotine formulation comprises protonated nicotine;

c. the ~~nicotine salt formulation comprises nicotine lactate~~ lactic acid concentration is sufficient to protonate most of the nicotine;

d. the biologically acceptable liquid carrier comprises propylene glycol and glycerol; and

resistively heating at least a portion of the nicotine salt formulation between about 100°C and about 300°C to generate an inhalable aerosol comprising nicotine lactate,

wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma Tmax from about 3 min to about 8 min, and further

wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength.

19. (Currently amended) The method of claim 18, wherein a molar ratio of nicotine to ~~organic~~ lactic acid is between 1:1 and 1:3.

20. (Original) The method of claim 18, wherein the nicotine salt formulation further comprises at least one flavorant.

21. (Original) The method of claim 18, wherein the nicotine concentration is about 4.5%.

22. (Cancelled)

23. (Original) The method of claim 18, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

REMARKS

Claims 1-7, 9-15, 17-21 and 23 were pending in this application. By this response, claims 1, 5, 10, 13, 18 and 19 have been amended. No new claims have been added, and claims 2, 3, 6, 11 and 14 have been cancelled. The amendments to the claims and the new claims are supported throughout the specification, and particularly in paragraphs [0121]-[0122], [0130]-[0131], [0136]-[0137], [0181]-[0182], [0252] and [0267] and FIGS. 1 and 2. No new matter has been added. Cancellation or amendment of the claims is not to be considered a dedication to the public of any subject matter.

Thus, claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23 are currently under consideration. Reconsideration of these claims is requested in view of the amendments and the following remarks.

INFORMATION DISCLOSURE STATEMENT

Applicants note with thanks that the Examiner has considered all references submitted in Information Disclosure Statements dated 4/20/2016; 5/12/2016; and 6/1/2016. Supplemental Information Disclosure Statements were filed on 6/22/2016 and 7/12/2016. A Supplemental Information Disclosure Statement is filed herewith. It is respectfully requested that these Supplemental Information Disclosure Statements be considered and the PTO Forms 1449/SB08 be initialed and returned with the next Action.

DOUBLE PATENTING

Claims 1-7, 9-15, 17-21 and 23

Claims 1-7, 9-15, 17-21 and 23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 9,215,895 ("Bowen '895") in view of U.S. Patent Application Publication No. 2013/0255702 to Griffith, Jr. et al. ("Griffith").

The Applicants respectfully disagree.

The pending claims (claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23) have been amended herein, and recite features not present or suggested by the claims of Bowen '895. Thus, Applicants respectfully request withdrawal of the non-statutory double patenting rejection of the claims, and allowance of all of the pending claims.

Claims 1-2, 4-7, 9-15, 17-21 and 23

Claims 1-2, 4-7, 9-15, 17-21 and 23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 6-10 and 12 of co-pending Application No. 14/925,968.

The Applicants respectfully disagree.

The pending claims (claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23) have been amended herein, and recite features not present or suggested by the claims of co-pending Application No. 14/925,968. Thus, Applicants respectfully request withdrawal of the non-statutory double patenting rejection of the claims, and allowance of all of the pending claims.

Claim 3

Claim 3 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 6-10 and 12 of co-pending Application No. 14/925,968 in view of U.S. Patent Application Publication No. 2014/0261474 to Gonda ("Gonda").

The Applicants respectfully disagree.

The pending claims (claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23) have been amended herein, and recite features not present or suggested by the claims of co-pending Application No. 14/925,968, including in combination with Gonda. Thus, Applicants respectfully request withdrawal of the non-statutory double patenting rejection of the claims, and allowance of all of the pending claims.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-7, 9-15, 17-21 and 23

Claims 1-7, 9-15, 17-21 and 23 currently stand rejected under 35 U.S.C. § 103 as being unpatentable over Griffith, as evidenced by www.e-cigarette-forum.corn's PG-VG-PEG Discussion Posting ("the PG-VG-PEG Internet Posting") in view of Gonda and U.S. Patent Application Publication No. 2009/0151717 to Bowen et al. ("Bowen '717"). Applicants further note that Examiner Mayes has indicated (in a telephone interview of July 12, 2016 regarding a separate application, App. no. 14/925,968) that a second reference, U.S. Patent No. 8,881,737 to Collett et al. ("Collett") may be used in place of Griffith; in order to expedite prosecution, this reference is also discussed herein.

The Applicants respectfully disagree.

By this response, claims 1-7, 9-15, 17-21 and 23 have been amended (and claims 2, 3, 6, 11 and 14 have been cancelled). The combination of Griffith, Gonda and Bowen '717 or alternatively, the combination of Collett, Gonda and Bowen '717 does not suggest all of the features recited in the claims. In particular, neither of these combinations suggests: (1) a liquid solution consisting essentially of: a nicotine lactate salt formulation that includes nicotine, a lactic acid, a biologically acceptable liquid carrier, and at least one flavorant... wherein the biologically acceptable liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% glycerol; (2) wherein the lactic acid concentration is sufficient to protonate most of the nicotine; and/or (3) wherein inhalation of the aerosol into a user's lungs at a rate of 10 puffs over a period of about 3 minutes from a first puff results in an increase in heart rate that peaks within 3 minutes from the first puff when measured for 10 minutes from the start of puffing.

First, the combination of Griffith, Gonda and Bowen '717 does not suggest a liquid solution consisting essentially of: a nicotine lactate salt formulation that includes nicotine, a lactic acid, a biologically acceptable liquid carrier, and at least one flavorant... wherein the biologically acceptable liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% glycerol. Similarly, the combination of Collett, Gonda and Bowen '717 does not suggest

this element. Both Griffith and Collette mention solutions including solutions in which the propylene glycol is present in a small amount compared to the glycerol (e.g., "glycerol can be present in an amount of about 70% to about 90%" and "propylene glycol can be present in an amount of about 1% to about 10% by weight", see Griffith paragraphs [87]-[88] or Collett, col. 19, lines 20-43). Gonda mentions only that "Glycerin and glycols have been also used in inhalation products" and similarly, Bowen '717 mentions only that "Propylene glycol (PG), glycerin, or a combination of both can be used". None of these references, alone or in combination, suggest a liquid solution consisting essentially of: a nicotine lactate salt formulation that includes nicotine, a lactic acid, a biologically acceptable liquid carrier, and at least one flavorant... wherein the biologically acceptable liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% glycerol, as recited by claims 1, 4-5, 7, and 9.

Second, none of these references, alone or in combination, suggest such a liquid solution *wherein the lactic acid concentration is sufficient to protonate most of the nicotine.* Only Griffith and Collett mention lactic acid, and both describe only the use of lactic acid as a flavorant, typically in combination with other acids, including levulinic acid and pyruvic acid. For example, paragraph [0088] of Griffith reads:

> "...Organic acids particularly may [be] incorporated into the aerosol precursor to affect the flavor, sensation, or organoleptic properties of medicaments, such as nicotine, that may be combined with the aerosol precursor. For example, organic acids, such as levulinic acid, lactic acid, and pyruvic acid, may be included in the aerosol precursor with nicotine in amounts up to being equimolar (based on total organic acid content) with the nicotine. Any combination of organic acids can be used. For example, *the aerosol precursor can include about 0.1 to about 0.5 moles of levulinic acid per one mole of nicotine, about 0.1 to about 0.5 moles of pyruvic acid per one mole of nicotine, and about 0.1 to about 0.5 moles of lactic acid per one mole of nicotine, up to a concentration wherein the total amount of organic acid present is equimolar to the total amount of nicotine present in the aerosol precursor.*"

Griffith (and in identical language in Collett, col. 18, lines 52-68) states that the total amount of lactic acid in the solution is limited to 0.5 moles of lactic acid per one mole of nicotine. Although the total amount of acid may be equimolar with nicotine, only a maximum of 0.5 moles per mol of nicotine is lactic acid in that case, and the difference must be either levulinic acid or pyruvic acid. Limiting the amount of a particular organic acid in a nicotine

formulation is typical when these acids are used simply as flavorants. Thus, neither Griffith nor Collett suggests a liquid solution having a *lactic acid concentration is sufficient to protonate most of the nicotine*. At best, Griffith and Collett limit the amount of lactic acid to an amount sufficient to protonate only half of the nicotine. This deficiency cannot be cured by Gonda or Bowen '717, which do not mention lactic acid.

As described in the applicants specification (e.g., paragraph [130]), the protonation of nicotine by the lactic acid is important to seeing the effect. Not every acid is equivalent, despite protonation of the nicotine, which was unexpected ("[u]nexpectedly, different nicotine salt formulations produced varying degrees of satisfaction in an individual... a nicotine salt may be best performing when it is at its optional extend of protonation..."). Further, when there is not enough lactic acid to associate with all nicotine molecules, the "free base nicotine left unprotonated in the formulation may reduce the satisfaction the formulation provides."

Thus, none of these references, alone or in combination, suggest a liquid solution *wherein the lactic acid concentration is sufficient to protonate most of the nicotine*, as recited by claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23.

Finally, none of these references, alone or in combination, suggest a method of vaporizing a liquid solution in which inhalation of the aerosol into a user's lungs at a rate of 10 puffs over a period of about 3 minutes from a first puff results in an increase in heart rate that peaks within 3 minutes from the first puff when measured for 10 minutes from the start of puffing.

None of the cited references, including Griffith, Collett, Gonda or Bowen '717 suggest or even mention this feature. Although Gonda mentions only that it would be *desirable* to mimic the effect of inhaling smoke form a traditional cigarette, neither Gonda nor any of Griffith, Collett or Bowen '717 suggests a method (e.g., using a formulation as recited in the instant claims) including this element, or provide any suggestion for a method of vaporizing a liquid nicotine solution in which this effect may be achieved.

For example, Griffith, or alternatively Collett, describes a nicotine formulation in which an organic acid (such as lactic acid) is used as a flavorant; neither reference suggests the recited application of a nicotine formulation including lactic acid in a particular PG/VG carrier solution to form nicotine lactate salt solution for vaporization at low temperature in which inhalation of the aerosol into a user's lungs at a rate of 10 puffs over a period of about 3 minutes from a first puff *results in an increase in heart rate that peaks within 3 minutes from the first puff when measured for 10 minutes from the start of puffing.* This feature is not inherent in all formulations of nicotine solutions, as shown in FIGS. 1 and 2 of the Applicants' specification, or even nicotine solutions including an organic acid, as not all organic acids will work. Finally, not even all nicotine solutions including lactic acid will work, as described in the Applicant's specification; the lactic acid must be present to sufficiently protonate all or nearly all of the freebase nicotine.

The final Office Action suggests only that this element "would naturally flow from the modified combination of Griffith (or, presumably, Collett), Gonda and Bowen '717 "as it meets all of the structural limitations". This is incorrect. The effect of the formulation recited in the claims is to mimic the increased heart rate of a traditional cigarette; this effect would not be inherent in every combination of nicotine and even lactic acid, particularly the lactic acid suggested by Griffith and/or Collett (e.g., 0.5 molar per 1 mol of nicotine). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 177 (Fed. Cir. 2002) (quoting *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991)); see also *In re Robertson,* 169 F.3d 743,745 (Fed. Cir. 1999).

For at least the reasons discussed above, the combination of Griffith, as evidenced by the PG-VG-PEG Internet Posting in view of Gonda Bowen '717 does not suggest all of the features recited in claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23. Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejection of claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23 and allowance of all of the pending claims.

CONCLUSION

In light of the remarks set forth above, Applicants respectfully request the Examiner expedite the prosecution of this patent application to issuance. If it is determined that a telephone conference would aid in the prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 287-2164.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-4050** referencing docket no. 13211-713.302. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: September 16, 2016

Richard D. Shoop
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Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Richard Douglas Shoop/Mary Buggie
Attorney Docket Number:	13211-713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
RCE- 1st Request	2801	1	600	600
		Total in USD ($)		**2670**

Electronic Acknowledgement Receipt

EFS ID:	26956943
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Mary Buggie
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	16-SEP-2016
Filing Date:	28-OCT-2015
Time Stamp:	21:20:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2670
RAM confirmation Number	6337
Deposit Account	504050
Authorized User	SHOOP, RICHARD D

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_RCE_Track1_Response_9-16-2016.pdf	740586 2260757dd186aca229e402cd4fa0e38f259f6680	yes	15

Multipart Description/PDF files in .zip description

Document Description	Start	End
Request for Continued Examination (RCE)	1	1
TrackOne Request	2	2
Amendment Submitted/Entered with Filing of CPA/RCE	3	3
Claims	4	8
Applicant Arguments/Remarks Made in an Amendment	9	15

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	34444 126a749d24ade757bea1af8572e67e48e33f65cb	no	2

Warnings:

Information:

Total Files Size (in bytes):	775030

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	680	US- 5,240,012	8/31/1993	Ehrman et al.	
	666	US- 8,809,261	8/19/2014	Elsohly et al.	
	669	US- 8,881,737	11/11/2014	Collett et al.	
	667	US- 2015/0038567	2/5/2015	Herkenroth et al.	
	580	US- 2016/0174611**	6/23/2016	Monsees et al.	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	668	EP2152313B1	9/3/2014	McNeil AB		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	587	MONSEES et al.; U.S. Pat. Appl. # 15/165,954 entitled "Devices for vaporization of a substance," filed 5/26/2016	
	588	MONSEES et al.; U.S. Pat. Appl. # 15/166,001 entitled "Electronic vaporization device," filed 5/26/2016	
	589	MONSEES et al.; U.S. Pat. Appl. # 15/165,972 entitled "Portable devices for generating an inhalable vapor," filed 5/26/2016	
	665	BOWEN et al.; U.S. Pat Appl. # 15/101,303 entitled "Nicotine liquid formulations for aerosol devices and methods thereof," filed 6/2/2016	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	26955758
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop
Filer Authorized By:	
Attorney Docket Number:	13211-713.302
Receipt Date:	16-SEP-2016
Filing Date:	28-OCT-2015
Time Stamp:	21:22:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_9-16-2016.pdf	350733 54c68805752f126cefa46bc607e463e5082a4bdc	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	5

Warnings:					
Information:					
2	Foreign Reference	EP2152313B.pdf	8630620 b964bc79855e9ccb2a5804467fe593d8436850d8	no	28
Warnings:					
Information:					
		Total Files Size (in bytes):	8981353		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on September 16, 2016.

/Mary Buggie/
Mary Buggie

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☒ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☒ **4).** With or after the filing of a request for continued examination (RCE) under § 1.114 but before the mailing date of a first Office Action (after RCE).
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☐ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☒ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **3).** A copy of each application specification is not submitted because the application is stored in the IFW.

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☐ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☒ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☐ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☐ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s):

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. Cite no(s):

☐ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement. Cite no(s):

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: September 16, 2016

By: _____
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/16/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 15	Minus	** 23	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
ROLITA WIMBUSH

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	684	US- 5,031,646	7/16/1991	Lippiello et al.	
	685	US- 5,133,368	7/28/1992	Neumann et al.	
	488	US- 8,511,318	8/20/2013	Hon	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	687	EP0283672B1	9/22/1993	R J Reynolds Tobacco		
	688	EP2319934B1	9/2/2015	Stichting Dienst		
	689	WO2007/078273A1	7/12/2007	Augite Inc.		
	690	WO2015/009862A2	1/22/2015	Altria Client Services		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	683	BURCH et al.; Effect of pH on nicotine absorption and side effects produced by aerosolized nicotine; Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung; 6(1); pp. 45-52; 1993	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	26970208
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	19-SEP-2016
Filing Date:	28-OCT-2015
Time Stamp:	18:08:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_9-19-2016.pdf	337080 bc1d3ca5770f4ac21869ba2dcb99adbbb66bc3c6	yes	5

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	5	
Warnings:					
Information:					
2	Foreign Reference	EP283672B1.pdf	3867930 7f9eb1f19eeaf5644df8592a26ad3a644ad2e54a	no	23
Warnings:					
Information:					
3	Foreign Reference	EP2319934B1.pdf	22795970 fc0974973589815821 9f09eea56f7ed742142b35	no	103
Warnings:					
Information:					
4	Foreign Reference	WO2007078273A1.pdf	399703 6a9fb5cbeb0bcf9e4930704c0b6aba049a2b71cd	no	13
Warnings:					
Information:					
5	Foreign Reference	WO2015009862A2.pdf	1682368 6e44adca6a616c91976e43fe6417eb350b192f6f	no	29
Warnings:					
Information:					
6	Non Patent Literature	Burch_et_al-EffectOfpHOnNicotineAbsorption.pdf	2286776 75e63872d4e2d57f082dc3da685332142911f433	no	8
Warnings:					
Information:					
		Total Files Size (in bytes):	31369827		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on September 19, 2016.

/Brian Flick/
Brian Flick

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☒ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☒ **4).** With or after the filing of a request for continued examination (RCE) under § 1.114 but before the mailing date of a first Office Action (after RCE).
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☐ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☒ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☒ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☐ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☐ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s):

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. Cite no(s):

☐ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement. Cite no(s):

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: September 19, 2016

By: _____
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

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SEP 27 2016
OFFICE OF PETITIONS

SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO CA 94403

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/925,961

1. THE REQUEST FILED September 16, 2016 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	714	US- 2014/0190501	7/10/2014	Liu	
	713	US- 2015/0157054	6/11/2015	Liu	
		US-			
		US-			
		US-			
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		US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	712	EP3024343A2(WO2015/013327)	1/29/2015	Altria Client Serv. Inc.		
	716	WO 03/103387A2	12/18/2003	S.C. Johnson & Son Inc.		
	715	WO2014/159982A1	10/2/2014	R.J. Reynolds Tobacco Co.		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	703	MONSEES et al.; U.S. Pat. Appl. # 15/257,748 entitled "Cartridge for use with a vaporizer device," filed 9/6/2016	
	704	MONSEES et al.; U.S. Pat. Appl. # 15/257,760 entitled "Vaporizer apparatus," filed 9/6/2016	
	705	MONSEES et al.; U.S. Pat. Appl. # 15/257,768 entitled "Vaporizer apparatus," filed 9/6/2016	
	706	MONSEES et al.; U.S. Pat. Appl. # 15/261,823 entitled "Low temperature electronic vaporization device and methods," filed 9/9/2016	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	27331239
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	26-OCT-2016
Filing Date:	28-OCT-2015
Time Stamp:	16:24:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing__10-26-2016.pdf	347224 34c8f3e3d8221c5667bc7d15fee6af3f5ad2221c	yes	5

	Multipart Description/PDF files in .zip description			
	Document Description	Start	End	
	Transmittal Letter	1	3	
	Information Disclosure Statement (IDS) Form (SB08)	4	5	
Warnings:				
Information:				
2	Foreign Reference	EP3024343_WO2015013327A2.pdf	1551941 38b90b391e5bac610c8ecc13d2064b30bc1cb7b2	no	29
Warnings:				
Information:				
3	Foreign Reference	WO2003103387A2.pdf	2281687 5d69a17bf4b6e3d684a5bc376351096a89b6ca1f	no	57
Warnings:				
Information:				
4	Foreign Reference	WO2014159982A1.pdf	3297006 fd807d68a49865ed1945bd6c5b092fb648c255f7	no	52
Warnings:				
Information:				
		Total Files Size (in bytes):	7477858		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on October 26, 2016.

/Brian Flick/
Brian Flick

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☒ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☒ **4).** With or after the filing of a request for continued examination (RCE) under § 1.114 but before the mailing date of a first Office Action (after RCE).
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☐ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **3).** A copy of each application specification is not submitted because the application is stored in the IFW.

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☐ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☒ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☐ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☐ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s):

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. Cite no(s):

☐ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement. Cite no(s):

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: October 26, 2016

By: /Richard D. Shoop/
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	14/925,961
	Filing Date	October 28, 2015
	First Named Inventor	Adam BOWEN
	Art Unit	1747
	Examiner Name	Mayes, Dionne Walls
	Practitioner Docket No.	13211-713.302

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I. To authorize permission for Internet Communications.

☑ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 45,763.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Richard D. Shoop/ — Signature

November 11, 2016 — Date

Richard D. Shoop — Typed or printed name

(650) 287-2164 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	27491935
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Mary Buggie
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	11-NOV-2016
Filing Date:	28-OCT-2015
Time Stamp:	21:01:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Internet Communications Authorized	13211-713-302_Authorization_Interent_Communications.pdf	82171 ab39aa6aab6e5f5713ba5af14d1612630d19c832	no	2

Warnings:

Information:	
Total Files Size (in bytes):	82171

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08A (04-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	718	US- 6,603,924	8/5/2003	Brown et al.	
	719	US- 2013/0298905	11/14/2013	Levin et al.	
		US-			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	27634341
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	29-NOV-2016
Filing Date:	28-OCT-2015
Time Stamp:	12:56:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filling_AfterRCE_11-29-2016.pdf	273883 5191437319fd17512c7ccca4f4891829f0e13ec0	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	273883	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on November 29, 2016.

/Brian Flick/
Brian Flick

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☒ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☒ **4).** With or after the filing of a request for continued examination (RCE) under § 1.114 but before the mailing date of a first Office Action (after RCE).
  - ☒ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☐ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☐ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☐ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☐ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☐ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s):

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.

☒ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

STATEMENT UNDER 37 CFR § 1.704(d)

☒ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: November 29, 2016

By: /Richard D. Shoop/
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

Electronic Acknowledgement Receipt

EFS ID:	27805406
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Richard Douglas Shoop/Brian Flick
Filer Authorized By:	Richard Douglas Shoop
Attorney Docket Number:	13211-713.302
Receipt Date:	15-DEC-2016
Filing Date:	28-OCT-2015
Time Stamp:	13:58:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13211-713-302_IDS_Filing_SupplIDS_12-15-2016.pdf	774519 73f806640f176ab8761dc8827c3b54d381b4d65f	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	9

Warnings:					
Information:					
2	Foreign Reference	EP2856893A1.pdf	3797855 9e9e535e97febc0832fb271b2d51ddddc5024ca6	no	17
Warnings:					
Information:					
3	Foreign Reference	EP2908675A1.pdf	2851612 18617c20f28d55beeb6be340e76a7896f5f4abb3	no	26
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Information:					
4	Foreign Reference	EP2915443A1.pdf	3131188 edc6785026730a393e33a42f16b2c43177494d5d	no	11
Warnings:					
Information:					
5	Foreign Reference	EP3062646-WO2015066136.pdf	1920287 78ca85cae85f5ab9b5d8561b19d31e643b3dc74e	no	37
Warnings:					
Information:					
6	Foreign Reference	EP3065581-WO2015068044.pdf	729371 db68ce2ef9dae6813f00c055614d9cb7896df474	no	15
Warnings:					
Information:					
7	Foreign Reference	EP3068244-WO2015073975.pdf	797485 6548a386aa02b67a4008be4094745bac81b4382d	no	16
Warnings:					

Information:					
8	Foreign Reference	WO2004080216A1.pdf	749955 a28bfe15199fdd2375c7ddd887e7bbf63036e369	no	18
Warnings:					
Information:					
9	Foreign Reference	WO2008077271A1.pdf	827852 05b9db2349cb9260c6d037bf6a571ccf0e41be68	no	21
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10	Foreign Reference	WO2012120487A2.pdf	3158287 ede9fa584af52f2d97df4cbbdaa0708545f1ef31	no	79
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11	Foreign Reference	WO2013089551A1.pdf	1094113 33c2a25276d66ea2bff596b18c46f1f606c609d6	no	36
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12	Foreign Reference	WO2014040915A1.pdf	781426 b4fca67d78087fa18028b2fd3d734bee21816da5	no	20
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Information:					
13	Foreign Reference	WO2014101734A1.pdf	728234 c1d700ac238628f508823ccef0ecb737fb652c26	no	18
Warnings:					
Information:					
14	Foreign Reference	WO2014150704A2.pdf	828026 394f7aaf1d89f7d22a7e415029137a7bba8cf56a	no	19
Warnings:					
Information:					

15	Foreign Reference	WO2014205263A1.pdf	1056949 6db12fe466b36da318f6c948f7acc69fe1c2e dae	no	35
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Information:					
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Warnings:					
Information:					
17	Foreign Reference	WO2015058387A1.pdf	931263 341e193f14ba9602ebfd6abe761969c79c4 4fc8b	no	23
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Information:					
18	Foreign Reference	WO2015063126A1.pdf	1411710 e0ef6164425104 31ce0ffff8802d5ad5f81cb 1c2	no	39
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19	Foreign Reference	WO2015089711A1.pdf	1209458 7e7365e68bb5bc9fe94eafda5fccd512f93a 6dcb	no	27
Warnings:					
Information:					
20	Foreign Reference	WO2015109616A1.pdf	667054 d3aafca22d01992c54b1a974c2f1d23659d1 4517	no	18
Warnings:					
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21	Non Patent Literature	Bradley_et_al_ElectronicCigare tteAerosol_2012.pdf	5098764 f8b6e76ddde2d5e4306ba1de5d0ec91180c 45a66	no	10
Warnings:					
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Warnings:					
Information:					
23	Non Patent Literature	Caponnetto_et_al_SuccessfulSmokingCessation_2011.pdf	2503183 756b138489ce9750e025de03abdef56f0d476156	no	6
Warnings:					
Information:					
24	Non Patent Literature	Farsalinos_et_al_ElectronicCigarettesDoNotDamage_2012.pdf	60065 60439509eb9ffb3386f6b00a5c61f547def2e017	no	4
Warnings:					
Information:					
25	Non Patent Literature	Hurt_et_al_TreatingTobaccoDependence_2009.pdf	13685927 a8e5b848e6aac6a987c0fc18291c770e1fd3bc6d	no	13
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Information:					
26	Non Patent Literature	Vansickel_et_al_ElectronicCigarettesEffective_2013.pdf	1994756 6e5877e04f3be9d23e60ca8831e34168e1faf8e8	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	56039650		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8
I hereby certify that this correspondence is being transmitted to the USPTO via EFS-Web on December 15, 2016.

/Brian Flick/
Brian Flick

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 14/925,961	Confirmation No.: 1528
First Named Inventor	: Adam Bowen	
Filed	: October 28, 2015	
Art Unit	: 1747	
Examiner	: Mayes, Dionne Walls	
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Customer No.	: 66854	

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97 & § 1.98

Sir:

In accordance with 37 CFR § 1.97-1.98, applicants hereby submit an Information Disclosure Statement, including attached forms(s) PTO/SB/08. A copy of each reference is being submitted herewith, along with a concise explanation in English for those publications in a foreign language.

Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application. Applicants further request that the Examiner initial and return a copy of the attached form(s) PTO/SB/08 in accordance with MPEP §609.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and /or to prove that this information may not be enabling for the teachings purportedly offered.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in 37 CFR §1.56.

FILING OF INFORMATION DISCLOSURE STATEMENT

☒ **37 CFR §1.97(b)**

This statement is being submitted under 37 CFR §1.97(b) because the IDS is being filed:

- ☐ **1).** Within 3 months of the application filing date, or
- ☐ **2).** Within 3 months of entry of a national stage as set forth in § 1.491, or
- ☐ **3).** Before the mail date of a first Office Action on the merits, or
  - ☐ **3a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below
- ☒ **4).** With or after the filing of a request for continued examination (RCE) under § 1.114 but before the mailing date of a first Office Action (after RCE).
  - ☐ **4a).** Certifications as specified in § 1.97(e) and § 1.704(d) are provided below

☐ **37 CFR § 1.97(c)**

This statement is being filed after the latest of:

☐ **1).** Three months beyond the filing date of a national application, or

☐ **2).** Three months beyond the date of entry of the national stage as set forth in § 1.491 in an international application, or

☐ **3).** The mailing date of a first Office Action on the merits, but before the mailing date of the earlier of a final Office Action under § 1.113 or a Notice of Allowance under § 1.311, and then either:

☐ **A).** A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this statement.

or

☐ **B).** A certification as specified in § 1.97(e) is provided below; thus no fee is required.

☐ **37 CFR § 1.97(d)**

This statement is being filed after the mailing date of a Final Office action, a Notice of Allowance under §1.311, or an action that otherwise closes prosecution, but on or before payment of the issue fee, and then:

A). A fee of $180 ($90 for small entity) as set forth in § 1.17(p) is authorized below, enclosed, or payment is included with other papers filed together with this statement

--AND--

B). A certification as specified in § 1.97(e) is included below.

CONTENT OF INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.98

☒ **37 CFR §1.98 (a)(2)(ii), U.S. patents or patent application publication(s) cited**

☒ **1).** Since not requested by the Office, U.S. patents and U.S. patent application publications are not included.

☐ **2).** At the request of the Office, a copy of the following U.S. patent or patent application publication is attached:

☐ **3).** Items identified by a double asterisk (**) on the SB08A are *commonly-owned U.S. patents and U.S. patent application publications.

☐ **37 CFR §1.98 (a)(2)(iii) and (d), *Commonly-owned, unpublished U.S. applications cited**

☐ **1).** A copy of each application specification including the claim(s), and any drawing, or that portion of the application that caused it to be listed, is attached.

☐ **2).** A copy of each application specification is not submitted because the specification was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☐ **3).** A copy of each application specification is not submitted because the application is stored in the IFW. Cite no(s):

Applicant(s) assume the Examiner has access to the file histories of these items. However, if the Examiner would like to receive copies of Office Actions in any of the commonly-owned applications, publications and/or patents identified on the attached SB08, please inform the undersigned and copies will be provided.

☒ **37 CFR §1.98 (a)(2)(iii) and (d), English language publication (other than U.S. patents, patent applications, or pending unpublished applications) cited**

☒ **1).** A legible copy of each publication or that portion which caused it to be listed is attached.

☐ **2).** A copy of each publication or that portion which caused it to be listed is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i) and (d), Foreign patent(s) in English cited**

☒ **1).** A legible copy of each foreign patent or that portion which caused it to be listed is attached.

☐ **2).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date:

☒ **37 CFR §1.98 (a)(2)(i), (a)(3)(i-ii) and 609.04(a)III, Foreign patent(s) or other foreign documents not in English cited. Either:**

☒ **1).** A legible copy of each foreign patent, each publication or that portion which caused it to be listed, is attached **--AND—**

☒ **2a).** An English language abstract or an English language copy of a foreign search report or other action by a foreign patent office is provided herewith to fulfill the requirement for a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language: Cite no(s): 416, 420, 433, 446, 450, and 452

--AND/OR--

☐ **2b).** A copy of a written, English-language translation or portion thereof is readily available and attached: Cite no(s):

--OR--

☐ **3).** A copy of each foreign patent is not submitted because the publication was previously submitted in the IDS of the following, earlier filed application relied on for an earlier effective filing date: .

STATEMENT UNDER 37 CFR § 1.97(e)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. Cite no(s):

☐ No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement. Cite no(s):

STATEMENT UNDER 37 CFR § 1.704(d)

☐ Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

FEE AUTHORIZATION

☒ The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 50-4050.

Respectfully Submitted,

Dated: December 15, 2016

By: /Richard D. Shoop/
Richard D. Shoop, Reg. No. 45,763

Shay Glenn LLP
2755 Campus Drive, Suite 210
San Mateo, CA 94403
(650) 212-1700
Customer No. 66854

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	13211-713.302	1528

66854 7590 12/20/2016

SHAY GLENN LLP
2755 CAMPUS DRIVE
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SAN MATEO, CA 94403

EXAMINER	
MAYES, DIONNE WALLS	

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
12/20/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@shayglenn.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN ET AL.	
	Examiner DIONNE W. MAYES	Art Unit 1747	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09-19-2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,4,5,7,9,10,12,13,15,17-21 and 23* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,4,5,7,9,10,12,13,15,17-21 and 23* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 19, 2016, and also the Supplemental Amendment filed on September 19, 2016, has been entered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Regarding independent claims 1, 10 and 18, Applicant has recited that "the nicotine is protonated", but further recites in the same claim that "the lactic acid concentration is sufficient to protonate **most** of the nicotine" (emphasis added); hence, it is not clear whether Applicant intends to claim that "most" of the nicotine is protonated, or "all" of the nicotine is protonated. Clarification and/or amendment is requested.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly

owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

8. Claims 1, 4-5, 7, 10, 12-13, 15, 18-21 are rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638).

Regarding independent claims 1, 10 and 18, and dependent claims 4, 7, 12, 15, 20-21, Sebastian et al discloses an electronic smoking article (i.e., electronic cigarette) that provides for delivery of aerosolized components of an aerosol precursor composition to at least one heating element which heats the aerosol precursor, preferably, to a temperature of from about 120 to about 350 degrees C (see abstract and para. [0043])(corresponding to the claimed "deploying an electronic cigarette…resistively heating…between about 100 degrees C and about 300 degrees C to generate an inhalable aerosol").

The aerosol precursor composition may include one or more medicaments, such as nicotine, which may comprise up to 10% of the weight of the aerosol precursor; and one or more flavorants, such as menthol or peppermint (see para. [0055], [0059]-[0060]) (corresponding to the claimed “at least one flavorant” (claims 1, 10 and 20)).

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor, sensation, or organoleptic properties. Organic acids, including lactic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059]). Since the nicotine and lactic acid can be provided in equimolar ratios (i.e., 1:1),

it is presumed, at this proportion, that "nicotine lactate" is thereby formed (which, inherently, means that "the nicotine is protonated"), resulting in the claimed "nicotine lactate salt formulation that includes nicotine, lactic acid".

The aerosol precursor composition may include both glycerol and propylene glycol. A non-limiting example discloses that glycerol can be present in an amount of about 70% to about 90% by weight, and the propylene glycol can be present in an amount of up to 10% (see para. [0060]-[0061]). While this latter percentage falls below the lowest range limit of the claimed propylene glycol concentration of 20%, Applicant is reminded that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40℃ and 80℃ and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100℃ and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more

recent cases applying this principle, see Merck *& Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert.denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). See MPEP 2144.05. Hence, it would have been obvious to one having ordinary skill in the art to have arrived at the claimed propylene glycol amount after determining that this glycerol/propylene glycol mixture percentage provides for superior aerosolization characteristics of the aerosol precursor (corresponding to the claimed "a biologically acceptable liquid carrier...the biologically acceptable liquid carrier comprises 20% to 50% of propylene glycol and 80% to 50% glycerol").

Further, Sebastian et al discloses that, as a non-limiting example, an aerosol precursor composition may include nicotine in an amount of about 0.1-5.0%. This would motivate one of ordinary skill to undergo routine experimentation to find the optimal amount of nicotine to add to the precursor composition and, in doing so, selected the high end of this range, i.e. 3-5%, after determining that such nicotine concentration provided for superior flavor, sensation and organoleptic properties for the user (Note: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (corresponding to the claimed "the nicotine lactate concentration is from about 4% to about 12% (w/w)"; and the "wherein the nicotine concentration is about 4.5%" recitation of claims 7, 15 and 21).

Lastly, it follows to reason, that the upon inhalation of the aerosolized vapor resulting from heating the aerosol precursor composition in the modified Sebastian et al electronic smoking article, the user would experience the claimed heart rate and nicotine plasma T_{max} upon inhaling in the claimed manner as, absent any indication to the contrary, such effects would "flow naturally" from use of said article (corresponding to the claimed "wherein inhalation of the aerosol into a user's lungs at a rate of 10 puffs over a period of about 3 minutes results in an increase in heart rate that peaks within 3 minutes when measured for 10 minutes from the start of puffing (claim 1) and the claimed "a method of delivering nicotine from an inhalable aerosol so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette…wherein inhalation of the aerosol into a user's lungs over a period of about 5 minutes at a rate of about one inhalation per 30 seconds results in a nicotine plasma from about 3 min to about 8 min, and further wherein the user may modify the amount of nicotine delivered by adjusting an inhalation strength" (claim 10, 18); the "wherein deploying results in an increase in heart rate comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco" recitation of claims 4 and 12).

Regarding claims 5, 13 and 19, as stated above, Sebastian et al discloses that its aerosol precursor can include nicotine and lactic acid provided in equimolar ratios (see para. [0059]) (corresponding to the claimed "wherein a molar ratio of nicotine to organic acid is between about 1:1 and 1:3").

9. Claims 9, 17, and 23 are rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638) in view of Gonda (US. Pat. No. 2014/0261474).

Regarding claims 9, 17, and 23, based on the disclosure of Gonda, that by decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels, it would have been obvious to one having ordinary skill in the art to have optimized the particle size of its aerosol to fall between 0.1 - 5 microns (corresponding to the claimed “wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns”).

Response to Arguments

10. Applicant’s arguments with respect to the claims have been considered but are moot in view of the new grounds for rejection, presented above, involving a new combination of prior art references, which were necessitated because of the amendments made to the claims, filed on September 19, 2016.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Rabinowitz et al (US. Pat. App. Pub. 2014/0345635)

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE W. MAYES whose telephone number is

(571)272-5836. The examiner can normally be reached on Tuesdays and Thursdays, 8:00A - 4:30P.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael H. Wilson can be reached on (571) 270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE W MAYES/
Examiner, Art Unit 1747

Notice of References Cited	Application/Control No. 14/925,961	Applicant(s)/Patent Under Reexamination BOWEN ET AL.	
	Examiner DIONNE W. MAYES	Art Unit 1747	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2014/0000638 A1	01-2014	Sebastian et al	A24F47/008	131/328
*	B	US-2014/0345635 A1	11-2014	Rabinowitz et al	A24B15/16	131/352
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
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	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	684	US- 5,031,646	7/16/1991	Lippiello et al.	
	685	US- 5,133,368	7/28/1992	Neumann et al.	
	488	US- 8,511,318	8/20/2013	Hon	
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	687	EP0283672B1	9/22/1993	R J Reynolds Tobacco		
	688	EP2319934B1	9/2/2015	Stichting Dienst		
	689	WO2007/078273A1	7/12/2007	Augite Inc.		
	690	WO2015/009862A2	1/22/2015	Altria Client Services		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	683	BURCH et al.; Effect of pH on nicotine absorption and side effects produced by aerosolized nicotine; Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung; 6(1); pp. 45-52; 1993	

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

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	714	US- 2014/0190501	7/10/2014	Liu	
	713	US- 2015/0157054	6/11/2015	Liu	
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	712	EP3024343A2(WO2015/013327)	1/29/2015	Altria Client Serv. Inc.		
	716	WO 03/103387A2	12/18/2003	S.C. Johnson & Son Inc.		
	715	WO2014/159982A1	10/2/2014	R.J. Reynolds Tobacco Co.		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

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Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	703	MONSEES et al.; U.S. Pat. Appl. # 15/257,748 entitled "Cartridge for use with a vaporizer device," filed 9/6/2016	
	704	MONSEES et al.; U.S. Pat. Appl. # 15/257,760 entitled "Vaporizer apparatus," filed 9/6/2016	
	705	MONSEES et al.; U.S. Pat. Appl. # 15/257,768 entitled "Vaporizer apparatus," filed 9/6/2016	
	706	MONSEES et al.; U.S. Pat. Appl. # 15/261,823 entitled "Low temperature electronic vaporization device and methods," filed 9/9/2016	

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

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1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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PTO/SB/08A (04-07)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	718	US- 6,603,924	8/5/2003	Brown et al.	
	719	US- 2013/0298905	11/14/2013	Levin et al.	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

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Sheet 1 of 2

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U. S. PATENT DOCUMENTS

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	595	US- 9,220,302	12/29/2015	DePiano et al.	
	596	US- 9,226,526	1/5/2016	Liu	
	597	US- 9,271,525	3/1/2016	Liu	
	598	US- 9,271,529	3/1/2016	Alima	
	599	US- 9,272,103	3/1/2016	Storz	
	600	US- 9,277,769	3/8/2016	Liu	
	601	US- 9,282,772	3/15/2016	Tucker et al.	
	602	US- 9,282,773	3/15/2016	Greim et al.	
	603	US- 9,289,014	3/22/2016	Tucker et al.	
	604	US- 9,308,336	4/12/2016	Newton	
	605	US- 9,326,547	5/3/2016	Tucker et al.	
	606	US- 9,351,522	5/31/2016	Safari	
	608	US- 2015/0282525	10/8/2015	Plojoux et al.	
	609	US- 2015/0313275	11/5/2015	Andersonet al.	
	611	US- 2015/0351456	12/10/2015	Johnson et al.	
	614	US- 2016/0021931	1/28/2016	Haweset al.	
	607	US- 2016/0058071	3/3/2016	Hearn	
	618	US- 2016/0058072	3/3/2016	Liu	
	621	US- 2016/0081395	3/24/2016	Thorens et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	639	WO2015/149647A1(w/ Eng Abs)	10/8/2015	Kimree Hi-Tech Inc.		
	640	WO2015/168828A1(w/ Eng Abs)	11/12/2015	Kimree Hi-Tech Inc.		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

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Sheet 2 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	623	US- 2016/0106154	4/21/2016	Lord	
	624	US- 2016/0106155	4/21/2016	Reevell	
	627	US- 2016/0120218	5/5/2016	Schennum et al.	
	630	US- 2016/0135503	5/19/2016	Liu	
	632	US- 2016/0143359	5/26/2016	Xiang	
	635	US- 2016/0143365	5/26/2016	Liu	
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	590	US- 2013/0199528	8/8/2013	Goodman et al.	
	591	US- 2014/0144429	5/29/2014	Wensley et al.	
	592	US- 2015/0272220	10/1/2015	Spinka et al.	
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	585	JP10-501999A(w/EngEquiv)	2/24/1998	Boehringer Ingelheim		

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14925961	BOWEN ET AL.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC- SEARCHED		
Symbol	Date	Examiner
A24F47/008	1/11/2016	DWM
updated above	6/11/2016	DWM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM
Inventor Search updated	6/11/2016	DWM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1595	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/12/14 13:14
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine	US-PGPUB;	ADJ	ON	2015/01/20

		benzoate	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			15:51
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48

S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:59
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and	US-PGPUB;	ADJ	ON	2015/05/14

		nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	USPAT; USOCR			16:08
S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31

		blood) and (ph near5 "7") and heat$4 and lung				
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48

		(plasma or blood)				
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	(14/925961).APP.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30
S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33
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S81	1	(14/925961).APP.	US-PGPUB; USPAT	OR	OFF	2016/12/13 15:38
S82	1	("20140000638").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/13 16:16

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S66	723	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2015/09/17 14:46
S67	246	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB	ADJ	ON	2015/09/17 14:47
S68	196	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB	ADJ	ON	2015/09/17 14:49
S72	833	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2016/01/11 23:26

12/ 14/ 2016 1:16:43 PM
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PTO/SB/08A (04-07)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	680	US- 5,240,012	8/31/1993	Ehrman et al.	
	666	US- 8,809,261	8/19/2014	Elsohly et al.	
	669	US- 8,881,737	11/11/2014	Collett et al.	
	667	US- 2015/0038567	2/5/2015	Herkenroth et al.	
	580	US- 2016/0174611**	6/23/2016	Monsees et al.	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	668	EP2152313B1	9/3/2014	McNeil AB		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	587	MONSEES et al.; U.S. Pat. Appl. # 15/165,954 entitled "Devices for vaporization of a substance," filed 5/26/2016	
	588	MONSEES et al.; U.S. Pat. Appl. # 15/166,001 entitled "Electronic vaporization device," filed 5/26/2016	
	589	MONSEES et al.; U.S. Pat. Appl. # 15/165,972 entitled "Portable devices for generating an inhalable vapor," filed 5/26/2016	
	665	BOWEN et al.; U.S. Pat Appl. # 15/101,303 entitled "Nicotine liquid formulations for aerosol devices and methods thereof," filed 6/2/2016	

Examiner Signature	/DIONNE W. MAYES/	Date Considered	12/13/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on April 20, 2017.

MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO pc

By: /Teri Barnett /

PATENT
Attorney Docket No.: 52210-501C03US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: Dionne W. MAYES

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION DATED DECEMER 20, 2016

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Non-Final Office Action dated December 20, 2016, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims begin on page **2** of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed.

1. (Currently amended) A method of delivering nicotine from an inhalable aerosol **to a user of an electronic cigarette** ~~so that the inhaled aerosol causes a physiological response similar to smoking a tobacco cigarette~~, the method comprising:

deploying an electronic cigarette comprising a liquid solution **thereby forming an inhalable aerosol, said liquid solution comprising** ~~consisting essentially of~~: ~~a nicotine lactate salt formulation that includes nicotine, a lactic acid, a biologically acceptable liquid carrier, and at least one flavorant wherein:~~

a. ~~the~~ nicotine ~~concentration is from about 4% (w/w) to about 12% (w/w)~~;

b. ~~the nicotine is protonated;~~

~~c. the~~ **a** biologically acceptable liquid carrier **comprising** ~~comprises 20% to 50% of propylene glycol and 80% to 50%~~ **glycerol**; **and**

[[d.]] c. ~~the lactic~~ **an organic** acid ~~concentration is sufficient to protonate most of the nicotine;~~

~~and resistively heating at least a portion of the liquid solution between about 100°C and about 300°C to generate an inhalable aerosol comprising protonated nicotine~~, **and**

delivering said inhalable aerosol to said user, said inhalable aerosol comprising an amount of protonated nicotine effective to increase the heart rate of said user ~~wherein inhalation of the aerosol into a user's lungs at a rate of 10 puffs over a period of about 3 minutes from a first puff results in an increase in heart rate that peaks within 3 minutes from the first puff when measured for 10 minutes from the start of puffing~~.

2. (Cancelled)

3. (Cancelled)

4. (Currently amended) The method of claim 1, wherein **the** ~~**deploying results in an**~~ increase in heart rate **is** comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco.

5. (Currently amended) The method of claim 1, wherein a molar ratio of nicotine to ~~**lactic**~~ **organic** acid is between 1:1 and 1:3 **in said liquid solution**.

6. (Cancelled)

7. (Currently amended) The method of claim 1, wherein the nicotine concentration in **said liquid solution** is about 4.5%.

8. (Cancelled)

9. (Original) The method of claim 1, wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns.

10. (Cancelled)

11. (Cancelled)

12. (Cancelled)

13. (Cancelled)

14. (Cancelled)

15. (Cancelled)

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Cancelled)

20. (Cancelled)

21. (Cancelled)

22. (Cancelled)

23. (Cancelled)

24. (New) The method of claim 1, wherein said biologically acceptable liquid carrier further comprises a propylene diol.

25. (New) The method of claim 24, wherein said propylene diol is propylene glycol.

REMARKS

Claim Status

Claims 1, 4, 5 and 7 are amended. Claims 24 and 25 are newly added. Claims 10, 12, 13, 15, 17-21 and 23 are cancelled. Therefore, after entry of this amendment, claims 1, 4, 5, 7, 9, 24 and 25 are pending. Support for the amendments to claims 1, 4, 5 and 7 and new claims 24 and 25 may be found in the original specification and claims as filed. Therefore, no new matter is entered with this amendment.

Claim Rejections

35 U.S.C. § 112(b)

The Office asserts claims 1, 4-5, 7, 9-10, 12-13, 15, 17-21 and 23 are rejected under 35 U.S.C. § 112(b), second paragraph, as allegedly indefinite for recitation of the phrase "the lactic acid concentration is sufficient to protonate most of the nicotine." Applicants respectfully disagree.

Nonetheless, in an effort to expedite prosecution, Applicants have deleted the phrase from the pending claims. Therefore, in view of the amendments to the claims, Applicants respectfully request withdrawal of the indefiniteness rejection.

35 U.S.C. § 103

Claims 1, 4-5, 7, 10, 12-13, 15 and 18-21 are rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Sebastian et al. (U.S. Patent Publication No. 2014/0000638) hereinafter "Sebastian". Claims 9, 17 and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Sebastian in view of Gonda (U.S. Patent Publication No. 2014/0261474) hereinafter "Gonda". Applicants respectfully disagree.

Nonetheless, in an effort to expedite prosecution, Applicants have amended the claims to specify that the recited aerosol includes protonated nicotine in an amount effective to increase the heart rate of a user.

None of the art cited by the Office teaches or suggests ***an aerosol containing a protonated nicotine*** as set forth in the pending claims as amended. For example, Sebastian merely teaches that certain organic acids may be included as a component of a composition ***prior to aerosolization*** for the purpose of ***altering flavor***. Sebastian lists several organic acids as flavoring agents, including levulinic acid, lactic acid and pyruvic acid, in addition to other flavoring agents such as vanillin, tea, coffee, fruit, cocoa, and many others. *See* Sebastian at paragraph [0059].

Nothing in Sebastian indicates that the suggested use of organic acids in a composition prior to aerosolization for the purpose of altering flavor would somehow result in protonated nicotine in the resulting aerosol, much less a sufficient amount of protonated nicotine to increase the heart rate of the user, as set forth in Applicants' amended claims.

Indeed, Sebastian teaches that acids and other flavoring agents can be delivered to the heating element ***separately*** from other components, such as nicotine. *See* Sebastian at paragraph [0059]. In fact, the entire purpose of Sebastian is to provide ***separate delivery of two or more components*** of an aerosol precursor composition to one or more heaters so as ***to separately control the rate of delivery or heating*** of the separate components of the various portions of the aerosol precursor composition. *See e.g.* Sebastian at Abstract and Title. There is no disclosure in Sebastian indicating that separately supplying nicotine and an organic acid to one or more heaters so as to separately control their respective rate of delivery or heating would somehow result in protonated nicotine in the aerosol as set forth in Applicants' amended claims.

Moreover, Sebastian teaches that flavorants "can be provided ***on a substrate*** positioned within the aerosolization zone so as ***to be stored separate*** from the further components of the aerosol precursor composition." *See* Sebastian at paragraph [0059]. There is no disclosure in Sebastian indicating that the inclusion of an acid on a substrate within the aerosolization zone would somehow result in protonated nicotine in the aerosol, much less produce a sufficient amount of protonated nicotine to increase the heart rate of the user as set forth in Applicants' amended claims.

Nothing in Sebastian indicates that sufficient amounts of acid are combined with nicotine ***in a single nicotine formulation***, as presently claimed, in order to achieve formation of an aerosol containing protonated nicotine. Moreover, nothing in Sebastian indicates that sufficient amounts of acid are combined with nicotine ***with glycerol in a single nicotine formulation***, as presently claimed, in order to achieve formation of an aerosol containing protonated nicotine.

Because Sebastian fails to teach or suggest protonated nicotine in the aerosol, much less any benefits of having protonated nicotine in the aerosol, a person having ordinary skill in the art would

have ***no reason*** to modify the teachings of Sebastian to provide an aerosol having protonated nicotine. Even if the cited art did provide some reason to form an aerosol with protonated nicotine, nothing in the cited art indicates that a person having ordinary skill in the art would have ***reasonably expected*** to successfully increase the heart rate of the user.

Applicants further submit herewith a Declaration of Adam Bowen as additional evidence that a person having ordinary skill in the art would have had no reason to modify the teaching of Sebastian to provide an aerosol having a protonate nicotine, much less have reasonably expected to successfully do so. Applicants note that this declaration was previously submitted during prosecution of USSN 14/925,968 on November 17, 2016. As set forth in the Declaration of Adam Bowen, prior to Applicants' invention, "those of skill in the art believed that vaporized nicotine did not result in an effect on heart rate comparable to that seen with a traditional cigarette." *See* the Declaration of Adam Bowen at paragraph (7). It was Applicants' invention that protonated nicotine resulted in a significant increase in heart rate. Prior to this discovery, a person having ordinary skill in the art would have had ***no reason*** to form an aerosol with protonated nicotine and certainly ***no reasonable expectation*** of successfully doing so.

With regard to the rejection of claims 9, 17 and 23, Applicants respectfully submit that Gonda fails to cure the defects of Sebastian. Like Sebastian, nothing in Gonda teaches or suggests ***an aerosol containing a protonated nicotine*** as set forth in the pending claims as amended, much less a sufficient amount of protonated nicotine to increase the heart rate of the user as set forth in Applicants' amended claims.

For at least the reasons recited above, Applicants respectfully request withdrawal of the obviousness rejection.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration is respectfully requested. This application should now be in condition for allowance; a notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Commissioner is authorized to charge any fees that may be due in connection with the filing of this paper, or to credit any overpayment thereof, to Deposit Account No. 50-0311 referencing the above-identified attorney docket number.

Respectfully submitted,

/Ken Jenkins/
Kenneth E. Jenkins, Ph.D.
Registration No. 51,846

MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO, P.C.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 14/925,968	Confirmation No.	: 2707
Inventor(s)	: Adam BOWEN		
Filing Date	: October 28, 2015		
Art Unit	: 1747		
Examiner	: Mayes, Dionne Walls		
Title	: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF		
Customer No.	: 66854		

DECLARATION UNDER 37 C.F.R. § 1.132

I, Adam Bowen, declare as follows:

(1) In January of 2005, I co-founded Ploom, Inc., now PAX Labs, which develops and produces nicotine vaporizers ("electronic cigarettes"), and am currently the Chief Technical Officer (CTO) of the company.

(2) I am also an inventor on the patent application, U.S. Application no. 14/925,968, tiled "NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF" (hereafter "the '968 application"), as well as on U.S. provisional patent application 61/820,128, filed on May 6, 2013 (hereafter "the '128 provisional application"), to which the '968 application claims priority.

(3) The '968 patent application describes the use of liquid nicotine salts formulations in a vaporizer to form an aerosol of nicotine. The nicotine in these formulations is formed by a nicotine salt in a liquid carrier such as a glycerol, glycol or mixture of these. As described in the '128 provisional application, the use of certain nicotine salts, including carboxylic acid nicotine salts such as nicotine lactate, produces a physiological effect when vaporized that is comparable to that from inhaling a traditional burned cigarette. Specifically, the resulting vapor produces an increase in heart rate that peaks within the first five minutes, just as seen when inhaling traditional burned cigarettes. FIG. 1 of the '128 provisional application was provided as an example of this. This figure is reproduced in the attached Exhibit A. The data shown in FIG. 1 of the '128 provisional application was for nicotine levulinate.

(4) Although nicotine lactate was included as an example of a nicotine salt in the '128 provisional application, the experimental data was not explicitly included in FIG. 1. Nicotine lactate also has a physiological effect on the heart rate that closely resembles that of smoking a tobacco cigarette. Specifically, nicotine lactate also causes an increase in heart rate that peaks within about 5 minutes from the first puff. This data is shown in Exhibit B, attached herewith.

(5) The data shown in Exhibit B was collected in the same manner as is shown in FIG. 1 of the '128 provisional application. A 6.5% (w/w) solution of nicotine lactate solution was prepared in glycerol by adding neat nicotine lactate into the glycerol, which was mixed thoroughly. A 4.0% (w/w) solution of nicotine lactate was similarly prepared. Both formulations were administered as to a subject as described for FIG. 1 of the '128 provisional application, and heart rate measurements (e.g., at 30-second intervals) were taken for ten minutes from start of puffing. The test participant took 10 puffs over 3 minutes in each case. The increase in heart rate seen with both the 6.5% and 4.0% nicotine lactate solutions are directly comparable to that seen for nicotine levulinate, and are similar to that seen with a traditional burned cigarette. This is in contrast with freebase nicotine which did not induce a peak in heart rate within the first five minutes, as shown in FIG. 1 of the '128 provisional application.

(6) This result was unexpected. Prior to my work, it was widely believed by those of skill in the art that vaporized nicotine did not evoke the same physiological response as traditional burned cigarettes. This belief was supported by data showing that vaporized nicotine did not evoke the same or similar peak increase in heart rate as traditional burned cigarettes. In FIG 1 of the the '128 provisional, the bottom trace (freebase nicotine) is typical for the heart rate effect of prior art nicotine vaporizers showing a more gradual increase in heart rate. It was surprising and unexpected that nicotine salt formulations such as nicotine lactate instead produce a peak heart rate that matches that produced by traditional burned cigarettes.

(7) Prior to my invention, those of skill in the art believed that vaporized nicotine did not result in an effect on heart rate comparable to that seen with a traditional cigarette. At the time of my invention, published data comparing the physiological effect of vaporized nicotine delivered from an electronic cigarette to that caused by traditional burned cigarettes concluded that vaporized nicotine differed from traditional tobacco cigarettes, and either did not produce any significant change in hear rate, or resulted in only a slowly increasing, sustained increase in heart rate, in contrast to the rapid onset (within 5 minute) peak increase in heart rate that seen with burned cigarettes. For example, Vansickel et al. ("A Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction 2012;107:1493–500, attached hereto as Exhibit C) examined the effect on hart rate between vaporized nicotine and burned cigarettes, and reported that there were not any significant changes in heart rate following two 10-puff bouts with a 16 or 18 mg nicotine/cartridge e-cigarette (n=32; n=16). Significant increases in HR were reported with burned cigarettes. Vansickel et al. used a protocol that was similar to what I used in generating the data shown in FIG. 1 of the '128 provisional and Exhibit B. Heart rate was measured every 20 seconds, and subjects were instructed to take 10 puffs with a 30-second interpuff interval. The electronic

cigarettes used included nicotine (16- or 18-mg), propylene glycol, water and flavorants. Vansickel et al. reported that there was a peak in heart rate within the first 5 minutes for the burned cigarettes, while there was no significant peak in the same time period for any of the electronic cigarettes ("Heart rate increased from an average (SD) of 65.7 (10.4) bpm at baseline to a peak of 80.3 (10.9) bpm five minutes after the first administration under the own-brand condition [burned cigarettes]. No significant changes in heart rate were observed for the Hydro EC, NPRO EC [electronic cigarettes], or sham conditions."). Later work by the same researchers (Vansickel AR, Eissenberg T. Electronic cigarettes: Effective nicotine delivery after acute administration. Nicotine Tob Res 2013;15:267–70, attached hereto as Exhibit D) reported that even when higher levels of nicotine were included in the electronic cigarette, such as 18 mg/ml nicotine, 9 mg/ml nicotine and 24 mg/ml nicotine, only a gradual increase in heart rate was seen which did not peak within 5 minutes, but continued to increase and remain elevated over a longer time period ("heart rate increased significantly within 5 min of the first puff and remained elevated throughout the ad lib puffing period."). Similar or identical effects were reported by others (see, e.g., the European Society for Cardiology, http://www.escardio.org/The-ESC/Press-Office/Press-releases/Electronic-cigarettes-do-not-damage-the-heart, attached hereto as Exhibit E), comparing how a heart reacts to cigarette smoke compared to inhaling nicotine vapor, and pointing out that heart rate and blood pressure increases quickly and dramatically when smoking a traditional cigarette, but the inhaling vapor from an electronic cigarette results in only a slight uptick in blood pressure, and "hardly any increase in heart rate." In light of the published literature, it was surprising unexpected that the use of nicotine lactate to form the nicotine in the solution being vaporized would have a physiological effect on a body that closely resembles that of smoking a tobacco cigarette such that inhaling 10 puffs of the aerosol over a period of about 3 minutes would result in an increase in heart rate that peaks within about 5 minutes from the first puff.

(8) I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under the provisions of 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of any patent issuing upon U.S. Application Serial No. 14/632,161, or any continuing application thereof.

Signature: _____ Date: 11/17/16

Adam Bowen

EXHIBIT A

Figure 1 of U.S. provisional patent application 61/820,128 (filed on May 6, 2013)

FIG. 1

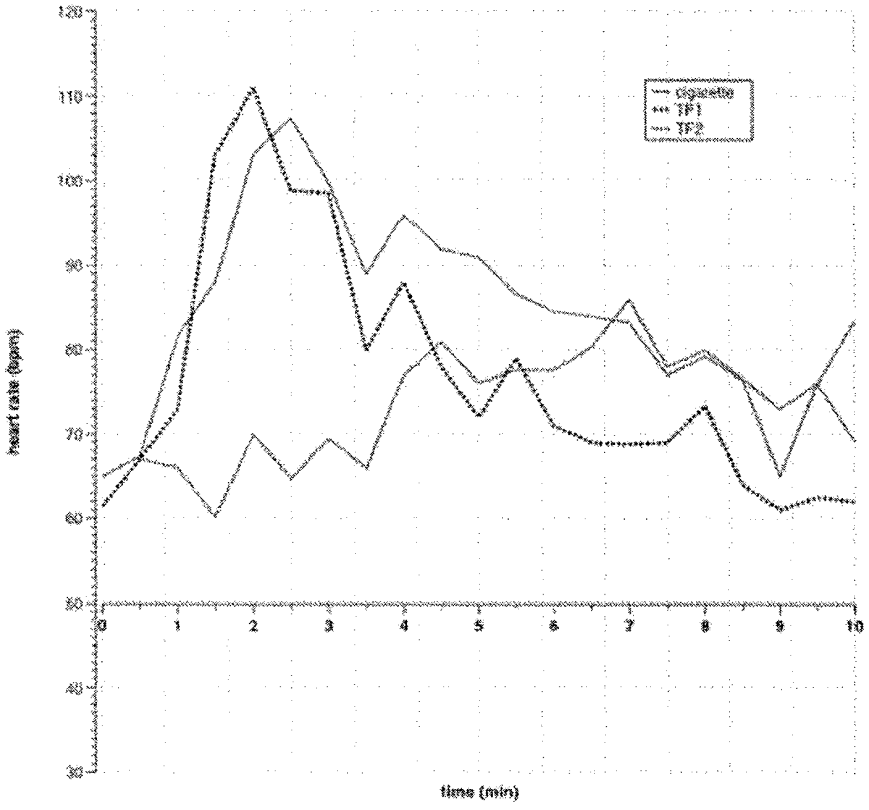
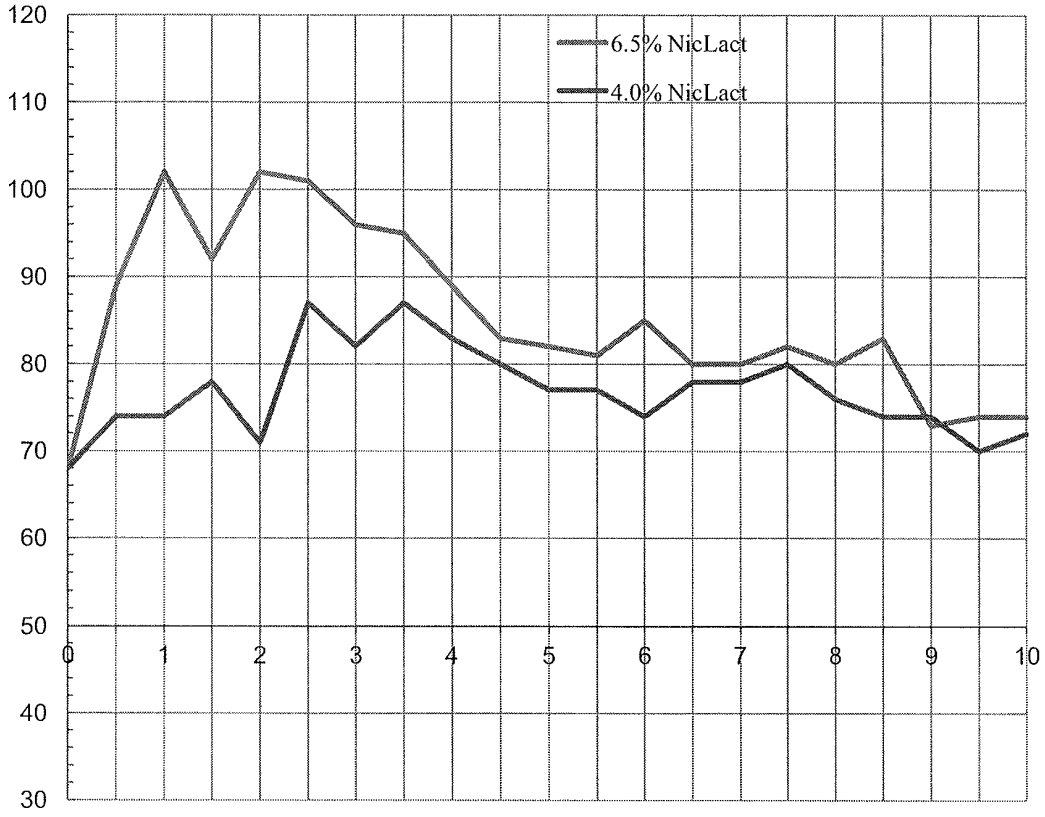


EXHIBIT B

Nicotine Lactate effect on heart rate



Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Title	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
Art Unit	1747
Examiner Name	D. W. Mayes
Attorney Docket Number	52210-501C03US

SIGNATURE of Applicant or Patent Practitioner

Signature	/Ken Jenkins/	Date (Optional)	April 20, 2017
Name	Kenneth E. Jenkins, Ph.D.	Registration Number	51,846
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of 1 forms are submitted.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[x] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 64046

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[x] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

PAX Labs, Inc.

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[x] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	4/5/17
Name	Ashley C. Gould		
Title	General Counsel, Chief Regulatory and Communications Officer		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[ ] Total of 1 forms are submitted.

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: PAX Labs Inc.

Application No./Patent No.: 14/925,961 Filed/Issue Date: 10/28/2015

Titled: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

PAX Labs Inc. (Name of Assignee) , a corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [x] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [x] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: Adam Bowen; Chenyue Xing To: Ploom, Inc.
      The document was recorded in the United States Patent and Trademark Office at Reel 037990, Frame 0840, or for which a copy thereof is attached.

   2. From: Ploom, Inc. To: PAX Labs, Inc.
      The document was recorded in the United States Patent and Trademark Office at Reel 037990, Frame 0859, or for which a copy thereof is attached.

68279945v.1

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/ Ken Jenkins/	April 20, 2017
Signature	Date
Kenneth E. Jenkins	51,846
Printed or Typed Name	Title or Registration Number

68279945v.1

Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Kenneth Edwin Jenkins/Teri Barnett
Attorney Docket Number:	13211-713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	28984322
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	66854
Filer:	Kenneth Edwin Jenkins/Teri Barnett
Filer Authorized By:	Kenneth Edwin Jenkins
Attorney Docket Number:	13211-713.302
Receipt Date:	20-APR-2017
Filing Date:	28-OCT-2015
Time Stamp:	16:51:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$100
RAM confirmation Number	042117INTEFSW00004085500311
Deposit Account	500311
Authorized User	Teri Barnett
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.19 (Document supply fees) 37 CFR 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		52210_501C03US_Response.pdf	182032 8d9419dd1ffdde5dd736eb65b3e79deeb0e4753f	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:

Information:

2	Affidavit-traversing rejectns or objectns rule 132	52210_501C03US_Adam_Bowen_Declaration.pdf	285044 d4a859aa65069b0352802269c7dfa2c3689f9da6	no	5

Warnings:

Information:

3		52210_501C03US_POA.pdf	116694 c60dcd1a2b9121363d09e5588a5e206b8316c6e5	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	2
	Assignee showing of ownership per 37 CFR 3.73	3	4

Warnings:

Information:

4	Fee Worksheet (SB06)	fee-info.pdf	30759 31a8dfec65b38a684f043818b70630edde8d867d	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	614529

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/20/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 7	Minus	** 20	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
ANGELA s. WHITE

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/925,961	10/28/2015	Adam BOWEN	52210-501C03US

CONFIRMATION NO. 1528

64046
Mintz Levin/San Diego Office
One Financial Center
Boston, MA 02111

POA ACCEPTANCE LETTER

OC000000090871971

Date Mailed: 04/25/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/20/2017.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/rmohamed/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/925,961	10/28/2015	Adam BOWEN	13211-713.302

CONFIRMATION NO. 1528

66854
SHAY GLENN LLP
2755 CAMPUS DRIVE
SUITE 210
SAN MATEO, CA 94403

POWER OF ATTORNEY NOTICE

OC000000090871930

Date Mailed: 04/25/2017

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/20/2017.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/rmohamed/

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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	REQUEST ID
14/925,961		1747	40385

PAIR Correspondence Address/Fee Address Change

The following fields have been changed to Customer Number 148514 on 05/23/2017 via Private PAIR in view of the certification copied below that authorized the change.

- Correspondence Address

The address for Customer Number 148514 is:
148514
Mintz Levin/PAX
One Financial Center
Boston, MA 02111

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature:	/Ken Jenkins/
Name:	Kenneth E. Jenkins
Registration Number:	51846

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	52210-501C03US / 713.302	1528

148514 7590 06/02/2017

Mintz Levin/PAX
One Financial Center
Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
06/02/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN ET AL.	
	Examiner DIONNE W. MAYES	Art Unit 1747	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/20/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,4-7,9,24 and 25* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,4-7,9,24 and 25* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24-25 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amendment filed on April 20, 2017, Applicant added new claims 24-25. Claim 24 recites "wherein said biologically acceptable liquid carrier further comprises a propylene diol", and claim 25 further recites “wherein said propylene diol is propylene

glycol" (emphases added); however, this recitation does not at all appear to be supported by the instant disclosure.

First, the instant written specification makes no mention of the term "propylene diol". It appears as if Applicant is now trying to claim a genus of "propylene diol" compounds - which includes any propane compound containing two alcohol groups - as opposed to a single compound. If so, this is, in essence, broadening the scope of the disclosure and, as such, finds no support in the originally filed written specification.

Second, the Examiner notes that in the instant specification, Applicant has disclosed that its liquid carrier may include "propylene glycol" - which is also named 1,2 **propane**diol - however, as stated above, **propylene** diol, and ***not*** 1,2 **propane**diol, is recited in the newly added claims. Correction is requested.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

7. Claims 1, 4-5 and 7 are rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638).

Regarding independent claim 1, and dependent claims 4 and 7, Sebastian et al discloses an electronic smoking article (i.e., electronic cigarette) that provides for delivery of aerosolized components of an aerosol precursor composition, which may contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed “A method of delivering nicotine from an inhalable aerosol to a user of an electronic cigarette”).

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor, sensation, or organoleptic properties. Organic acids, such as lactic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059]). Since the nicotine and lactic acid can be provided in equimolar ratios (i.e., 1:1), it is presumed,

at this proportion, that "nicotine lactate" is thereby formed (which, inherently, means that "the nicotine is protonated").

The aerosol precursor composition may include glycerol and/or propylene glycol. Further, Sebastian et al discloses that, as a non-limiting example, an aerosol precursor composition may include nicotine in an amount of about 0.1-5.0%. This would motivate one of ordinary skill to undergo routine experimentation to find the optimal amount of nicotine to add to the precursor composition and, in doing so, selected the high end of this range, i.e. 3-5%, after determining that such nicotine concentration provided for superior flavor, sensation and organoleptic properties for the user (Note: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (corresponding to the claimed "deploying an electronic cigarette comprising a liquid solution thereby forming an inhalable aerosol, said liquid solution comprising nicotine and a biologically acceptable liquid carrier comprising glycerol and an organic acid"; and the "wherein the nicotine concentration is about 4.5%" recitation of claim 7).

Lastly, it follows to reason, that the upon inhalation of the aerosolized vapor resulting from heating the aerosol precursor composition (which includes nicotine lactate) in the modified Sebastian et al electronic smoking article, the user would experience the claimed heart rate increase (comparable to that of smoking a traditional cigarette) upon inhaling as, absent any indication to the contrary, such effects would "flow naturally" from use of said article (corresponding to the claimed "delivering said

inhalable aerosol to said user, said inhalable aerosol comprising an amount of protonated nicotine effective to increase the heart rate of said user"; and the "wherein the increase in heart rate is comparable to an increase in heart rate resulting from inhalation of traditional burned tobacco" recitation of claim 4).

Regarding claim 5, as stated above, Sebastian et al discloses that its aerosol precursor can include nicotine and lactic acid provided in equimolar ratios (see para. [0059]) (corresponding to the claimed "wherein a molar ratio of nicotine to organic acid is between about 1:1 and 1:3 in said liquid solution").

8. Claim 9 is rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638) in view of Gonda (US. Pat. No. 2014/0261474).

Regarding claim 9, based on the disclosure of Gonda, which states that by decreasing the particle size, the aerosolized particles of nicotine will deposit deeper in the lungs, which increases the rate of absorption of the nicotine and leads to an increase in peak nicotine plasma levels, it would have been obvious to one having ordinary skill in the art to have optimized the particle size of its aerosol to fall between 0.1 - 5 microns (corresponding to the claimed "wherein the inhalable aerosol has a particle size from about 0.1 microns to about 5 microns").

Response to the Declaration of Adam Bowen Under 32 CFR 1.132

9. The Declaration of Adam Bowen, submitted with the instant amendment filed on April 20, 2017 (but originally filed in Application No. 14/925,968, on November 17, 2016) to the extent that it provides additional experimental evidence in support of the heart rate effect of vaporizing nicotine lactate has been accepted and, for the purposes of

Examination, the subject matter thereof will be considered to have been incorporated into Applicant's Provisional Application filed on May 6, 2013. This same Declaration, to the extent that it articulates “unexpected results” is insufficient to establish the same. As shown in the above prior art rejection over Sebastian et al, the use of as much as 10% (w/w) nicotine in a equimolar ratio with lactic acid (hence, forming nicotine lactate) in a liquid solution of glycerol by heating the same in an electronic cigarette and being inhaled by a user is already known, and would provide the claimed increases in heart rate comparable to inhaling a traditional burned cigarette. As such, the results indicated by Applicant, and that which is instantly claimed, are not “unexpected”.

Response to Applicant’s Arguments

10. Applicant's arguments filed April 20, 2017 have been fully considered but they are not persuasive.

-Applicant argues that the prior art fails to teach or reasonably suggest the claimed “aerosol containing a protonated nicotine”. Specifically, Applicant submits, nothing in the Sebastian reference indicates that the suggested use of organic acids in a composition (prior to aerosolization) for the purpose of altering flavor would somehow result in protonated nicotine in the resulting aerosol, much less a sufficient amount of protonated nicotine to increase the heart rate of the user. The Examiner, however, disagrees. First, it is true that Sebastian lists several acids (lactic acid, included) to be included in the nicotine composition for the purpose of altering flavor (“flavoring agents”)(see Sebastian para. [0060]); however, regarding the instant invention, it is to be noted that Applicant has also

articulated that organic acids (including lactic acid) coupled with nicotine to produce nicotine lactate can be used to provide flavor (see instant published application para. [0131]). Second, because Sebastian teaches an equimolar ratio of nicotine to organic acid, as stated above, it is more than reasonable to presume that "nicotine lactate" is thereby formed, resulting in the claimed "nicotine formulation that comprises nicotine lactate" which, in turn, would produce an "inhalable aerosol comprising an amount of protonated nicotine". Lastly, Applicant points out that Sebastian states that lactic acid can be delivered to the heating element separately from other components, such as nicotine and/or the liquid carrier, and separately supplying the components to one or more heaters. Applicant further seems to suggest that, in such an arrangement, the formation of protonated nicotine is doubtful or uncertain. The Examiner submits that while Sebastian may disclose the separate delivery of the various components of the nicotine formulation, the Examiner wishes to point out that this appears to be one of many different ways in which the formulation of Sebastian can be delivered to the heater. Note the use of the words "can be" (see para. [0059]) of Sebastian. As disclosed above, the Examiner has also provided evidence in Sebastian that it envisions a formulation that includes a homogeneous mixture of nicotine, lactic acid (hence, forming nicotine lactate) in a liquid carrier. Further, Sebastian even clearly articulates the same in para, [0058] where it states that "components [of the aerosol precursor composition]

can be separately or simultaneously delivered to the resistive heating element for aerosolization in an air stream to be inhaled by a user".

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE W. MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Tuesdays and Thursdays, 8:00A - 4:30P.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael H. Wilson can be reached on (571) 270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE W MAYES/
Examiner, Art Unit 1747

/MICHAEL H WILSON/
Supervisory Patent Examiner, Art Unit 1747

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	1998	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/05/25 21:46
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine	US-PGPUB;	ADJ	ON	2015/01/20

		benzoate	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			15:51
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48

S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:59
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and	US-PGPUB;	ADJ	ON	2015/05/14

		nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	USPAT; USOCR			16:08
S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31

		blood) and (ph near5 "7") and heat$4 and lung				
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	(14/512311).APP.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48

		(plasma or blood)				
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	(14/925961).APP.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30
S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33
S79	225	("1067531" | "1163183" | "1299162" | "1505748" | "1552877" | "1632335" | "1706244" | "1845340" | "1972118" | "1998683" | "2031363" | "2039559" | "2104266" | "2231909" | "2327120" | "2460427" | "2483304" | "2502561" | "2765949" | "2830597" | "2860638" | "2897958" | "2935987" | "20010015209" | "20010032643" | "20010032795" | "20010052480" | "20020078951" | "20020175164" | "20030005926" | "20030089377" | "20040031495" | "20040099266" | "20040149296" | "20040149624" | "20040173229" | "20040182403" | "20040221857" | "20040237974" | "20050016549" | "20050016550" | "20050034723" | "20050061759" | "20050118545" | "20050145533" | "20050172976" | "20050244521" | "20050268911" | "20060018840" | "20060054676" | "20060102175" | "20060150991" | "20060191546" | "20060191548" | "20060254948" | "20060255105" | "20070006889" | "20070045288" | "20070062548" | "20070074734" | "20070098148" | "20070102013" | "20070144514" | "20070163610" | "20070215164" | "20070235046" | "20070267033" | "20070280652" | "20070283972" | "20080023003" | "20080029095" | "20080092912" | "20080149118" | "20080216828" | "20080241255" | "20080257367" | "20080276947" | "20090004249" | "20090095287" | "20090126745" | "20090133691" | "20090230117" | "20090255534" | "20090267252" | "20090272379" | "20090288668" | "20090288669" | "20090293892" |	US-PGPUB; USPAT	ADJ	ON	2016/12/13 13:42

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S80	85	("5708258" | "5730118" | "5730158" | "5746587" | "5810164" | "5819756" | "5845649" | "5865185" | "5881884" | "5931828" | "5934289" | "5938018" | "5944025" | "5954979" | "5967310" | "5975415" | "5979460" | "5994025" |	US-PGPUB; USPAT	ADJ	ON	2016/12/13 13:42

		"5996589" | "576653" | "595070" | "6053176" | "6095153" | "6102036" | "6125853" | "6155268" | "6164287" | "6234169" | "6269966" | "6349728" | "6381739" | "6386371" | "6431363" | "6446793" | "6510982" | "6532965" | "6536442" | "6557708" | "6598607" | "6606998" | "6615840" | "6622867" | "6655379" | "6672762" | "6688313" | "6726006" | "6772756" | "6799576" | "6803545" | "6805545" | "6810883" | "6827573" | "6954979" | "7000775" | "7488171" | "7546703" | "7621403" | "7644823" | "7767698" | "7815332" | "7832410" | "7886507" | "7988034" | "720007" | "799844" | "8141701" | "8156944" | "8322350" | "8371310" | "8381739" | "8387612" | "8443534" | "8490629" | "8539959" | "8541401" | "8596460" | "8671952" | "8741348" | "8915254" | "8925555" | "968160" | "969076" | "D590990" | "D590991" | "D624238" | "D642330" | "D644375" | "D653803" | "D691324" | "D695450" | "D707389").PN.				
S81	1	(14/925961).APP.	US-PGPUB; USPAT	OR	OFF	2016/12/13 15:38
S82	1	("20140000638").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/13 16:16
S83	1595	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/12/14 13:14
S84	1	("9215895").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/14 13:23

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S66	723	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2015/09/17 14:46
S67	246	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB	ADJ	ON	2015/09/17 14:47
S68	196	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB	ADJ	ON	2015/09/17 14:49
S72	833	(A24F47/008).cpc.	US-PGPUB	ADJ	ON	2016/01/11 23:26

5/25/2017 9:47:29 PM
C:\Users\dmayes\Documents\EAST\Workspaces\14925961.wsp

PTO/SB/08A (04-07)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 6

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	694	US- 3,271,719	9/6/1966	Ovshinsky	
	670	US- 3,443,827	5/13/1969	Acker et al.	
	671	US- 5,497,791	3/12/1996	Bowen et al.	
	672	US- 5,529,078	6/25/1996	Rehder et al.	
	117	US- 6,089,857	7/18/2000	Matsuura et al.	
	673	US- 6,196,232	3/6/2001	Chkadua	
	150	US- 7,015,796	3/21/2006	Snyder	
	675	US- 7,801,573	9/21/2010	Yazdi et al.	
	173	US- 8,820,330	9/2/2014	Bellinger et al.	
	174	US- 8,851,081	10/7/2014	Fernando et al.	
	178	US- 9,095,175	8/4/2015	Terry et al.	
	722	US- D725310	3/24/2015	Eksouzian	
	695	US- 2004/0050382	3/18/2004	Goodchild	
	696	US- 2007/0277816	12/6/2007	Morrison et al.	
	674	US- 2009/0111287	4/30/2009	Lindberg et al.	
	263	US- 2010/0200008	8/12/2010	Taieb	
	676	US- 2011/0240047	10/6/2011	Adamic	
	297	US- 2012/0285475	11/15/2012	Liu	
	310	US- 2013/0319440	12/5/2013	Capuano	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	387	EP2856893A1	4/8/2015	Fontem Holdings		
	388	EP2908675A1(asWO2014/060268)	8/26/2015	Nicoventures Holdings Ltd		
	389	EP2915443A1	9/9/2015	Fontem Holdings		
	757	EP3062646A1 (WO2015/66136)	9/7/2016	Rai Strategic Holdings Inc		
	758	EP3065581A2 (WO2015/68044)	9/14/2016	SIS Resources Ltd		
	759	EP3068244A1 (WO2015/73975)	9/21/2016	VMR Products LLC		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	05/24/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 6

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

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	312	US- 2013/0340775	12/26/2013	Juster et al.	
	313	US- 2014/0000638	1/2/2014	Sebastian et al.	
	723	US- 2014/0007891	1/9/2014	Liu	
	314	US- 2014/0014126	1/16/2014	Peleg et al.	
	316	US- 2014/0053856	2/27/2014	Liu	
	318	US- 2014/0060556	3/6/2014	Liu	
	319	US- 2014/0096782	4/10/2014	Ampolini et al.	
	320	US- 2014/0109921	4/24/2014	Chen	
	321	US- 2014/0116455	5/1/2014	Youn	
	322	US- 2014/0123990	5/8/2014	Timmermans	
	323	US- 2014/0150810	6/5/2014	Hon	
	324	US- 2014/0174459	6/26/2014	Burstyn	
	327	US- 2014/0196735	7/17/2014	Liu	
	328	US- 2014/0216450	8/7/2014	Liu	
	329	US- 2014/0230835	8/21/2014	Saliman	
	331	US- 2014/0270727	9/18/2014	Ampolini et al.	
	332	US- 2014/0301721	10/9/2014	Ruscio et al.	
	333	US- 2014/0305450	10/16/2014	Xiang	
	336	US- 2014/0355969	12/4/2014	Stern	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	416	WO2004/080216A1(EngAbs)	9/23/2004	Hon, Lik		
	420	WO2008/077271A1(EngAbs)	7/3/2008	Maas, Bernard		
	427	WO2012/120487A2	9/13/2012	Chong Corp		
	430	WO2013/089551A1	6/20/2013	Foo, Kit Seng		
	433	WO2014/040915A1(EngAbs)	3/20/2014	Snoke Gmbh & Co		
	435	WO2014/101734A1	7/3/2014	Shenzhen Smoore Tech		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	05/24/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 6

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	340	US- 2015/0020825	1/22/2015	Galloway et al.	
	341	US- 2015/0020831	1/22/2015	Weigensberg et al.	
	343	US- 2015/0027472	1/29/2015	Amir	
	344	US- 2015/0034103	2/5/2015	Hon	
	724	US- 2015/0034104	2/5/2015	Zhou	
	345	US- 2015/0040929	2/12/2015	Hon	
	346	US- 2015/0101625	4/16/2015	Newton et al.	
	347	US- 2015/0122252	5/7/2015	Frija	
	348	US- 2015/0122274	5/7/2015	Cohen et al.	
	349	US- 2015/0128965	5/14/2015	Lord	
	351	US- 2015/0136153	5/21/2015	Lord	
	697	US- 2015/0136158	5/21/2015	Stevens et al.	
	352	US- 2015/0142387	5/21/2015	Alarcon et al.	
	355	US- 2015/0164141	6/18/2015	Newton	
	356	US- 2015/0164144	6/18/2015	Liu	
	698	US- 2015/0164147	6/18/2015	Verleur et al.	
	357	US- 2015/0181928	7/2/2015	Liu	
	358	US- 2015/0189695	7/2/2015	Xiang	
	359	US- 2015/0196059	7/16/2015	Liu	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	439	WO2014/150704A2	9/25/2014	Altria Client Svs Inc.		
	442	WO2014/205263A1	12/24/2014	Loec Inc.		
	444	WO2015/028815A1	3/5/2015	British American Tobacco		
	446	WO2015/058387A1(EngAbs)	4/30/2015	Kimree Hi-Tech Inc.		
	447	WO2015/063126A1	5/7/2015	Choukroun, B.		
	450	WO2015/089711A1(EngAbs)	6/25/2015	Kimree Hi-Tech Inc.		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	05/24/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 6

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	699	US- 2015/0196060	7/16/2015	Wensley et al.	
	361	US- 2015/0208731	7/30/2015	Malamud et al.	
	700	US- 2015/0216237	8/6/2015	Wensley et al.	
	362	US- 2015/0223521	8/13/2015	Menting et al.	
	363	US- 2015/0224268	8/13/2015	Henry et al.	
	364	US- 2015/0237917	8/27/2015	Lord	
	365	US- 2015/0237918	8/27/2015	Liu	
	366	US- 2015/0245654	9/3/2015	Memari et al.	
	367	US- 2015/0245660	9/3/2015	Lord	
	368	US- 2015/0257445	9/17/2015	Henry Jr. et al.	
	369	US- 2015/0258289	9/17/2015	Henry Jr. et al.	
	370	US- 2015/0282527	10/8/2015	Henry Jr.	
	701	US- 2015/0305409	10/29/2015	Verleur et al.	
	702	US- 2016/0021933	1/28/2016	Thorens et al.	
	750	US- 2016/0242466	8/25/2016	Lord et al.	
	751	US- 2016/0249680	9/1/2016	Liu	
	753	US- 2016/0295924	10/13/2016	Liu	
	754	US- 2016/0302483	10/20/2016	Liu	
	717	US- 2016/0309784	10/27/2016	Silvestrini et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	452	WO2015/109616A1(EngAbs)	7/30/2015	Kimree Hi-Tech Inc.		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	05/24/2017

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 6

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	726	US- 2016/0324215	11/10/2016	Mironov et al.	
	735	US- 2016/0331033	11/17/2016	Hopps et al.	
	737	US- 2016/0331038	11/17/2016	Farine et al.	
	738	US- 2016/0331040	11/17/2016	Nakano et al.	
	745	US- 2016/0338410	11/24/2016	Batista et al.	
	746	US- 2016/0338411	11/24/2016	Liu	
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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/DIONNE W. MAYES/	Date Considered	05/24/2017

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Sheet 6 of 6

Complete if Known	
Application Number	14/925,961
Filing Date	October 28, 2015
First Named Inventor	Adam Bowen
Art Unit	1747
Examiner Name	Mayes, Dionne Walls
Attorney Docket Number	13211-713.302

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	481	BRADLEY et al.; Electronic cigarette aerosol particle size distribution measurements; Inhal. Toxicol.; 24(14); pp. 976-984; Dec. 2012	
	482	BULLEN et al.; Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial; Tobacco Control; 19(2); pp. 98-103; Apr. 2010	
	678	CAPPONNETTO et al.; Successful smoking cessation with cigarettes in smokers with a documented history of recurring relapses: a case series; Journal of Medical Case Reports; 5(1); 6 pages; (year of pub. sufficiently earlier than effective US filing date and any foreign priority date); 2011	
	721	FARSALINOS et al.; Electronic cigarettes do not damage the heart; European Society of Cardiology; 4 pages; retrieved from the internet (http://www.escardio.org/The-ESC/Press-Office/Press-releases/Electronic-cigarettes-do-not-damage-the-heart); August 25, 2012	
	677	HURT et al.; Treating tobacco dependence in a medical setting; CA: A Cancer Journal for Clinicians; 59(5); pp. 314-326; Sept. 2009	
	720	VANSICKEL et al.; Electronic cigarettes: effective nicotine delivery after acute administration; Nicotine & Tobacco Research; 15(1); pp. 267-270; January 2013	

Examiner Signature	/DIONNE W. MAYES/	Date Considered	05/24/2017

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14925961	BOWEN ET AL.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC- SEARCHED		
Symbol	Date	Examiner
A24F47/008	1/11/2016	DWM
updated above	6/11/2016	DWM
updated above	5/25/2017	DWM

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM
Inventor Search updated	6/11/2016	DWM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	REQUEST ID
14/925,961		1747	45212

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The address for Customer Number 148514 is:
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Boston, MA 02111

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature:	/npm/
Name:	Nicholas Mouton
Registration Number:	75306

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14925961	Filing Date	2015-10-28	Docket Number (if applicable)	052210-501C03US	Art Unit	1747
First Named Inventor	Adam Bowen			Examiner Name	D. W. Mayes		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 50-0311

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Signature of Registered U.S. Patent Practitioner			
Signature	/Robert E. Bolcome III/	Date (YYYY-MM-DD)	2017-12-04
Name	Robert E. Bolcome III, Ph.D., J.D.	Registration Number	69032

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 052210-501C03US
Application Number 14/925,961	Filed October 28, 2015
For NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	
Art Unit 1747	Examiner D. W. Mayes

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☒	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 700.00
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-0311 .

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 69,032 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Robert E. Bolcome III/	December 4, 2017
Signature	Date
Robert E. Bolcome III, Ph.D., J.D.	(617) 348-3027
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

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EXHIBIT A

Attorney Docket No. 35196-713.301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1747
Inventors: Adam Bowen et al.	Examiner: Mayes, Dionne Walls
Serial No.: 14/512,311	Confirmation No.: 9943
Filed: October 10, 2014	Customer No. 21971
Title: **NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF**	

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Commissioner:

I, Dr. Bradley James Ingebrethsen do hereby declare as follows:

1. I received my PhD in Physical Chemistry from Clarkson University in 1982, and since then I have spent over three decades as a scientist and consultant in both the tobacco and electronic cigarette ("e-cigarette") industry. I have also for the last decade served in academia as a lecturer, instructor, and adjunct professor of Chemistry at Monmouth University. I have authored over twenty peer reviewed papers and book chapters on subjects of relevance to the tobacco cigarette and electronic cigarette industries, and am listed as an inventor on several issued patents that are directed to various aspects of electronic cigarette technology. In 1989 I received the Philip Morris Award for Distinguished Achievement in Tobacco Science. My CV is attached as **Exhibit A.**

2. I have reviewed the present Application and its Office Action dated May 21, 2015, pending and proposed claims, and remarks (including exhibits thereto) that I understand will be filed in response to the Office Action. It is my understanding that the claims filed in the Applicant's response dated April 24, 2015 are rejected on the basis of 35 USC § 112 that the claims allegedly contain subject matter not in the description. Specifically the May 21, 2015 Office Action alleges that "the nicotine formulation has a pH <7," is not supported. It is also my understanding that the pending claims are rejected on the basis of 35 USC § 103(a) as allegedly

being obvious over a combination of Hon (US/2006/0196518), Gonda (US/2014/0261474) and Bowen (US/2009/0151717). Specifically it is alleged in the May 21, 2015 Office Action that one would be motivated to formulate a nicotine solution with a pH below 7 for use with an e-cigarette based on the teachings in the disclosure of Gonda.

3. First, nicotine formulations having "a pH <7" are indeed supported by the present Application. The pH of an aqueous solution is relatively simple to calculate for one of skill in the art of chemistry, especially with regard to the nicotine formulations as claimed in the present Application which comprise nicotine, wherein "the nicotine concentration is from about 2% (w/w) to about 6% (w/w)," and the acids of pending Claim 10. Using the pK_a of nicotine and pK_a of these acids, along with the molar ratios of nicotine to acid as described in the specification (ranging from 1:1 nicotine:acid to 1:4 nicotine:acid) of the present Application at paragraph [0063], and the corresponding solution concentrations, one of skill in the art can calculate that the pH of such nicotine solutions after a 1 to 10 dilution in water are from 6.7 to 2.1. These results are attached in **Exhibit B** *(explanation of the bases of such calculations is provided therein).* It is expected, and similarly easily calculable, for the pH's to also be acidic when the extended range of nicotine concentration of about 20% from the present Application is considered. Moreover, actual pH measurements of formulations made according to the teaching of Example 1 of the present Application using the acids noted therein and other acids disclosed in the present Application confirm the calculations (measured pH from 6.5 to 2.4). *See* Chenyue Declaration filed concurrently herewith. Thus, a pH<7 as claimed is supported by the specification of the present Application, as demonstrated by pH calculations for the formulations disclosed therein, at least.

4. Second, Nicotine is a diprotic organic base, as such it can exist in three different forms in aqueous solution described as diprotonated, monoprotonated, and the unprotonated free base form depending on the pH of the solution. *See*, for example, http://www.bob-r.com/ENI/Nicotine%20Titration%20Notes-HCl.pdf, attached as **Exhibit C**. The free base form of nicotine is predominant at a pH above 8, and is substantially ***not*** present, ~10% or less, at or below a pH of 7. *Id* at 2. Similarly, monoprotonated nicotine and diprotonated nicotine are predominant at and below a pH of 7. *Id.* Of these three forms the electrically neutral, free base form is known in the art to be the form that is most readily absorbed across cell membranes, and has been widely and commonly assumed over a long time period to be the form that will be most

readily and rapidly absorbed from cigarette smoke into the blood upon inhalation. *See, e.g.* El-Hellani *et. al*, *Free-Base and Protonated Nicotine in Electronic Cigarette Liquids and Aerosols*, Chem. Res. Toxicol. Available on-line July 22, 2015 at A (citing primary research from 1994), attached as **Exhibit D.** Hence, the free base form of nicotine has widely been considered to be the most desirable form of nicotine in nicotine solutions for use in an e-cigarette for effective absorption of nicotine and for production of nicotine's physiological effects from e-cigarettes which resemble the effects of traditional cigarettes. *Id.* That is, under these assumptions, it is commonly held knowledge amongst those that produce nicotine formulations for e-cigarettes that optimum nicotine absorption occurs when nicotine formulations have basic pH's because at basic pH nicotine exists predominantly in its free base form. *Id.*

5. Despite the publication in January 2015 of the present patent application, and the publication of its parent application (US 2014/0345631) in November 2014, the belief that optimum nicotine absorption occurs in nicotine formulations that have basic pH's (i.e., have nicotine present predominantly in the free base form) continues throughout industry as evidenced by El Hellani's July publication and Gonda, at least. It would be consistent with this longstanding belief, that commercial e-cigarette products would be formulated with a basic pH in order to increase the nicotine free base of their formulations. El-Hellani *et al.* at D.

6. In examining Gonda, particularly at paragraph [0033], also found in paragraph [0026] of the Gonda provisional App. No. 61/794,907, I find no indication that one of skill in the art making the assumptions that Gonda makes regarding pH and absorption rate and having the purpose that Gonda states, would formulate a nicotine solution with a pH below 7. Gonda maintains, "Although it is desirable to have a low pH formulation (acidic) to avoid interaction with certain types of plastic containers, it may be more desirable for a current user of cigarettes to have a high pH formulation (basic) to increase the absorption rate of the nicotine from the lung into the circulatory system to emulate the nicotine experience from cigarette smoke. Such high pH may, however, also cause greater airway irritation to the user." From this passage it is clear that it is **more** desirable to have a basic pH to increase absorption since nicotine absorption to "cause one or more sensory effects" is the point of Gonda. *See* paragraph [0013] of Gonda, also found in paragraph [0010] of the Gonda provisional App. No. 61/794,907. Acting with this common belief, one of skill in the art would first seek to prepare a basic nicotine formulation to maximize absorption, and only then adjust pH within this basic range to reduce airway irritation

or reduce interactions with the container. Without proper absorption to begin with, the purpose of Gonda, and Hon as well, are defeated. Thus, making the assumptions that Gonda makes regarding pH and absorption rate, and having the purpose that Gonda states, one would reasonably strive to reduce the pH of a nicotine solution within a range that does not prevent absorption, which under the common understanding described would be when nicotine is in its free base form, predominantly occurring at a pH above 8, and substantially occurring at or above a pH of 7.

7. The widely held understanding, even according to the Gonda reference cited by the Examiner, is that nicotine free base is the most desirable form of nicotine for a smoker for the purpose of effective nicotine absorption, as such based on this commonly held wisdom, the acidic nicotine formulations in the present Application show surprising, even striking, results. The data in FIGs 1, 2, 4, 5 and 6 of the present Application show that all acidic nicotine formulations invoke physiological responses (heart rate) that are more intense and absorption (blood nicotine levels) kinetics that are more rapid than those produced by nicotine in its free base form. **FIG. 4** of the Applicants' filing (reproduced below for ease of reference) illustrates these results in the most succinct way. The nicotine formulations with benzoic acid, citric acid, salicylic acid, succinic acid, malic acid all produce blood nicotine levels that peak at 3 times that of a nicotine free base solutions, and are closer to that of a traditional cigarette by this metric. These are striking results that run counter to a long held belief in the field of nicotine formulation.

8. Also surprising in the present Application, based on the commonly held pH absorption relationship for nicotine, is that some acidic nicotine salt solutions perform better than others. FIG. 1 of the present Application (reproduced below for ease of reference), for example, shows that nicotine formulations with benzoic acid, pyrivuc acid, malic acid, and levulinic acid invoke a stronger physiological response than nicotine formulations including succinic acid and citric acid.. Again, these results demonstrated in the present Application are striking, and represent an additional level of surprising result in addition to the afore-mentioned results obtained with a formulation having an acidic pH.

9. While normal or traditional cigarette manufacturers in the past have experimented with specific acids mixed with dry tobacco, one of skill in the art would not necessarily look to the teachings relevant to nicotine delivery in normal cigarettes in order to predict nicotine

delivery characteristics of nicotine formulations for an e-cigarette. This lack of correspondence is due to important distinctions between the nicotine formulations of e-cigarettes and the dry tobaccos used in normal cigarettes with respect to both their initial states and their transformations into aerosols. There are numerous differences between the low temperature vaporization of the liquid nicotine formulation of an e-cigarette, and the high temperature burning of the solid organic matter like the dry tobacco of a normal cigarette. Foremost, the dry solid organic matter of a normal cigarette contains thousands of distinct chemicals that produce a larger number of products when burned through several mechanisms including combustion, pyrolysis or thermal degradation, pyrosynthesis reactions,, and simple vaporization. *See, e.g.* Baker, *Smoke Generation Inside a Burning Cigarette: Modifying Combustion to Develop Cigarettes that may be less Hazardous to Health*, 32 Prog Energy Combust Sci. 373, 373-385 (2006) at 377, attached as **Exhibit E**. E-cigarettes, on the other hand, operate at much lower temperatures compared to a normal cigarette and simply vaporize or evaporate their constituents to form the aerosol to be inhaled. *See*, for example, the present Application at paragraph [0055]. Moreover, the complexity in the conversion process from starting material to aerosol in tobacco cigarettes, alone, leads to significant uncertainty for the skilled artisan when trying to translate knowledge from the tobacco industry to liquid nicotine formulations used in the e-cigarette industry. Further, pH is a measure of acidity or basicity of an aqueous solution not of a solid, such as a dry tobacco product, thus, one of skill in the art would not assume that the effects observed with dry tobacco additives would be predictors for pH based effects in liquid formulations used in e-cigarettes in order to aid in absorption, particularly when the prior evidence of e-cigarette formulation data has been interpreted to show that free base nicotine solutions having basic pH are essential to achieving proper absorption. In sum, the difference between the two types of nicotine delivery is great enough that one would not reasonably nor necessarily expect to successfully replicate results generated with dry tobacco in a liquid nicotine formulation.

10. Additionally, I do not believe that the experience of tobacco manufacturers with adding acids to dry tobacco and their understanding of the acids' effects would lead one of skill in the art to an e-cigarette nicotine formulation with the surprising results of the present Application. The prevailing understanding within the tobacco industry was that when added to dry tobacco, acids resulted in enhanced "perceptions of smoothness and mildness" that increased

the "potential for cigarette smoke to be inhaled deeper into the lungs" thereby resulting in higher nicotine impact because the smoker will be more likely to inhale the smoother and milder smoke. *See* Keithly *et al.*, *Industry research on the use and effects of levulinic acid: A case study in cigarette additives*, 7 Nicotine and Tob. Res. 761 (2005), attached as **Exhibit F**. I believe that this latter understanding is based in part on the fact that nicotine from inhaled cigarette smoke, when adjusted for total nicotine delivered, has been observed to be absorbed in the plasma of smokers at the same efficiency regardless of cigarette or tobacco type. These experimental findings and related observations are discussed at length in Ingebrethsen, *Numerical Simulation of the Effects of Dilution Level, Depth of Inhalation, and Smoke Composition on Nicotine Vapor Deposition* 18 Inhal. Toxicol. 1071, 1071-1076 (2006), attached as **Exhibit G**. Thus, I believe that the Applicants' discovery that the addition of acids to e-cigarette formulations results in higher and more rapid absorption of nicotine in blood plasma from inhaled aerosols when compared to free base nicotine, is unexpected from tobacco manufacturers' experience with the addition of acids to dry tobacco, and is indeed surprising.

11. All statements made herein are true to the best of my knowledge, or if made upon information and belief, are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: 9/4, 2015

Bradley James Ingebrethsen, PhD

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FIG. 1[1]

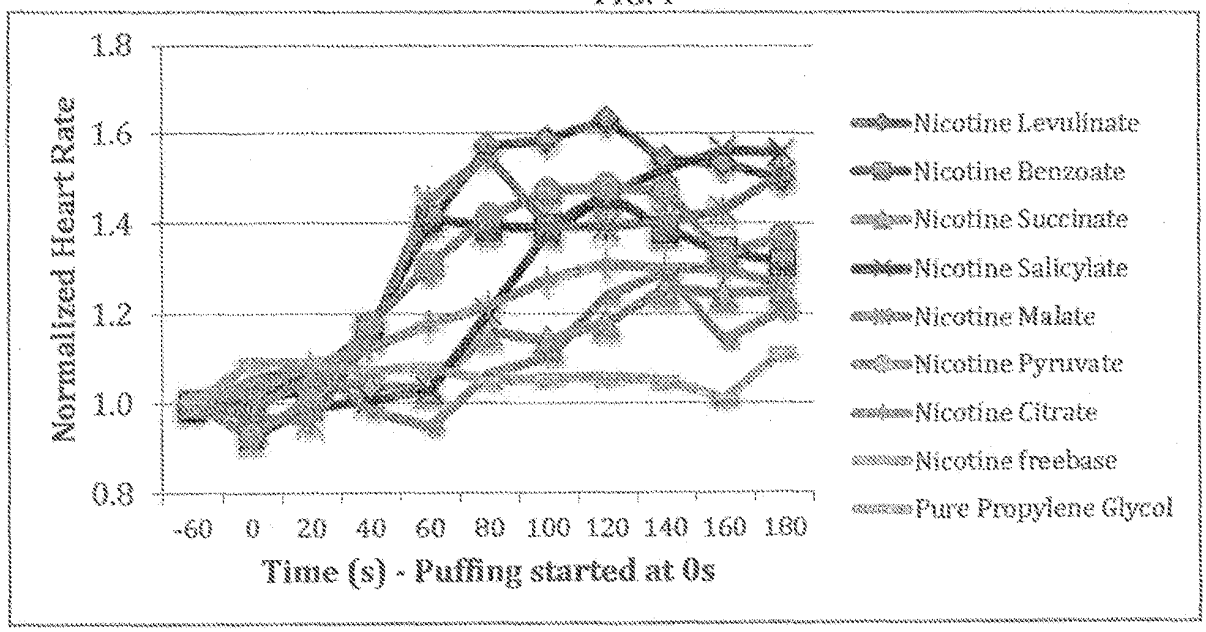
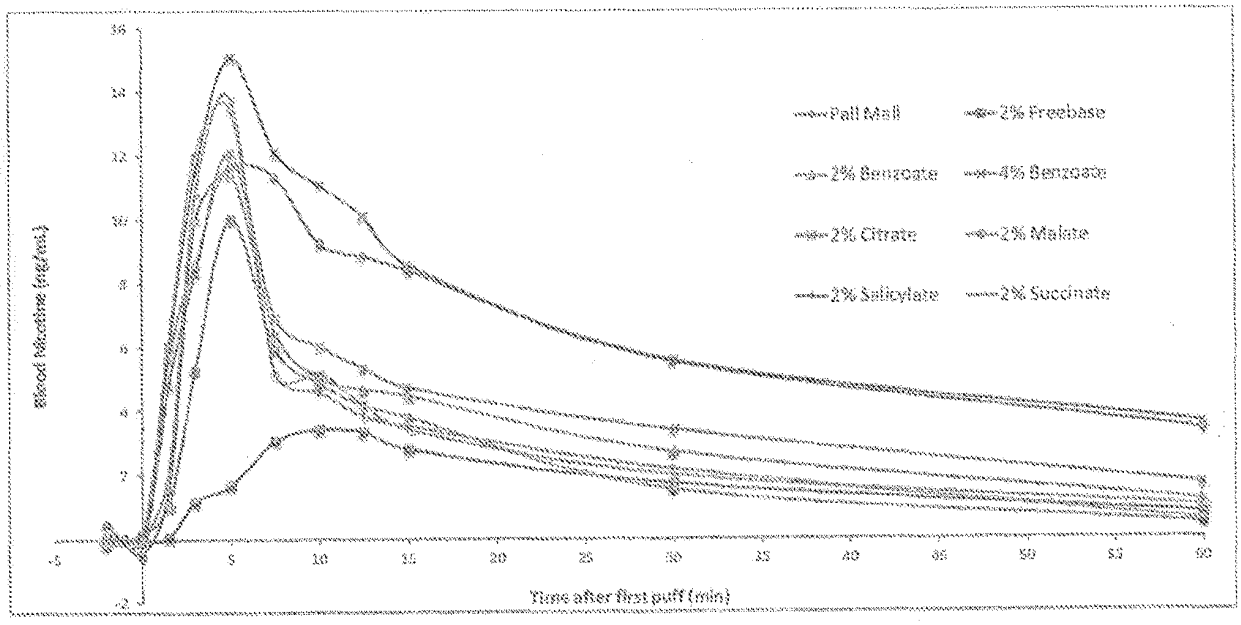


FIG. 4[1]



[1] Reproduced from US/2015/0020824

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EXHIBIT A

CURRICULUM VITAE

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EDUCATION:

Clarkson University
1982 Ph.D. Physical Chemistry
1979 M.S. Physical Chemistry

Brooklyn College
City University of New York
1976 B.S. Chemistry

EMPLOYMENT:

2002-present Monmouth University, West Long Branch, New Jersey
Lecturer of Chemistry
Instructor of Chemistry
Adjunct Professor of Chemistry

2000-present Consultant on aerosol science

2000-2001 Marist College, Poughkeepsie New York
Visiting Assistant Professor of Chemistry

R.J. Reynolds Tobacco Company
Research and Development Department
Winston-Salem, North Carolina
1996 - 1999 Principal Scientist
Manager - Product Applications
1990 - 1996 Master Scientist
Section Head - Product Applications
1986 - 1990 Sr. Staff R&D Chemist
1983 - 1986 Senior R&D Chemist
1981 - 1983 R&D Chemist

1996 - 1996 Winston-Salem State University
Winston-Salem, North Carolina
Adjunct Professor of Physics

1977 – 1981 Clarkson University
Potsdam, NY 13676
Research Assistant/ Teaching Assistant

HONORS AND AWARDS:

B.S. - Magna Cum Laude, Brooklyn College
1989 Philip Morris Award for Distinguished
Achievement in Tobacco Science

PROFESSIONAL ACTIVITIES:

Reviewer *Journal Aerosol Science* and *Aerosol Science and Technology*

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EXHIBIT B

EXHIBIT B

Theoretical pH Values for exemplary nicotine acid formulations		
Acid (nicotine: Acid)	2% Nicotine	6% Nicotine
Malic 1:1	3.52	3.28
Malic 1:4	2.83	2.63
Succinic 1:1	3.66	3.43
Succinic 1:4	3.07	2.86
Citric 1:1	3.34	3.09
Citric 1:4	2.63	2.43
Lactic 1:1	5.97	5.97
Lactic 1:4	3.53	3.53
Benzoic 1:1	6.12	6.12
Benzoic 1:4	3.81	3.81
Pyruvic 1:1	5.61	5.61
Pyruvic 1:4	2.51	2.45
Lauric 1:1	6.66	6.66
Lauric1:4	4.83	4.83
Levulinic 1:1	6.31	6.31
Levulinic 1:4	4.16	4.15
Sorbic 1:1	6.39	6.39
Sorbic 1:4	4.31	4.31
Salicylic 1:1	5.68	5.68
Salicylic 1:4	2.85	2.83

Methodology

The theoretical pH values are determined by standard, textbook calculations for weak acids and bases in aqueous solutions, see "Quantitative Chemistry", William B. Guenther (1968) Addison-Wesley Chapter 6. The calculations are performed by combining the equilibrium equations with mass balance and electroneutrality equations to yield a single equation with hydrogen ion concentration, or pH, as the only unknown. In the present case, equilibrium equations for water, nicotine and the weak acid present in each solution were used and analytic concentrations for nicotine and the acids were specified. Substitution among the equations yielded a single polynomial in acid concentration that could be solved with the values for the equilibrium constants and the analytic concentrations to yield pH.

1. The equations that are combined to solve for pH:

   1.1. Water equilibrium: $Kw = [H+][OH-]$

   1.2. First acid ionization: $Ka1 = [H+][HA-]/[H_2A]$

   1.3. Second acid ionization: $Ka2 = [H+][A--]/[HA-]$

   1.4. First nicotine ionization: $Kn1 = [Nic][H+]/[NicH+]$

   1.5. Second nicotine ionization: $Kn2 = [NicH+][H+]/[NicH_2++]$

   1.6. Mass balance for acid: $Ca = [H_2A] + [HA-] + [A--]$

   1.7. Mass balance for nicotine: $Cn = [Nic] + [NicH+] + [NicH_2++]$

   1.8. Electroneutrality :

$$[H+]+[NicH+]+2*[NicH_2++] = [OH-]+ [HA-] + 2*[A--]$$

2. Substitutions are made with the equations above to yield a single equation that can be solved for [H+] shown here as x:

$$0 = x + Cn*x/(Kn1+x+x^2/Kn2) + 2*Cn*x^2/(Kn1*Kn2 + Kn2*x + x^2) - Kw/x - Ka1*Ca*x/(x^2+Ka1*x +Ka1*Ka2) - 2*Ka1*Ka2*Ca/(x^2+Ka1*x+Ka1*Ka2)$$

Where :

[ ]	square brackets indicated molar concentration
$x = [H^+]$	is the molar concentration of hydronium ions
pH	is the negative base ten log of [H+]
Kw	is the water auto-ionization constant
Cn	is the analytic, or total concentration of all nicotine derived species
Kn1	is the acid ionization constant for mono-protonated nicotine
Kn2	is the acid ionization constant for di-protonated nicotine
Ka1	is the first ionization constant of the weak acid
Ka2	is the second ionization constant of the weak acid
Ca	is the analytic concentration of weak acid

*For mono-protic acids the Ka2 value is set to a very small value effectively reducing the equations to the mono-protic case.

*For tri-protic citric acid the very weak third ionization was not included in the calculations and would not be expected to significantly effect the calculation for citric acid.

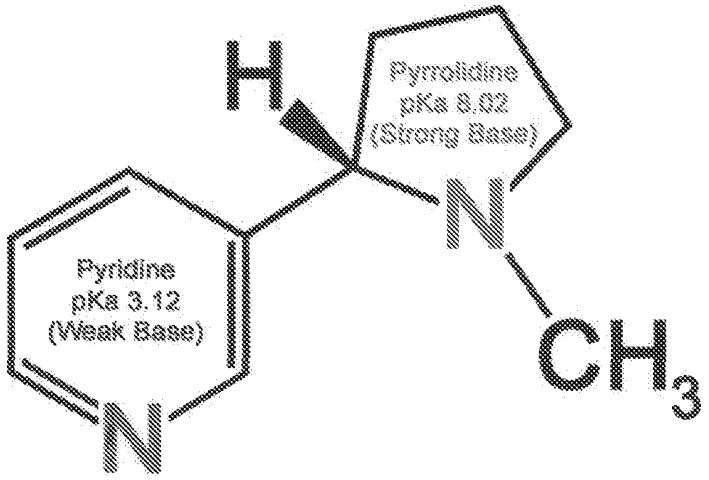
EXHIBIT C

Nicotine

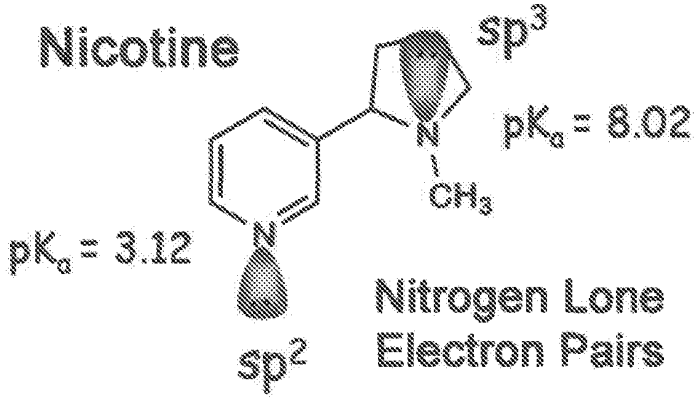
"Nicotine and other tobacco alkaloids that possess a basic pyrrolidine nitrogen readily form stable salts with both mineral and organic acids." (Analytical Determination of Nicotine and Related Compounds and Their Metabolites)

"Nicotine reacts with hydrochloric acid to form a water-soluble salt called nicotine hydrochloride." (General, Organic, and Biochemistry: An Applied Approach)

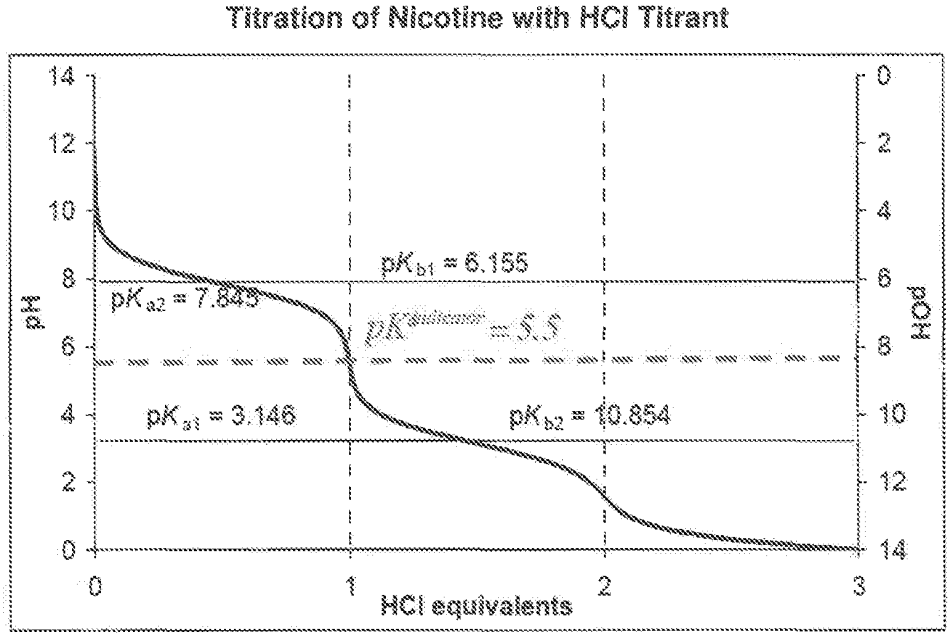
"Nicotine is a Diprotic Base with pKa's of 3.12 (pyridine ring) and 8.02 (pyrrolidine ring)." (Optimization Study for the Reversed-Phase Ion-Pair Liquid Chromatographic Determination of Nicotine in Commercial Tobacco Products)

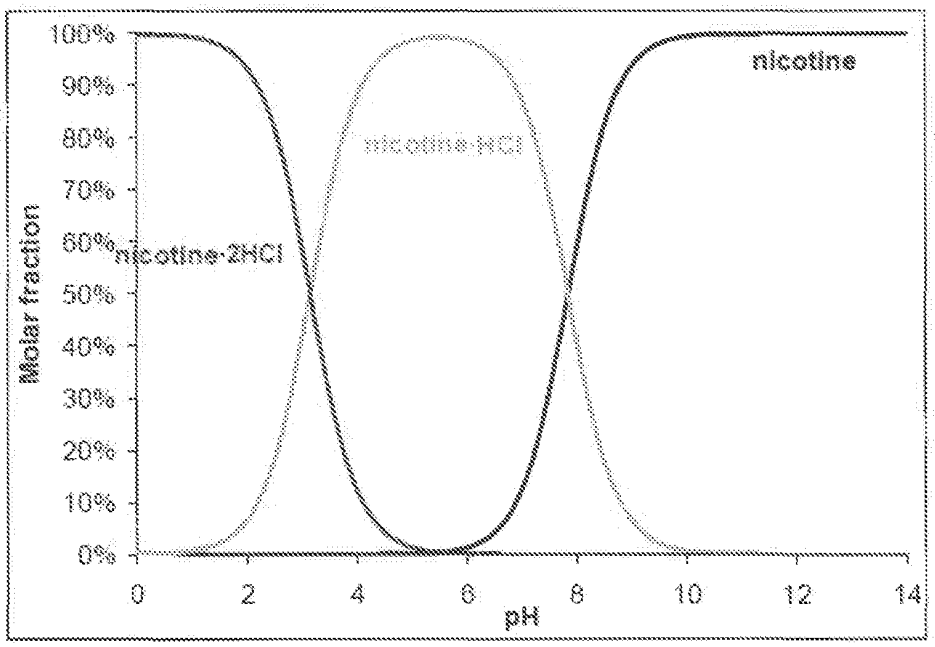


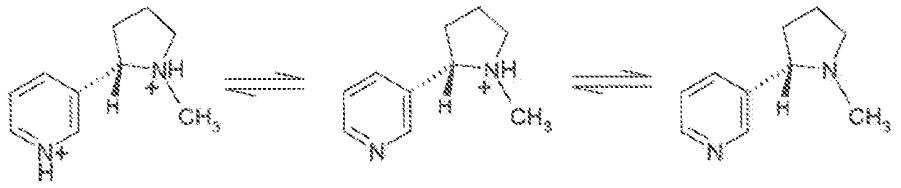
The Nicotine Molecule contains two Nitrogen Atoms capable of accepting a Proton
The Pyrrolidine Nitrogen is considerably more basic than the Pyridine Nitrogen



Nitrogen Lone Electron Pairs form Coordinate (Dative) Covalent Bonds with Protons







Nicotine-2HCl Nicotine-HCl Nicotine

Nicotine Dissociation in Water

$C_{10}H_{14}N_2 + H_2O \rightarrow C_{10}H_{15}N_2^+ + OH^-$

$C_{10}H_{15}N_2^+ + H_2O \rightarrow C_{10}H_{16}N_2^{2+} + OH^-$

Hydrochloric Acid Dissociation in Water

$HCl + H_2O \rightarrow H_3O^+ + Cl^-$

Nicotine Neutralization with Hydrochloric Acid

$C_{10}H_{14}N_2 + HCl \rightarrow C_{10}H_{15}N_2^+ + Cl^-$ (Nicotine Hydrochloride Salt)

$C_{10}H_{15}N_2 + HCl \rightarrow C_{10}H_{16}N_2^{2+} + Cl^-$ (Nicotine Dihydrochloride Salt)

Molar Masses (Molecular Weights)

Nicotine $C_{10}H_{14}N_2$
Carbon Atoms: 10 x 12.0107 = 120.107
Hydrogen Atoms: 14 x 1.00794 = 14.11116
Nitrogen Atoms: 2 x 14.00674 = 28.01348
Molecular Weight = 162.23164

Hydrochloric Acid HCl
Hydrogen Atom = 1.00794
Chlorine Atom = 35.453
Molecular Weight = 36.46094

Dilution of Solution – M1V1 = M2V2

(Molarity 1 X Volume 1 = Molarity 2 X Volume 2)

Moles of HCl (Hydrochloric Acid) vs. Moles of Nicotine

1. 0.10N HCl Contains 0.1 Moles of HCl/Liter.
2. To Calculate Moles of HCl in 1 ml of 0.10N HCl:
   0.10N HCl = 0.1 Moles HCl/Liter
   1 ml = 0.001 Liter
   0.001 Liter X 0.1 Moles = 0.0001 Moles
3. 0.0001 Moles of 0.10N HCl will Neutralize 0.0001 Moles of Nicotine.
4. 0.0001 Moles of Nicotine = 16.223 mg (162.23 X 0.0001 = .016223 Grams)
5. 1 ml of 0.10N HCl Neutralizes 1 ml of 16.223 mg/ml Nicotine.

Nicotine Oxidation

$C_{10}H_{14}N_2 + O_2 \rightarrow CO_2 + H_2O + N_2$

Nicotine Oxidation Balanced Equation

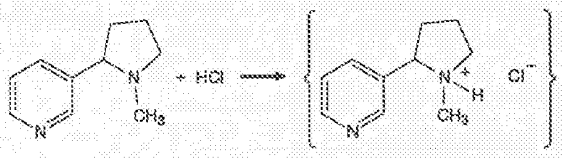
$2\ C_{10}H_{14}N_2 + 27\ O_2 \rightarrow 20\ CO_2 + 14\ H_2O + 4\ N$

Drawing the salt of a physiologically active amine

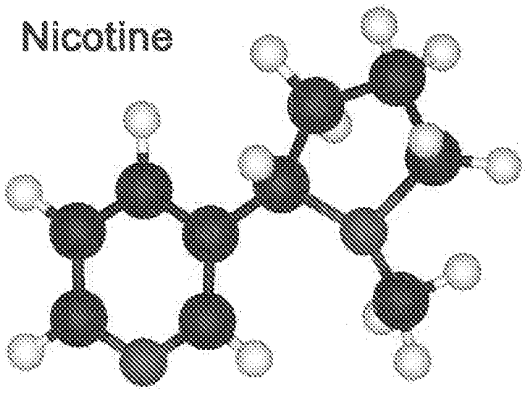
Nicotine reacts with hydrochloric acid to form a water-soluble salt called nicotine hydrochloride. In this salt, the hydrogen ion is bonded to the nitrogen atom in the five-membered ring. Draw the structure of this salt. (See Figure 11.6 for the structure of nicotine.)

SOLUTION

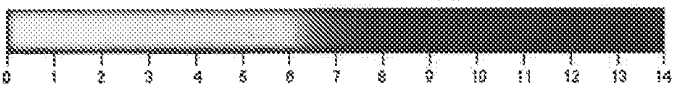
Attaching the hydrogen ion from HCl to the correct nitrogen atom in nicotine gives us the conjugate acid of nicotine. The salt contains this conjugate acid and a chloride ion, as shown here:



The structure of nicotine hydrochloride



bromothymol blue



Also known as: 3',3"-dibromothymolsulfonephtalein

Type: $HIn + H_2O \rightleftharpoons In^- + H_3O^+$

pK: 7.30

Approximate pH range for color change: 6.0-7.6

Color of acid form: yellow

Color of base form: blue

pH Scale ($pH = -Log_{10}[H+]$)

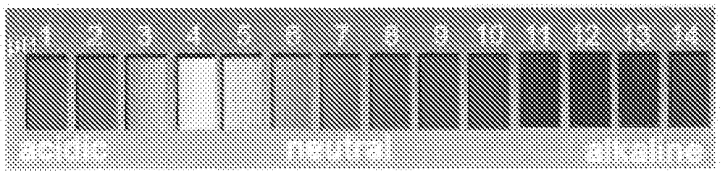


EXHIBIT D

Chemical Research in Toxicology

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Free-Base and Protonated Nicotine in Electronic Cigarette Liquids and Aerosols

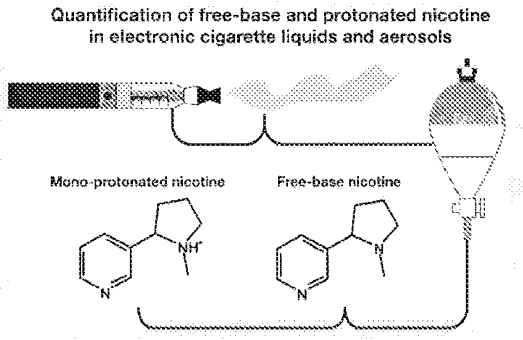
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[†]Chemistry Department, Faculty of Arts and Sciences, and [‡]Mechanical Engineering Department, Faculty of Engineering and Architecture, American University of Beirut, Beirut, Lebanon

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Supporting Information

ABSTRACT: As with other tobacco aerosols, nicotine delivery from e-cigarettes (ECIG) depends on the total nicotine and its partitioning between free-base (Nic) and protonated ($NicH^+$) forms. Previous studies of ECIG nicotine emissions have generally reported "nicotine yield" without attention to whether the methods employed resulted in quantification of the total nicotine or only one of its forms, making reported results difficult to compare across studies or to evaluate against reported blood exposure. This study reports a convenient solvent extraction method for determining total nicotine and its partitioning in ECIG liquids and aerosols by gas chromatography. Commercial ECIG liquids and aerosols were analyzed, and it was found that most of the nicotine was in the Nic form, with aerosols exhibiting higher Nic fraction than the parent liquids. Apparent pH was found to correlate with nicotine partitioning and can provide a useful indirect measure when chromatography is unavailable. Finally, labeled ECIG liquid nicotine concentration in commercial products was often inconsistent with measured nicotine.



1. INTRODUCTION

Electronic cigarettes (ECIGs) are rapidly gaining popularity around the globe. This phenomenon is likely driven by a number of factors, including the perception that, in comparison to conventional cigarettes, they present a safer method for obtaining nicotine.[1,2] This perception stems from the fact that ECIGs are electrically powered devices that heat and vaporize a nicotine-containing flavored liquid to produce an inhalable aerosol, without involving combustion and presumably much of the exposure to combustion-related toxicants such as CO, PAH (polycyclic aromatic hydrocarbon), and nitric oxide that are characteristic to conventional tobacco products.[3] ECIGs liquids do not contain tobacco but rather a nicotine solution in propylene glycol or glycerol (or a mixture of both) with flavors to make the ECIG attractive.[4,5] In summary, the central concept behind smoking or what is now accepted as "vaping" is volatilization of nicotine into an aerosol of liquid droplets and vapors that will be delivered to the "vaper's" body.[6]

Nicotine has two basic nitrogen groups in its chemical structure ($pk_{a_1} = 3.12$; $pk_{a_2} = 8.02$), and thus, it can exist in three forms, namely, free-base (Nic), monoprotonated ($NicH^+$), or diprotonated salt ($NicH_2^{+}$) depending on the pH of the matrix.[7−9] This intrinsic characteristic is quite important since it affects the bioavailability of nicotine;[10] Nic is thought to be the only form that diffuses through epithelial tissues in the human body. Thus, all else being equal, an ECIG with a higher proportion of Nic will increase the rate of uptake of nicotine by the user's body.

To date, most published ECIG studies have reported total nicotine content in ECIG solutions and aerosols without reference to the nicotine form. In addition to the modified NIOSH 2551 method to quantify total nicotine in cartridges, sample preparation methods included steps that converted all the nicotine in a given sample to its free-base or protonated forms by the addition of ammonia, sodium hydroxide, or acidic solutions prior to quantification by gas chromatography (GC),[11−15] without an attempt to measure each fraction separately. Hence, despite its critical importance to systemic nicotine delivery processes,[16] there is no direct information available about the free-base fraction of ECIG nicotine in liquids and aerosols. There are reports of indirect measures of the free-base fraction based on pH measurements.[17] These measures might not give accurate distribution of Nic and $NicH^+$ in the matrix due to the presence of flavors and other additives that may affect the pH measurements.[18]

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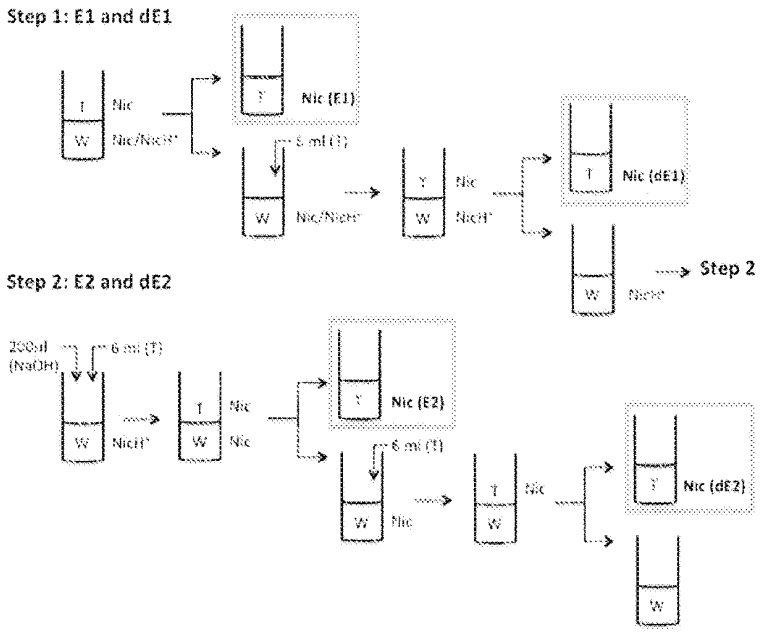


Figure 1. Schematic diagram for the extraction procedure adopted to separate Nic from $NicH^+$. "T" stands for toluene and "W" for water. E1, dE1, E2, and dE2 are the toluene extracts that were analyzed by GC-MS.

In this work, Nic and $NicH^+$ were separated and quantified using a convenient analytical method consisting of a liquid–liquid extraction technique followed by gas chromatography coupled with mass spectrometry (GC-MS) analysis. The extraction technique uses a solvent system consisting of water and toluene and exploits the fact that due to its chemical structure, toluene will extract only Nic from a solution containing both Nic and $NicH^+$ (detailed discussion of the mechanism of selective extraction at different pHs is presented in the Supporting Information). In this study, we validated the analytical method against laboratory standard solutions (STD) and then deployed it to study a series of ECIG liquids and aerosols to determine the forms of nicotine present in these systems. In addition, we compared measurements of nicotine fractions to theoretical estimates based on pH and pk_a of the pyrrolidine ring. Finally, total nicotine content was compared to labeled nicotine content on commercial products.

2. MATERIALS AND METHODS

The analytical method developed in this study exploits the relative difference in solubility of Nic and $NicH^+$ in toluene and water, respectively. With a solubility of water in toluene of 3.3×10^{-3} mole fraction,[19,20] 6 mL of toluene absorbs a minimal amount of 3.36 μL from the water phase. The extracted Nic in the toluene phase was then introduced into a gas chromatograph coupled with a mass spectrometer for quantification. $NicH^+$ remaining in the water phase was transformed into Nic by sodium hydroxide and then extracted by toluene to be analyzed.

2.1. Materials. Prefilled ECIG cartridges of the Vapor for Life (V4L), V2, Green Smoke, Apollo, Bull Smoke, Halo, G6, Bluewater, and Blu brands in various nicotine concentrations were procured from US Internet vendors as were samples of ECIG liquid refill solutions of the brand My Freedom Smoke Do It Yourself (DIY) (100 mg/mL). Selected solutions were smoked (vaped) using a commercial tank based ECIG (VaporZone [Platinum], 2.4 Ohms). HPLC grade toluene (CAS registry number 108-88-3) was obtained from Aldrich. Pure nicotine (CAS registry number 54-11-5) was purchased from Acros Organics. Hexadecane (CAS registry number 544-76-3) procured from Sigma-Aldrich was used as internal standard (IS). Glass fiber and quartz were purchased from Pall Corporation and Whatman International Ltd., respectively.

We note that the nicotine content for 9 of the 17 e-liquids studied were labeled with units "mg", without clear indication whether this corresponded to the mass of nicotine in an entire cartridge, or the mass of nicotine per mL of liquid, or both (i.e., that a given cartridge contained 1 mL of liquid). Following common practice among ECIG users[21,22] and based on communication with one of the manufacturers,[23] we interpreted for the purposes of this study the unit "mg" to mean mg/mL of ECIG liquid, and "%" to indicate mg/g, where unity specific gravity is assumed (i.e., 1.2% was taken to mean 12 mg/mL).

2.2. pH Measurements. The pH of the prefilled cartridges and DIY liquids and tank solutions was measured using a Starter 3100 OHAUS pH-meter. Prior to measurement, a volume of each commercial solution was added to deionized water in order to prepare a final nicotine concentration of 600 ppm in a final volume of 6 mL. It is noted that because the nicotine concentration varied across commercial ECIG refill liquids, the volume of refill liquid required to attain a final aqueous solution concentration of 600 ppm also varied across samples.

2.3. Liquid–Liquid Extraction (LLE). Samples were extracted from standard nicotine solutions, ECIG cartridges (or tanks), and filters collecting ECIG aerosols described in section 2.7 below. To extract samples from ECIG cartridges, the polyester filler was removed from each prefilled cartridge, transferred into a 1 mL plastic syringe, and then pressed into a glass vial. As with the pH measurements, a calculated volume of e-liquid is dissolved in 6 mL of water in order to prepare a final nicotine concentration of 600 ppm. Then 6 mL of toluene was added (Figure 1), and the mixture was shaken for 30 min. The mixture was then allowed to separate into toluene and aqueous phases. The toluene phase (denoted as "E1" in Figure 1), which is capable of dissolving only Nic, was removed from the sample and then introduced into a GC-MS for quantification against hexadecane as internal standard (IS) added prior to injection. To verify that all Nic has been extracted, the extraction step was repeated by adding 6 mL of toluene and repeating the above steps. This resulted in a second toluene sample (denoted "dE1"). After separating toluene from water as before, 200 μL of NaOH solution (1N) was added to the aqueous layer to convert $NicH^+$ in solution into Nic.

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Table 1. % Nic Recovery at Different Stages of the Extraction (E1, dE1, E2, and dE2) for Known Concentrations of Standard Solutions[a]

sample	pH	% E1	% dE1	total Nic	% E2	% dE2	total $NicH^+$	measured Nic/$NicH^+$ (%)	theoretical Nic/$NicH^+$ (%)
STD(1)	9.7	90.0	7.7	97.7	2.3	...	2.3	97.7/2.3 ± 0.3	97.8/2.2
STD(2)	8.5	69.3	9.9	79.2	20.8	...	20.8	79.2/20.8 ± 0.6	77.2/22.8
STD(3)	8.1	47.2	5.8	53.0	44.8	2.2	47.0	53.0/47.0 ± 1.4	52.9/47.1
STD(4)	7.5	22.3	5.5	27.8	65.9	6.2	72.2	27.8/72.2 ± 0.8	24.0/76.0
STD(5)	5.2	0.3	0.4	0.7	91.6	7.7	99.3	0.7/99.3 ± 0.1	0.2/99.8

[a]Each number is an average of triplicate samples, and the deviation from the mean is shown by the standard deviation. STD stands for standard solutions.

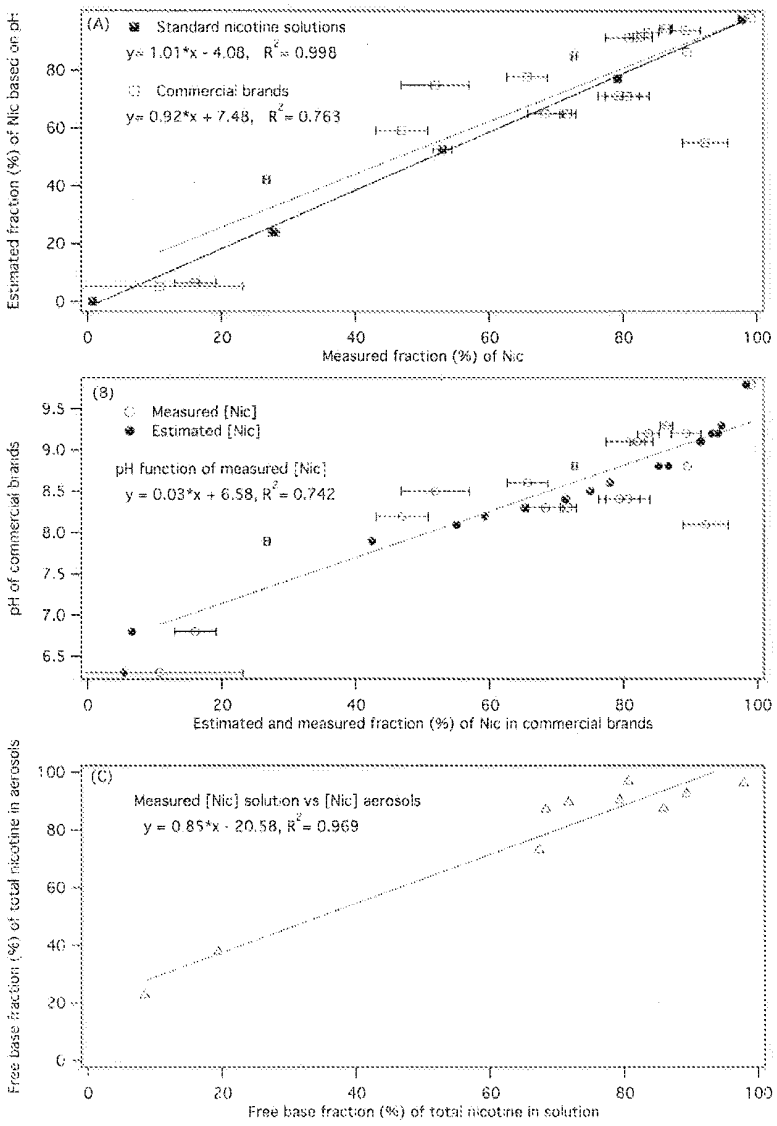


Figure 2. Correlations among (A) estimated versus measured free base nicotine in commercial and standard solutions, (B) pH and estimated or measured free base nicotine in commercial solutions, and (C) measured free base proportion of total nicotine in solution versus measured free base proportion of total nicotine in the aerosol phase for commercial and standard nicotine solutions.

Six milliliters of toluene was then added to the sample, and the previously described steps used to generate "E1" (and "dE1") were repeated to generate "E2" (and "dE2") samples. Thus, "E1" (and "dE1") contains Nic that was originally in the free-base form, while "E2" (and "dE2") contains Nic that was in the protonated form in the original sample.

2.4. Gas Chromatorgraphy–Mass Spectrometry (GC-MS) Conditions. The GC-MS analysis was performed on Thermo-Finnigan Trace GC-2000 Polaris QMS equipped with an AS 3000 II autosampler.

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Table 2. pH Measurements, Total Nicotine, and Percentages of Nic in Several e-Liquid of Commercial Cartridges and Tanks[a]

sample (flavor)	nicotine label (mg/mL)	measured total nicotine (mg/mL)	pH	% Nic estimated	% Nic measured
DIY(2) Myfreedom smoke (unflavored)	100	97.7	9.8	98.3	99.1
DIY Myfreedom smoke (caramel capuccino)	100	97.7	8.8	86.6	89.5
V4L (tobacco)	18	7.8 ± 0.1	6.3 ± 0.7	5.3 ± 6.5	10.7 ± 12.4
V4L (strawberry)	18	14.3 ± 0.9	8.1 ± 0.3	55.1 ± 14.9	92.2 ± 3.4
V2 (red)	12	7.4 ± 0.5	9.1 ± 0.1	91.5 ± 0.9	82.1 ± 1.1
V2 (green menthol)	12	8.3 ± 0.2	8.8 ± 0.0	85.2 ± 0.9	72.7 ± 0.3
Green Smoke (red label)	24	19.5 ± 1.1	9.1 ± 0.1	91.4 ± 1.0	80.9 ± 3.5
Green Smoke (menthol ice)	24	20.1 ± 0.4	9.2 ± 0.1	93.2 ± 0.8	83.7 ± 1.6
Apollo (tobacco black)	Med	7.6 ± 0.6	8.5 ± 0.1	75.0 ± 6.6	51.9 ± 5.1
Apollo (tobacco)	12	8.1 ± 0.5	8.3 ± 0.0	65.1 ± 0.4	68.3 ± 2.6
Apollo (banana cream)	12	9.3 ± 0.4	8.3 ± 0.0	65.2 ± 1.0	71.7 ± 1.2
Apollo (blueberry kona coffee)	12	9.7 ± 0.6	8.4 ± 0.0	71.4 ± 0.2	79.3 ± 3.1
Blu (classic tobacco black)	9−12	8.8 ± 0.4	7.9 ± 0.1	42.4 ± 2.7	26.7 ± 0.4
Blu (tobacco)	13−16	13.2 ± 0.2	6.8 ± 0.1	6.5 ± 1.6	16.0 ± 3.1
Bluewater (punch lights)	8	7.7 ± 0.4	9.2 ± 0.1	94. ± 1.0	89.3 ± 2.2
Bull smoke (Turkish tobacco)	18	10.8 ± 0.5	8.6 ± 0.1	77.9 ± 3.0	65.6 ± 3.0
Bull smoke (menthol breeze)	18	15.0 ± 0.5	9.3 ± 0.0	94.6 ± 0.1	86.4 ± 0.9
Halo (Tribeca)	18	14.0 ± 0.9	8.4 ± 0.0	71.2 ± 0.6	80.6 ± 3.3
G6 (Tribeca)	18	7.4 ± 0.2	8.2 ± 0.0	59.3 ± 1.4	46.9 ± 3.9

[a]Standard deviation (±STDEV) is calculated based on the analysis of triplicate sample.

Separation was achieved with a RTx-5MS (30 m × 0.25 mm × 0.25 μm film thickness) fused silica capillary column purchased from Restek. Splitless injection mode of 1 μL was utilized. The mobile phase was helium gas with 1 mL/min flow rate. The injector temperature was set at 250 °C. The oven temperature program was 70 °C for 2 min, 20 °C/min to 230 °C, and held for 1 min. The total run time was 11 min, and solvent delay time was 4 min. Quantification was done in the ion current mode (m/z = 84 for nicotine and 57 for IS).

2.5. Analytical Characteristics of the LLE Method. A standard calibration curve was prepared by extracting a range of concentrations (50−1000 ppm) (diluted 50 times before injection onto the GC) of laboratory-prepared standard nicotine solutions following the aforementioned method. The linearity of the method was assessed by linear regression, and the correlation coefficient (R^2) was found to be greater than 0.997. The accuracy of the method was measured by spiking blank filters with Nic standard solutions of pH 9.7 at a concentration of 500 ppm, and the recovery was found to be 101.0 ± 3.2%. Two triplicate measurements, which were completed by two different operators, were used to determine the recovery. The yields of % RSD were <4%. Furthermore, the precision of the method was examined by quantifying six replicate samples at three different concentrations spanning the whole calibration curve. These samples were subjected to the entire extraction procedure, and the relative standard deviation (% RSD) at each concentration was found to be ≤6%.

2.6. Validation of the LLE Method Using pH-Manipulated STD Nicotine Solutions. It has been reported that toluene is an effective agent for nicotine extraction in the liquid−liquid equilibrium of the nicotine/water/toluene system[20] and that, in comparison to other common solvents, toluene has the lowest water solubility.[23] Using the reported solubility of water in toluene of 3.3×10^{-3} mole fraction,[18] we calculated that less than 0.1% by volume of water can be dissolved in the toluene extract, resulting in a similarly negligible bias error in the determination of $NicH^+$. A high percent total Nic recovery of 92.1% (% Nic_E = ($(Nic_{E1})/(Nic_{total})$) = 92.1%) was obtained when the extraction method was tested on standard solutions of known concentrations as shown in Table 1. Furthermore, in order to ensure that we only extracted Nic with toluene, the extraction method was tested on acidified samples (STD(5), pH 5.2). More than 99% recovery of total nicotine was found in the form of $NicH^+$ in E2 and dE2, and less than 1% Nic was recovered from E1 and dE1 (for more details on the mechanism of selective extraction at different pHs, check Supporting Information).

For external validation, five standard solutions at pHs ranging between 5.2 and 9.7 were prepared and tested (Table 1). Starting with an original pH nicotine solution of 9.7, the STD solutions were prepared by adding the appropriate amount of acetic acid in order to reach the sought pHs. Measurements were then compared to the theoretical estimations using the Henderson−Hasselbalch equation ($pH = pK_a + \log[Nic]/[NicH^+]$). It was found that at $7 < pH < 9$ both forms of nicotine (Nic and $NicH^+$) were present in solution and that at pH > 9 or <5, Nic or $NicH^+$ predominates, respectively. Measurements were in excellent agreement with the estimated Nic/$NicH^+$ ratios with an $R^2 > 0.998$ and a slope of 1.01 as shown in Figure 2A.

2.7. Aerosol Generation and Sampling. A custom-designed digital puff production machine[25] was used to generate ECIG aerosols from the cartridges.[26] Puff topography (puff duration, interpuff interval, and flow rate) was selected to represent an experienced e-cigarette user (4 s puff duration and 10 s interpuff duration) with a puff velocity of 1 l/min.[26−28] The ECIG was powered using 3.3 V regulated DC power supply representing an average of the most commonly applied voltages (2.6−4.1 V). Total particulate matter was collected by drawing the ECIG aerosol generated in 15 puffs through a filter trap located at the ECIG mouthpiece outlet. Immediately after the 15th puff, each filter was immersed in 6 mL of water and shaken for 30 min, and then the same liquid−liquid extraction steps described above were carried out.

To investigate potential biases due to the interaction of nicotine with different filter materials, a sample of STD solution with pH of 8 was placed on quartz and glass fiber filters and then extracted. The Nic/$NicH^+$ ratio was found on the quartz filter to be 49.7/50.3, which is consistent with the predicted partitioning described above. In contrast, the solution extracted from the glass fiber filter condition exhibited a 100/0 ratio, clearly indicating that the glass fiber filter constructed from a basic borosilicate glass had converted all $NicH^+$ to Nic. Quartz filters were therefore used for the remainder of the study. We note that puff profile was not affected by the choice of filter material because the puff generating machine automatically compensates for varying flow resistance within and across puffs.[25]

Five analytical standard and five commercial ECIG liquids were aerosolized. The analytical standard solutions (labeled "STD6-STD10") were prepared by adding different amounts of pure and concentrated acetic acid to propylene glycol solutions of nicotine with different Nic/$NicH^+$ ratios each at a concentration of 8417 μg/mL.

3. RESULTS AND DISCUSSION

3.1. Quantification of Nic and $NicH^+$ in DIY, Cartridges, and Tank Solutions. pH measurements of different prefilled ECIG cartridges and e-liquid tanks showed a range of 6.3 < pH <

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9.3 (Table 2). Similar results were recently reported by Stepanov and Fujioka.[30] The range of reported pH values suggested and confirmed that e-liquid solutions contain both Nic and $NicH^+$.

As shown in Figure 2, measured free-base fractions in the commercial brands were correlated with estimated values only when the values for V4L (strawberry) were removed ($R^2 = 0.87$; $p < 0.05$). If added, R^2 becomes 0.76 but with a $p < 0.3$ (Figure 2A). A more significant correlation ($R^2 = 0.998$, $p < 0.001$; Figure 2A) was observed between measured and estimated Nic in laboratory-prepared analytical solutions. The correlation between measured free-base fractions in the commercial brands and pH was found to be $R^2 = 0.74$ and $p < 0.001$ in Figure 2B, indicating that pH can be used as an indicative measure for nicotine partitioning but lacks precision. The relative scatter between estimated and measured Nic fractions may be due to the fact that the Henderson–Hasselbalch equation does not account for the effects of glycols and flavor additives on the pH of the commercial solutions.

Table 2 also shows a wide range of discrepancies (1–67%) between labeled and measured total nicotine (Nic + $NicH^+$) concentrations. These discrepancies may result from poor quality control at the manufacturing facility, from variations in label definitions across brands, or both. As mentioned in the Materials and Methods section, nicotine content labels are commonly ambiguous as to the meaning of the reported numbers. The discrepancies shown in Table 2 underscore the need for the standardization of nicotine labeling and product conformance standards, as some users may attempt to regulate nicotine intake based on otherwise misleading user labels.

3.2. Quantification of Nic and $NicH^+$ in ECIG Aerosols.

For both analytical standard and commercial solutions, free-base nicotine fraction in the sampled aerosols was found to be highly correlated to that in the parent liquid ($R^2 = 0.94$; $p < 0.001$) (Figure 2C). This finding indicates that differences in nicotine partitioning across ECIG liquids carry over to the inhaled aerosol and may influence nicotine delivery (Table 3). To a significant, although lesser extent, the Nic fraction was also correlated to the pH of the liquid solution ($R^2 = 0.81$; $p < 0.001$). Aerosols derived from analytical standard and commercial solutions are enriched with Nic. This finding is consistent with the notion that Nic is the only form that can be volatilized upon heating.[18] We speculate that the presence of $NicH^+$ in the aerosol likely derives from the recombination of Nic with H^+ in the PG/VG matrix of the aerosol droplets as they condense downstream of the ECIG heater. In summary, the Nic fraction in ECIG aerosols depends on that of the liquid, which in turn is related to the liquid's pH. This finding suggests that partitioning in the parent liquid determines that in the ECIG aerosol.

Table 3. Comparison of the Percentage of Nic in e-Liquid and Its Corresponding Aerosol for Standard and Commercial Samples

sample (flavor)	nicotine label	liquid % Nic	aerosols % Nic
STD nicotine (6)[a]	8.4	98.0 ± 0.3	96.2 ± 0.3
STD nicotine (7)[a]	8.4	85.9 ± 0.8	87.4 ± 0.3
STD nicotine (8)[a]	8.4	67.3 ± 2.4	73.2 ± 0.3
STD nicotine (9)[a]	8.4	19.4 ± 0.9	37.8 ± 0.3
STD nicotine (10)[a]	8.4	8.4 ± 0.4	22.7 ± 0.3
Apollo (tobacco)	12	68.3 ± 2.6	87.2 ± 1.8
Apollo (banana cream)	12	71.7 ± 1.2	89.7 ± 0.6
Apollo (blueberry kona coffee)	12	79.3 ± 3.1	90.3 ± 0.4
Bluewater (punch lights)	8	89.3 ± 2.2	92.6 ± 1.8
Halo (Tribeca)	18	80.6 ± 3.3	96.9 ± 1.3

[a]STD Nicotine: standard nicotine solutions. Standard deviation (±STDEV) is calculated based on the analysis of triplicate samples.

4. CONCLUSIONS

Free-base and protonated nicotine fractions in ECIG liquids and aerosols can be conveniently and precisely analyzed using the liquid–liquid extraction (LLE) method presented here. Using this method, it is reported that nicotine partitioning varies considerably across commercial ECIG liquids and that these differences can persist when the liquids are vaped. To the extent that the nicotine form can affect nicotine delivery to the bloodstream, these findings suggest that ECIG liquids of a given total nicotine concentration may result in different nicotine uptake efficiencies when vaped. Future studies should empirically investigate this possibility in order to better inform product regulation.

ASSOCIATED CONTENT

Supporting Information

Mechanism of selective extraction of nicotine by toluene at different pHs. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.chemrestox.5b00107.

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Notes

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ABBREVIATIONS

ECIG, electronic cigarette; Nic, free-base nicotine; $NicH^+$, protonated nicotine; PAH, polycyclic aromatic hydrocarbons; NIOSH, National Institute for Occupational Safety and Health; DIY, do it yourself solution; STD, standard solution; IS, internal standard; LLE, liquid–liquid extraction; STDEV, standard deviation

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Smoke generation inside a burning cigarette: Modifying combustion to develop cigarettes that may be less hazardous to health ☆

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Abstract

The formation of smoke from a burning cigarette depends on a series of mechanisms, including generation of products by pyrolysis and combustion, aerosol formation, and physical mass transfer and filtration processes. Each mechanism, and their interactions, has a profound effect on the levels of chemical constituents in tobacco smoke. An enormous amount of research has been done on these subjects over the last 50 years. This work is briefly reviewed.

A burning cigarette is a complex system in which many types of chemical reactions and physical processes occur. There are two main regions inside the burning zone: a combustion zone and a pyrolysis/distillation zone. Inside the combustion zone, oxygen reacts with carbonised tobacco producing simple gases such as carbon dioxide, carbon monoxide and hydrogen, together with the heat that sustains burning. Temperatures up to 950 °C are generated when the cigarette is puffed. Immediately downstream of the combustion zone is the cooler pyrolysis/distillation zone, where the bulk of the 5000 or so chemicals in smoke are generated. As the super-saturated vapour generated rapidly cools within a few milliseconds it condenses into the aerosol particles that make up the smoke.

From the 1950s onwards many attempts have been made to selectively remove or reduce the chemicals in smoke that are thought to be associated with adverse health effects. Some new cigarettes have been developed in which the combustion and smoke formation processes have been modified, with the aim of producing cigarettes that may be potentially less hazardous. An overview is presented of the approaches taken.
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Keywords: Cigarette; Tobacco; Smoke formation; Toxicity; Pyrolysis; Less-hazardous

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1. Introduction

A burning cigarette is a classic example of an incomplete combustion system and the adverse health effects of its combustion products are well known. The combustion processes occurring inside a cigarette, and approaches to modelling them, have been described in detail elsewhere [1–3]. The objectives of this paper are to outline those aspects of cigarette combustion and smoke chemistry that are believed to be relevant to smoking-related diseases, and to summarise some attempts that have been made to modify combustion and develop smoking products that may be less hazardous to health. A historical approach will be taken.

Fifty years ago things happened that were to change the perception of smoking completely and forever. Firstly, five case-controlled studies were published in 1950, one in the UK [4] and four in the USA [5–8] in which the authors demonstrated that there was a strong statistical association between cigarette smoking and lung cancer. Before 1950 there had been suspicions, based largely on anecdotal evidence, that smoking might be injurious to health, going back to the statement by King James I of England (also known as King James VI of Scotland) in his 1604 book "A Counter-Blaste to Tobacco" that smoking was "lothsome to the Eye, Hatefull to the Nose, harmefull to the braine, dangerous to the Lungs (sic)....". Secondly, Wynder et al. [9] published the results of biological work showing the generation of tumours on mice following skin painting with tobacco smoke particulate matter. Thirdly, Cooper and Lindsey [10,11] and Cooper et al. [12] reported the presence of a known carcinogen, benzo[*a*]pyrene, in the particulate matter of tobacco smoke. Although their spectral evidence was criticised by Feiser [13] as inadequate, the issue was eventually resolved in 1959 by the isolation of crystalline benzo[*a*]pyrene from cigarette smoke particulate matter by Wynder and Hoffmann [14,15].

We now know that cigarette smoking is associated with an increased incidence of a variety of diseases. For each of these diseases, epidemiology suggests dose–response relationships. This means that groups of smokers that start smoking later, quit earlier and smoke fewer cigarettes per day tend to have lower incidences of these diseases than people who smoke more. The incidence of disease in low dose smokers is still higher than in people who do not smoke. The only way to avoid a smoking-related risk is not to smoke. For those that do smoke, the risks are primarily modified by the amount and duration of consumption. However, within this context, the design of cigarettes may also modify risks, and efforts to design "less hazardous" cigarettes have been conducted by tobacco companies for many years, often in collaboration with public health groups. One essential element of this work has been the development of a greater understanding of smoke chemistry.

2. Smoke generation mechanisms

In the 1950s, relatively little was known about the chemical nature of smoke or its generation. Since that time an enormous amount of work has been done to unravel the physical and chemical mechanisms occurring as the cigarette burns. This work has been done essentially to answer two questions [16]:

1. Which components of smoke are responsible for the human health risks associated with smoking?
2. Which components of smoke are important to the flavour, sensory experience and consumer acceptance of tobacco products?

To some, the second question may seem irrelevant. However, in seeking to produce cigarette modifications that may be regarded as "less hazardous", the second point remains important. Any tobacco product modification that may be accepted as "less hazardous" would be of little value unless it provided an acceptable alternative to conventional products to those people who decide that they want to smoke. The answers to these questions are the "holy grail" of tobacco research. However, after 50 years of research neither question can be answered completely.

Tobacco is a plant material and consists of some 3800 constituents, ranging from small organic and inorganic molecules to biopolymers [17]. The small molecules belong to numerous classes of

compounds such as hydrocarbons, terpenes, alcohols, phenols, acids, aldehydes, ketones, quinones, esters, nitriles, sulphur compounds, carbohydrates, amino acids, alkaloids, sterols, isoprenoids, Amadori compounds, etc. The biopolymers consist of cellulose, hemicellulose, pectin, lignin, starch, proteins and peptides, nucleic acids, etc. During smoking, these are all subjected to temperatures up to 950 °C in the presence of varying concentrations of oxygen in the burning zone of the cigarette or other tobacco product [2]. About 4800 individual substances have been identified in tobacco smoke [16]. Most of these are at trace levels and current limits of detection for smoke components are of the order of about 100 pg (i.e. 100×10^{-12} g). Many of the smoke components arise from a variety of different routes including distillation from tobacco, combustion, pyrolysis and pyrosynthetic reactions. Approximately 2800 constituents are found in tobacco smoke but not tobacco, indicating the importance of pyrolysis, pyrosynthetic and combustion formation mechanisms.

The approximate relationships of the major combustion processes involved in smoke generation have been described by Muramatsu [3] and are shown in Fig. 1. Many studies have been undertaken to determine the conditions inside the burning zone of the cigarette that influence product formation mechanisms. These include determination of the temperature and gas formation contour distributions at various times in the smoking cycle of a burning cigarette, using temperature probes and small sampling tubes inserted inside the burning zone and connected to a mass spectrometer [18–23]. This work has been summarised by Baker [1,2] and, from it, a pictorial representation of the major smoke formation mechanisms occurring inside the cigarette can be obtained (Fig. 2). The interior of the burning zone is oxygen-deficient and hydrogen-rich and can be effectively divided into two regions: an exothermic combustion zone and an endothermic pyrolysis/distillation zone. As air is drawn into the cigarette during the puff, oxygen is consumed by combustion with carbonised tobacco and the simple combustion products carbon monoxide, carbon dioxide and water are formed, together with the release of heat which sustains the whole burning process. Temperatures in this region of between approximately 700 and 950 °C are generated and heating rates as high as 500 °C s^{-1} are achieved. Immediately downstream of the combustion region is the pyrolysis/distillation

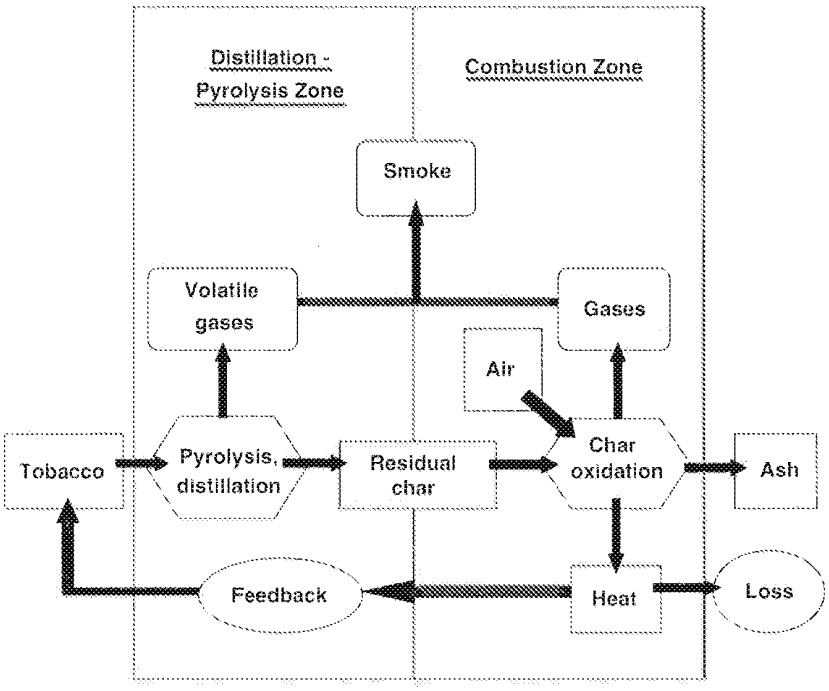


Fig. 1 Schematic diagram of the major processes occurring during cigarette combustion, after Muramatsu [3].

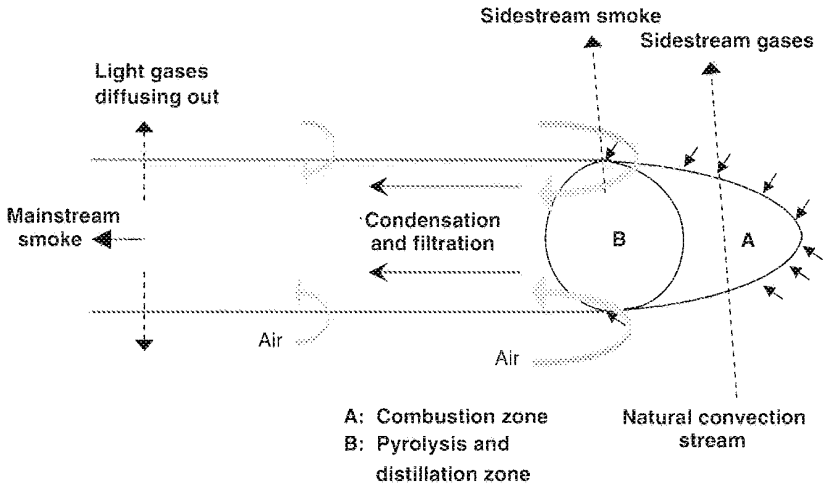


Fig. 2. The burning cigarette during a puff.

zone, where the temperatures are between approximately 200 and 600 °C and which is still low in oxygen. The majority of smoke products are generated in this region by a variety of mechanisms which are essentially endothermic. A highly concentrated, probably supersaturated, vapour is generated and, during a puff, is drawn down the tobacco rod to form the mainstream smoke. Its residence time in the formation region is only a few milliseconds.

As the generated vapour is drawn out of the pyrolysis/distillation region during the puff, it cools very rapidly in the presence of diluting air entering at the paper burn line. This brings the vapours of the less volatile compounds quickly to their saturation point and condensation occurs as the vapour cools below about 350 °C. A dense aerosol consisting of growing droplet particles is formed. The mainstream smoke emerging from the mouth-end of the cigarette during a puff is a highly concentrated, dynamic aerosol system. The smoke particles are liquid, with water making up approximately 20% of the droplet volume and, consequently, they have spherical shapes. There are some 10^9–10^{10} particles per ml in fresh mainstream smoke, making it an extremely dense aerosol. Initially the particles vary in diameter from less than 0.1 to 1.0 μm [24–26]. These very high concentrations and small sizes are such that the particles will rapidly coagulate, resulting in sizeable decreases in number concentration and increases in average particle diameter within fractions of a second.

The size of smoke particles will also increase in moist environments due to absorption of water vapour. This will be particularly important in the respiratory tract where the relative humidity is estimated to be 99.5% [27]. The relative humidity of mainstream smoke is 60–70% and little particle growth due to water absorption occurs below 90% relative humidity [25,26]. Particle growth increases sharply with humidity above 90% due to the absorption of water and smoke particles double in size at 99.5% relative humidity [28]. Smoke particle growth by absorption is a complex process dependent on the chemical composition of both the particles and surrounding gas phase. It occurs in milliseconds [29].

Carbon monoxide and dioxide are the major products in cigarette smoke and are formed by both thermal decomposition and combustion of many of the components of tobacco: starch, celluloses, sugars, carboxylic acids, esters, amino acids, etc. Studies in which the cigarette was smoked or pyrolysed in isotopically labelled oxygen and carbon dioxide [21,30,31] have shown that approximately 30% of the carbon monoxide is formed by thermal decomposition of tobacco constituents, about 36% by combustion of tobacco and at least 23% by the endothermic carbonaceous reduction of carbon

dioxide:

$$C + CO_2 \rightarrow 2CO$$

3. The chemical nature of cigarette smoke

Cigarette smoke is a complex mixture. Of the approximately 4800 identified substances in tobacco smoke [16], 45 are believed by Regulatory Authorities in Canada and the USA to be relevant to smoking-related diseases [32–34]. These include, inter alia, some volatile carbonyl compounds, tobacco-specific *N*-nitrosamines, aromatic amines, phenols, volatile alkenes, benzo[*a*]pyrene and metals. A summary of these substances, together with their approximate amounts in cigarette smoke and their phase in smoke, are listed in Table 1. These substances are sometimes colloquially called "Hoffmann analytes" since similar lists of toxicological substances have been proposed by Dietrich Hoffmann and co-workers of the former American Health Foundation in New York since the mid-1980s (e.g. [36–38]). The latest compilation by Hoffmann and colleagues in fact lists 82 substances. Those substances on the list of "Hoffmann analytes" are not necessarily the only cigarette smoke constituents that have toxicological properties. Rodgman and Green [39] have listed 149 substances in smoke, including more extensive lists of polynuclear aromatic hydrocarbons, *N*-nitrosamines, *N*-heterocyclic amines and other organic molecules. In addition, free radicals may also be important, (e.g. [40]).

Much effort has been devoted to determining the conditions under which smoke components are generated and the mechanisms by which they are formed, especially those that are believed to be implicated in tobacco-related diseases [2,41]. For example, tobacco smoke contains a large variety of hydrocarbon compounds. The type of hydrocarbon generated from tobacco is dependent on the temperature of the tobacco. The general results from a large number of studies indicate that, at temperatures between about 300 and 550 °C in the cigarette burning region, small hydrocarbon molecules (C_1 to C_3) are generated. Longer chain *n*-alkanes and alkenes are formed at temperatures between about 400 and 700 °C. At temperatures above about 500 °C, benzene and alkylbenzenes are formed. At temperatures above about 700 °C naphthalenes are formed. More than 75 monocyclic aromatic hydrocarbons such as benzene and toluene are formed from the pyrolysis of amino acids, fatty acids, cinnamic acid, sugars and paraffins, precursors with an aromatic or cyclohexane ring, and pyrosynthesis from primary hydrocarbon radicals. There are at least 80 naphthalenes present in smoke. Polynuclear aromatic hydrocarbons are formed at temperatures above 800 °C. Over 300 individual polynuclear aromatic hydrocarbons have been identified in tobacco smoke. The polynuclear aromatic hydrocarbons are formed by pyrolysis and pyrosynthetic reactions of long-chained hydrocarbons, terpenes, phytosterols such as stigmasterol, paraffins, sugars, amino acids, celluloses and many other tobacco components. They are also formed by pyrosynthetic reactions involving small, primary hydrocarbon free radicals in the high temperature region of the burning zone [42,43].

As a further example, tobacco smoke contains two general types of nitrosamines:

(1) Tobacco-specific nitrosamines, which are found only in tobacco and tobacco smoke particulate phase, are derived from tobacco alkaloids, and are non-volatile.
(2) Non tobacco-specific nitrosamines, which are found in many systems, are volatile and are present in the vapour or semi-volatile fraction of smoke.

Tobacco specific nitrosamines are not present in freshly harvested green tobacco. They are formed during curing by nitrosation of tobacco alkaloids. The nitrosating agent is nitrite, derived from tobacco nitrates by bacteria and enzymes during curing. When the cigarette is smoked, some of the nitrosamine transfers to smoke, some decomposes and some tobacco-specific nitrosamines are also formed pyrosynthetically in the burning zone. There is some conflict in the scientific literature on exactly how much is formed pyrosynthetically. The levels of non tobacco-specific nitrosamines in mainstream smoke are much lower than those of the tobacco-specific nitrosamines. They are not present in tobacco and are formed pyrosynthetically during tobacco combustion. These pyrosynthetic reactions involve nitrosation of amino acids and tobacco protein. The nitrosating agent is believed to be N_2O_3, formed by reaction of NO and NO_2. Thus amino acids, protein in tobacco (which can generate amines on burning), and nitrate (which can generate nitrogen oxides) are important precursors of the volatile nitrosamines.

Table 1
Modified 'Hoffmann List' of smoke toxins[a]

Class, constituents	Number in class	Yield[b]	Smoke phase[c]
Major components	3		
"Tar"		9.2 mg	P
Nicotine		0.77 mg	P
CO		13 mg	V
Inorganic gases	3		
NH_3		14 μg	V
HCN		140 μg	V–P
NO_x		310 μg	V
Tobacco-specific nitrosamines	4		
N′-Nitrosonornicotine (NNN)		100 ng	P
N′-Nitrosoanabasine (NAB)		23 ng	P
N′ Nitrosoanatabine (NAT)		110 ng	P
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)		89 ng	P
Phenols	7		
Phenol, *o*-cresol, *m*-cresol, *p*-cresol		3–10 μg	V–P
Catechol, hydroquinone		39 μg	P
Resorcinol		0.7 μg	P
Carbonyls	8		
Formaldehyde		19 μg	V–P
Acetaldehyde, acetone		610, 290 μg	V–P
Propionaldehyde, methyl ethyl ketone, acrolein		51–72 μg	V–P
Butyraldehyde, crotonaldehyde		32, 25 μg	V–P
Polynuclear aromatic hydrocarbons	1		
Benzo[*a*]pyrene		7.0 ng	P
Aromatic amines	4		
1-Aminonaphthalene, 2-aminonaphthalene		15, 10 ng	P
3-Aminobiphenyl, 4-aminobiphenyl		3.4, 2.1 ng	P
Semi-volatiles	3		
Pyridine, styrene		8 μg	P
Quinoline		0.4 μg	P
Vapour phase	5		
1,3-Butadiene, benzene, toluene, acrylonitrile		15–90 μg	V–P
Isoprene		400 μg	V–P
Metals	5		
Pb, Cr, Ni, Hg, As, Cd, Se		1–52 ng	P
Total	45		

[a]Abbreviated list as used in Canada and Massachusetts [33,34].
[b]University of Kentucky 1R4F reference cigarette, ISO machine-smoking conditions [35]. Many modern, commercial cigarettes have lower levels than these quoted reference cigarette levels. For example, in the European Union all cigarettes must have "tar", nicotine and CO yields below 10, 1 and 10 mg, respectively.
[c]P—particulate phase of smoke, V—vapour phase, V–P—partitioned between the vapour and particulate phases.

4. Approaches to developing cigarettes that may be potentially less hazardous to health

From the 1950s onwards the scientific literature on tobacco smoke, patent literature and internal tobacco company research reports have contained descriptions of many attempts to remove or reduce the identified biologically active chemicals in cigarette smoke. Unfortunately, many of the methods described were based on either an incomplete view

of smoke chemistry or produced adverse effects to the smoke, or both.

The earliest attempts were to remove benzo[*a*]-pyrene and the other polynuclear aromatic hydrocarbons (PAHs) from smoke. As discussed in Section 3, from the large amount of work done on the generation of these materials in tobacco smoke, it had become clear by the mid-1960s that their formation involved pyrosynthetic reactions of long-chained hydrocarbons, terpenes and phytosterols, and pyrosynthetic reactions involving small, primary hydrocarbon free radicals in the high temperature region of the burning zone. It is well known that high-temperature free radical reactions can be quenched by the presence of nitric oxide, itself a free radical. Nitric oxide is generated from the thermal decomposition of nitrites and nitrates. Consequently, the addition of nitrites, nitrates and high-nitrate tobacco material to the tobacco blend was found to be an effective method of significantly and selectively reducing the level of benzo[*a*]pyrene and PAHs in smoke relative to "tar", (e.g. [44]). In addition, removal of waxes from tobacco by solvent extraction reduced the proportion of long-chained hydrocarbons in tobacco, known precursors of benzo[*a*]pyrene and PAHs [45,46]. Thus, in the 1960s the belief was that removal of tobacco waxes and increasing the tobacco nitrate levels should be undertaken as a means of reducing the levels of polynuclear aromatic hydrocarbons in smoke.

However, as discussed above, nitrate is a precursor for the generation of nitrosamines in tobacco. Consequently, increasing the nitrate in the tobacco increases the level of both tobacco-specific and volatile nitrosamines in tobacco smoke [47,48]. In addition, selection of tobaccos with relatively high levels of long-chained hydrocarbons was also suggested as a means of reducing formation of nitrogen oxides and nitrosamines [47]. Thus, by 1982 the belief was that increasing tobacco waxes and reducing the tobacco nitrate was the best means of reducing the levels of nitrosamines in smoke.

Consequently, removal of tobacco waxes and adding nitrate to tobacco reduce the levels of the PAHs, and increase the levels of the nitrosamines, in tobacco smoke. This is just one example of the dilemmas facing those trying to produce acceptable product modifications. There are many separate processes involved in the generation of different smoke components, often interacting in a complex manner. Making a modification to reduce the level of one group of substances in smoke usually also produces other undesirable effects. That is why, historically, the most promising approach to the development of cigarettes that might be associated with reduced health risks has been to reduce all of the smoke components rather than selective reduction of specific substances. Thus for 30 years the tobacco industry has continuously sought to develop cigarettes with progressively lower "tar" yields. Indeed, it is possible that some of the health risks of smoking are not actually associated with individual compounds, or classes of compound, in smoke. Rather, these health risks may be associated with the smoke as a whole. If this were the case, total smoke yield would be more indicative of adverse health effects than individual chemical constituent. "Tar" is a collective term for all of the particulate matter of smoke, collected on an analytical filter, with the amounts of water and nicotine subtracted. Indeed, after considering the epidemiological and biological data available at the time, Wynder [49], a pioneer in the study of smoking epidemiology and biological activity, stated:

> It may be predicted that if the average smoker were exposed to only half the amount of tobacco tar to which the smoker of regular-sized cigarettes is now exposed, his cancer risk would be considerably reduced. Any measure designed to thus reduce man's exposure to tobacco tar, whether through modification of the tobacco or the cigarette, or through more efficient filtration, can significantly contribute to the decrease in risk.

Wynder re-emphasised this conclusion in a paper in the British Medical Journal in 1957 [50], and emphasised the importance of cigarette filtration, removal of precursors of smoke carcinogens and modification of tobacco pyrolysis. In the UK the development of lower "tar" cigarettes has been undertaken in association with various government bodies, in particular the UK Independent Scientific Committee on Smoking and Health. It has been accomplished by the use of filters and filter ventilation, modified cigarette paper and modified forms of tobacco and tobacco blends. In the UK the sales-weighted average "tar" yield has been gradually reduced from about 38 mg in the mid-1950s to below 10 mg today, when measured with the standard ISO smoking regime method [51]. In the USA the sales-weighted average "tar" yield has been reduced to about 12 mg. In fact there is now a "tar" ceiling of 10 mg for all cigarettes within the

European Union, i.e. all cigarettes sold must have a "tar" yield below 10 mg. Very low "tar" cigarettes are currently available with yields of below 1 mg. "Tar" is a collective term for the particulate-phase material in cigarette smoke (specifically, total particulate matter minus nicotine and water). Consequently, as "tar" levels have fallen over the last 40 years, all of the particulate-phase constituents listed in Table 1 will have been reduced to the same extent as the "tar", to a very good first approximation. The use of filters containing activated carbon also reduces the gas-phase constituents of cigarette smoke. However, the most effective means of reducing gas-phase components in smoke is by the use of porous cigarette papers and ventilated filters. In a ventilated cigarette filter, a zone of microscopic ventilation holes is provided around the circumference of the filter. Such filters have been available for over thirty years and were developed to reduce the yields of all smoke components. The effects of ventilation are more than just dilution of the smoke since the various smoke products are reduced by different amounts [52]. Increasing the level of ventilation at the filter causes a smaller proportion of the puff volume to be drawn in through the cigarette burning zone. The intensity of combustion is consequently reduced, less tobacco is burnt during the puff and the level of most mainstream components generated is decreased. The average velocity of flowing smoke/gases through the cigarette decreases so that the outward diffusion of light gases such as carbon monoxide, and the filtration of smoke aerosol particles are increased. All of these processes will reduce the levels mainstream smoke components. In addition, of course, the levels of all the mainstream smoke products will be diluted with incoming air as they are drawn along the cigarette.

For an 11-year period in the USA, from 1968 to 1979, the National Cancer Institute had a multi-million dollar Smoking and Health Programme on research into the development of less hazardous cigarettes, recently reviewed by Gori [53], one of the principal leaders of the programme. The programme had an advisory committee that included top academic and government researchers in the field as well as the research directors of the major US cigarette manufacturers. The programme had two main objectives:

1. Understanding the pharmacological aspects of smoke.
2. Identifying the hazardous components of cigarette smoke and the development of methods for minimising or eliminating those components.

The major concern of the programme was on the cancer-causing properties of cigarette smoke, i.e. the carcinogenicity or tumorigenicity of smoke. Within the programme, co-ordinated, broadly based research projects were carried out that included determining the detailed chemical composition of mainstream smoke and the biological properties of the smoke using the only standardised animal biological test available at the time, the skin painting of cigarette smoke "tar" onto the shaved backs of mice, to determine how fast and how severely tumours were produced. These studies were done on smoke from more than 150 differently modified cigarettes and 30 reference cigarettes that involved the manufacture of over 70 million experimental cigarettes. These design changes were brought about by modifications to the tobacco, tobacco fractions such as leaves and stem, the paper wrapper of the cigarette, filters, adding or removing nicotine, the use of additives and design changes that could affect the combustion of the cigarette, as well as the use of tobacco substitutes. From this programme it was determined that there were eight design technologies that could be utilised in the development of less hazardous cigarettes. These were modification of the tobacco blend, incorporation of reconstituted tobacco sheet into the blend, the use of additives such as citrates to cigarette paper, the use of filters to reduce smoke yields, the use of expanded tobacco and incorporation of additives such as triacetin as plasticizer in the filter, the use of paper of higher permeability to reduce smoke yields and the use of ventilated filters. In fact, all of these design technologies were developed by the tobacco industry and had begun to be used commercially before the National Cancer Institute's programme had started in 1968 [39,54]. The National Cancer Institute Programme gave independent confirmation that the technologies were likely to be in the right direction. The use of these technologies eventually permitted the mainstream yield of "tar" in commercial cigarettes to be reduced from 40 to less than 1 mg in some brands, with corresponding reductions in the yields of those smoke components considered harmful. Sadly, the programme was abandoned in 1979 before some of its projects were completed, when the prevailing philosophy of the National Institute of Cancer

changed from modification of cigarettes to abolition of smoking [53].

Concerns have been raised recently by some public health scientists as to whether the low "tar" approach is appropriate on the basis that people switching from higher to lower "tar" cigarettes may adjust their smoking behaviour, for example by taking more intense puffs or inadvertently blocking some of the filter ventilation zone with their lips or fingers. In this way, the reduction in smoke yields obtained by the human smoker would be less than the reduction indicated by smoke yields obtained on a smoking machine. This phenomenon, known as compensation, has been known for decades (e.g. [55]) and was considered as part of the UK's product modification programme in the 1970s. That programme determined that while compensation was likely to occur to some extent, it was not complete and hence lower "tar" was likely to be associated with some reduction in risk for some diseases. Scherer [56] has more recently reviewed all of the scientific literature on smoking compensation. He concluded that while human smoking behaviour is highly variable, on average partial compensation does occur shortly after smokers switch to cigarettes with different yields to their usual brand. Changes in the puff volume are the most probable mechanism of compensatory smoking. Baker and Lewis [57] have also shown that inadvertent blocking of the filter ventilation zone by the smoker's fingers or lips as it occurs in practice has only a relatively minor effect on human smoker yields compared to other smoker behaviour factors. Scherer has concluded from all of the available data taken as a whole that the mean compensation is about 50%. Thus, for example, on average a smoker who switches to a cigarette with a "tar" yield 50% lower than his/her current brand as measured on a smoking machine (ISO standard conditions) will actually receive a "tar" yield 25% lower than that received from their original cigarette. Consequently, it may be expected that, in general, smokers switching from a higher to a lower "tar" yield cigarette will obtain a reduction in smoke component uptake.

In the 1970s, several years of intense research and development in the UK led to the production of tobacco substitutes. These were developed jointly by tobacco companies and chemical companies and the substitutes contained cellulose, chalk, glycerol and other materials that were simpler than tobacco. The tobacco substitutes were known by various names, such as NSM (New Smoking Material, developed by ICI in the UK), Tabelle® (developed by Courtaulds, UK), Cytrel® (developed by the Celanese Corporation in the USA) and BAT-FLAKE (developed by British American Tobacco in the UK). Cigarettes were made containing mixtures of tobacco and the substitute material. The substitute material acted essentially as a diluent for the smoke generated by the burning tobacco. Smoke from the cigarettes had lower levels of many smoke constituents, and gave lower responses in various bioassays, than the equivalent all-tobacco, conventional cigarette (e.g. [58–60]). The chemical and testing regimes for the new cigarettes were developed by the tobacco industry in collaboration with a committee of independent scientists set up by the British Government [61]. Twelve cigarette brands containing various types of tobacco substitutes were launched in 1977. After some initial interest by the smoking public, smokers quickly decided that they did not like their taste and all the brands failed to gain any appreciable market share. Because of this market failure, all of the brands were subsequently withdrawn from sale.

In the 1980s a cigarette was developed by the R.J. Reynolds Tobacco Company in the USA that heated tobacco rather than burnt it. The cigarette consisted of four main parts. The first section consisted of a carbon fuel element, about 13 mm long and the same diameter (8 mm) as the cigarette. The next section contained a central aluminium capsule, which was partly ventilated, containing α-aluminium oxide spheres which were impregnated with spray-dried tobacco, glycerol and a small amount of flavour, and the capsule was wrapped in tobacco. The third section consisted of folded paper reconstituted tobacco made from tobacco fibre and softwood pulp. The last section, the mouth-holding section, consisted of a specifically designed polypropylene filter. When the carbon section at the front of the cigarette was lit, the hot air generated was drawn through the second section, where it vaporised nicotine and flavours and these were cooled, augmented and filtered in the next two sections. Since no products of tobacco combustion were generated the cigarette gave a much simpler smoke chemistry than conventional cigarettes. The levels of many of the toxic substances in its smoke were much lower than those in an equivalent conventional cigarette, or completely eliminated. The smoke gave significantly lower responses in a variety of bioassays than a conventional cigarette. Also, very little sidestream smoke was generated.

All of the results were published in a very comprehensive review [62]. The cigarette, known as Premier, went on sale in 1988. The cigarette was not liked by its consumers, who complained of the smoke flavour, its difficulty in lighting, and the nuisance problem of disposing of the spent cigarette. It was subsequently withdrawn from sale.

The R.J. Reynolds Tobacco Company subsequently developed the "heat but not burn" tobacco concept further and launched a modified version known as Eclipse in the USA in 1995, and later in Germany, Sweden and Japan. In this version, the second section of the cigarette contained a band cast reconstituted filler with added tobacco extracts, glycerol and flavours. The smoke from Eclipse is 75-80% water and glycerol and consequently the total "tar" content of 4 mg (US Federal Trade Commission machine-smoking conditions, effectively the same as ISO conditions [51]) has less than 1 mg "tar" from the pyrolysis of tobacco. There are much less smoke constituents in the smoke from Eclipse than those from an equivalent conventional low "tar" cigarette, and the overwhelming majority of the toxic compounds listed by health officials are reduced. These include carcinogens, tumour promoters, cytotoxins, mutagens, irritants and vapour-phase free radicals. Smoke and total particulate matter from Eclipse cigarettes have markedly reduced toxicity compared to conventional "low tar" cigarettes when evaluated in widely used and scientifically accepted biological tests. These tests included a battery of in vitro assays, Ames, sister chromatid exchanges, chromosome aberrations and cytotoxicity; in vivo assays, subchronic inhalation toxicology and 30-week dermal tumour promotion studies; and studies in human smokers. An independent panel of independent scientists, convened by the R.J. Reynolds Tobacco Company, concluded that all the chemical and biological data available indicated that the Eclipse cigarette may have the potential to significantly reduce the health risks compared to conventional cigarettes [63]. The Eclipse cigarette is still on sale in the USA.

In 1998 the Philip Morris Company in the USA marketed another version of a cigarette that heats tobacco rather than burns it, known as Accord. They have developed a hand held device about the same size as a small cell (mobile) phone, which contains a series of battery-operated electric heating elements. The Accord unfiltered cigarette is inserted into the device and the heating elements are activated when the smoker sucks on the cigarette. The heating elements then generate smoke from the cigarette by a low level of pyrolysis/combustion [64]. The smoke chemistry and responses in various bioassays were significantly reduced relative to a conventional reference cigarette. On a per cigarette basis, almost two thirds of 69 toxic chemicals in smoke identified by regulatory scientists as relevant to smoking-related diseases were reduced by at least 80% [65]. The total particulate matter from the electrically heated cigarette was up to 90% lower in an in vitro mutagenicity bioassay (Ames) than the reference cigarette on an equal particulate matter basis, and 40% less active in a cytotoxicity (neutral red uptake) bioassay [66]. In a 90-day rat inhalation study, the biological activity of mainstream smoke from the electrically heated cigarette was equal to that from the reference cigarette on an equal particulate matter basis and 65% lower on an equal cigarette basis [67]. Consumer acceptance of the Accord cigarette has been low although it is still on sale in parts of the USA.

As a final example of cigarette developments to potentially reduce the adverse health effects of smoke, in the late 1990s methods were developed which greatly reduced the formation of nitrosamines during the flue-curing of tobacco, leading to extremely low levels in the smoke from cigarettes made with the tobacco. One method, known as the "Star Process" after the American company that developed it, uses modified heating during tobacco curing, together with microwave heating in their original description of the process, to eliminate the bacteria that produce the nitrite that converts the tobacco alkaloids into nitrosamines [68]. The modified curing process developed by Star also replaces direct heating of the tobacco with indirect heating so that the NO_x, produced as a by-product of the combustion of liquid propane gas, does not have contact with the tobacco and so nitrosate the tobacco alkaloids during curing. The R.J. Reynolds Tobacco Company in the USA has also developed a modified flue-curing process that relies entirely on indirect heating to suppress formation of tobacco specific nitrosamines [69]. In 2001 the Brown and Williamson Tobacco Corporation in the USA (at that time the American company in the British American Tobacco Group) launched a cigarette brand called Advance. This cigarette incorporated tobacco cured by the Star process as well as a three section filter that contained cellulose acetate and activated charcoal/ion exchange resin that selectively reduced carbonyl compounds in the smoke.

The smoke from the cigarette had significantly reduced levels of nitrosamines and carbonyl compounds compared to smoke from conventional commercial cigarettes available in the USA However, Doolittle et al. [70] have demonstrated that marked reductions in nitrosamines in tobacco do not alter the biological activity of the smoke particulate matter in Ames mutagenicity and neutral red cytotoxicity in vitro bioassays. Thus, the health consequences to the smoker of reducing levels of nitrosamines in tobacco or tobacco smoke are unclear. However, the selective reduction of such substances in tobacco and smoke, where possible, would seem a sensible advance. That cigarette is no longer on sale in the USA.

Apart from the development of reduced "tar" cigarettes, the development of cigarettes to address the adverse health risks of smoking has not been commercially successful to date. However, the development of such cigarettes is continuing in tobacco companies and new cigarettes will continue to be marketed in the future. In 2001 the US Institute of Medicine published a report which stated that reducing the risk of disease from cigarettes is feasible by reducing exposure to tobacco toxins [71]. The report also stated that Potentially Reduced Exposure Products (PREPs) should be developed and that they need to be assessed for their reduced risk of disease compared to conventional cigarettes. The report also reiterated the message that the safest option was not to smoke at all, but that less hazardous cigarettes should be developed for those people who choose to smoke. The report is prefaced with the following words of Goethe:

> Knowing is not enough; we must apply.
>
> Willing is not enough; we must do.

This seems a fitting objective for the future direction of research and development in tobacco, where vast amounts of work have been done on the mechanisms of smoke formation and composition. In the future, this work will be enhanced and applied for the development of cigarettes that may be potentially less harmful to health.

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EXHIBIT F

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Industry research on the use and effects of levulinic acid: A case study in cigarette additives

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Public health officials and tobacco researchers have raised concerns about the possible contributions of additives to the toxicity of cigarettes. However, little attention has been given to the process whereby additives promote initiation and addiction. Levulinic acid is a known cigarette additive. Review of internal tobacco industry documents indicates that levulinic acid was used to increase nicotine yields while enhancing perceptions of smoothness and mildness. Levulinic acid reduces the pH of cigarette smoke and desensitizes the upper respiratory tract, increasing the potential for cigarette smoke to be inhaled deeper into the lungs. Levulinic acid also may enhance the binding of nicotine to neurons that ordinarily would be unresponsive to nicotine. These findings held particular interest in the internal development of ultralight and so-called reduced-exposure cigarette prototypes. Industry studies found significantly increased peak plasma nicotine levels in smokers of ultralight cigarettes following addition of levulinic acid. Further, internal studies observed changes in mainstream and sidestream smoke composition that may present increased health risks. The use of levulinic acid illustrates the need for regulatory authority over tobacco products as well as better understanding of the role of additives in cigarettes and other tobacco products.

Introduction

In response to growing public health concerns in the 1950s and 1960s, tobacco manufacturers recognized the need for cigarettes that provided reduced "tar" delivery. A number of major cigarette modifications, including the introduction of filters, ventilation, and processed tobaccos, resulted in lower machine-measured tar and carbon monoxide levels. Ventilation in particular became a primary technique for decreasing smoke yield; however, ventilation also reduced levels of nicotine, smoke strength, and tobacco taste, and left the smoker with a sensation of thinness and dryness (Hale, Kroustalis, Lin, Raymond, & Spielberg, 1990a; Kozlowski & O'Connor, 2002). Reduced smoke nicotine delivery was of particular concern to manufacturers because a high level of nicotine "contributes to smokers' physiological and also sensory satisfaction" (Hale et al., 1990a).

Manufacturers turned to chemical additives to accommodate the need for lower tar delivery with sustained smoking satisfaction. Cigarette additives may be used to offset the unpleasant taste associated with lower-tar products, alter product chemistry, and create the sensations of a full-flavor cigarette (Bates, McNeill, Jarvis, & Gray, 1999; Hurt & Robertson, 1998; Wells, 1995). Manufacturers today publicly acknowledge the use of hundreds of additives in their products. The modern U.S.-style cigarette generally contains about 10% additives by weight, mostly in the form of sugars, humectants, ammonia compounds, cocoa, and licorice (Browne, 1990). Most other additives are used in very small amounts—less than 0.01% of total weight. However, little is known about the role and effects of most individual additives. Federal law requires manufacturers to report the names of additives to the U.S. Department of Health and Human Services, but information is not provided for specific cigarette brands or for levels of use.

Internal tobacco industry documents made publicly available as a requirement of the 1998 Master

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Settlement Agreement provide an important resource for evaluating tobacco industry knowledge and practices. Although the tobacco industry has denied that use of additives has any known effect on the pharmacological properties or addiction potential of cigarettes, published research using industry documents suggests otherwise. An example is smoke pH, which is a measure for whether nicotine in smoke is found in its free-base or protonated (bound) form. Tobacco manufacturers used ammonia in the early 1970s to manipulate smoke pH levels, based on their belief that a higher smoke pH would increase the impact of nicotine and the rate at which inhaled nicotine is absorbed into the bloodstream (Henningfield, Pankow, & Garrett, 2004; Hurt & Robertson, 1998). Similarly, to increase product appeal among young adult users, R. J. Reynolds used additives in combination with other product changes in its Camel cigarette brand to increase smoothness and reduce irritation, while maintaining or increasing nicotine delivery in smoke (Ferris Wayne & Connolly, 2002). The industry has also used numerous additives to reduce sidestream irritation and odor, thereby lessening the perception of second-hand tobacco smoke and its associated risks (Connolly, Wayne, Lymperis, & Doherty, 2000).

In this industry document–based study, we sought to identify the potential pharmacological and behavioral effects that result from the use of one known additive in cigarettes, levulinic acid. We cataloged the internal industry use of levulinic acid in brand development and other product research. Our findings confirm that levulinic acid can play an important role in product delivery as well as influence smoke perception and the bioavailability of other constituents (including nicotine). Further, our findings demonstrate the unique importance of levulinic acid in the internal development of some low-yield and so-called reduced-exposure products. We conclude that use of additives, in particular levulinic acid, may result in significant unmeasured changes to product delivery, potentially increasing overall addictiveness or toxicity of the tobacco product.

Method

More than seven million tobacco industry documents discovered through ongoing trial litigation have been made publicly available as a result of the 1998 Master Settlement Agreement between the state attorneys general and major U.S. tobacco manufacturers (Philip Morris, R. J. Reynolds Tobacco Company, Brown & Williamson Tobacco Company, and Lorillard). These documents are now widely accessible via the Internet through archival databases such as those maintained at Tobacco Documents Online (tobaccodocuments.org) and the Legacy Tobacco Documents Library (legacy.library.ucsf.edu). Document identification and retrieval is performed using an index-based word search of titles, authors, recipients, and other document characteristics (such as date, document type, original file location) as well as key words, abstracts, and in many cases full-text optical character recognition of scanned document images.

In the present study, our goal was to provide a comprehensive assessment of industry studies addressing the intended use or role of levulinic acid in product research and development. Initial searches were conducted to assess areas of internal discussion. For example, a search on Tobacco Documents Online for the term *levulinic acid* yielded 2,797 documents (as of January 15, 2004) and for *nicotine levulinate* (the nicotine salt of levulinic acid) yielded 674 documents. From these documents, relevant ones were identified based on whether they described (a) historical measures or assessments of levulinic acid in commercial brands, (b) the additive's effects on product delivery, perception, or bioavailability, or (c) its use in product development and internal research projects. The documents identified as relevant were abstracted and indexed. These documents were surveyed for key words or projects that might suggest further avenues for retrieval. A final set of 284 documents (of which 51 are directly cited here) was cataloged for the present study. A full set of these documents, ranging in dates between 1968 and 1993, can be accessed and viewed at http://tobaccodocuments.org/product_design/list.php?field_id=7&resource_id=20926.

We believe the collection of documents identified in the present study is sufficient to draw general conclusions regarding industry testing and use of levulinic acid. It should be noted that the document collections are gathered from different manufacturers, spanning a number of distinct eras, and representing the findings and opinions of many different authors. In the present study, a majority of the relevant findings were obtained from a single manufacturer (R. J. Reynolds). Thus our findings should be interpreted not as representative of the entire tobacco industry but rather as instructive regarding the character of internal research on additives, assessment of their potential effects, and the use of this knowledge in product development.

Results

Historical use of organic acids in cigarettes

Organic acids have been used since the 1950s to improve smoothness of cigarettes, typically at low levels in top dressings, that is, sprayed onto the

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shredded tobacco (R. J. Reynolds, 1991b). Philip Morris tested organic acids in its Marlboro cigarettes in the 1970s and found that lactic acid decreased harshness and bitterness, and produced a sweeter flavor (Vinals, 1971). Other internal studies confirmed a smoothing effect when lactic acid was added to tobacco filler, with reduced smoke impact (Cipriano, Kounnas, & Spielberg, 1975), as well as a slight reduction in nicotine and tar deliveries (Meyer, 1963). Citric additives have been used not only for reduced harshness and flavor modification but also to reduce smoke pH, to "neutralize" nicotine impact, and to enhance sheet formation in reconstituted tobacco (Philip Morris, 1989). Tartaric and lactic acids likewise caused reductions in the pH of smoke (Backhurst, 1968). All of these organic acids increased smoothness but were associated with a decrease in nicotine impact.

A number of internal studies have explored the use of organic acids for manipulation of nicotine delivery in cigarette smoke. In 1978, an R. J. Reynolds author speculated that sorbic acid was being used in Philip Morris cigarettes for nicotine reduction (Thacker, 1978). The authors of a 1980 Lorillard study (Hurst & Slaven, 1980) reported that acid-impregnated papers (including lactic, citric, and malic) influenced migration of nicotine to the periphery, which elevated mainstream smoke nicotine delivery without affecting other smoke constituents. Another Lorillard study (Sudholt, 1985a), seeking to produce an increased impact in ultra-low-tar cigarettes, proposed cigarettes made with malic acid filters to test the migration of nicotine from tobacco to the filter. Despite an initial fourfold increase in the rate of migration (Sudholt, 1985a), the author later concluded that malic acid was not useful for promoting migration under typical construction and storage procedures (Sudholt, 1985b).

Philip Morris initiated a study of organic acids in 1975 to evaluate the contribution of individual acids to subjective acceptability, particularly in the development of low-delivery cigarettes (Cipriano et al. 1975). In one finding, the addition of formic acid produced "a distinct sour effect" and otherwise failed to improve subjective performance. However, the researchers observed an unexpected 25% increase in smoke nicotine delivery in cigarettes injected with formic acid. This nicotine increase did not correspond to an increase in perceived impact, and in fact appeared to reduce impact—a finding attributed by the authors to a likely reduction in free nicotine delivery consistent with a reduction in smoke pH. The authors concluded: "Perhaps another non-volatile acid can be found which might contribute to increased nicotine delivery without itself distilling through the rod and affecting either basic taste sensations or smoke pH" (Cipriano et al., 1975).

Indeed, in the late 1980s, R. J. Reynolds scientists discovered that when levulinic acid, another organic acid, was applied to high-nicotine blends of tobacco, harshness was reduced without a decrease in smoke nicotine delivery or unpleasant taste. Furthermore, the nicotine salt of levulinic acid, nicotine levulinate, decreased harshness as expected but also increased smoke nicotine delivery. A summary of this research commented, "Numerous ... organic acids were evaluated at varying application levels but none were found to work as effectively as levulinic acid" (R. J. Reynolds, 1991b).

On December 24, 1987, R. J. Reynolds filed for a patent for incorporating levulinic acid as an additive into cigarettes. The principle of the invention was to increase the smoke impact strength by raising the delivered nicotine in smoke, while reducing the inherent harshness of nicotine through levulinic acid or nicotine levulinate (Hale et al., 1990a). The patent application claimed that cigarettes "composed of high nicotine tobaccos and levulinic acid and cigarettes having a salt such as nicotine levulinate incorporated therein can exhibit low U.S. Federal Trade Commission (FTC) 'tar' to nicotine ratios while providing a smooth, palatable and flavorful taste" (Lawson, Bullings, & Perfetti, 1987).

Properties and effects of levulinic acid

According to the standard tobacco industry monograph on additives, levulinic acid is used in cigarettes as a flavorant because of its sweet caramel taste and body (Leffingwell, Young, & Bernasek, 1972). But results from various internal projects (discussed in detail below) indicate that levulinic acid has been used by manufacturers to improve sensory character (smoothness) of smoke and raise delivered nicotine. Further, this internal research suggests that levulinic acid may enhance the binding of nicotine to neurons that ordinarily would be unresponsive to nicotine. This combination of effects corresponds to increased levels of plasma nicotine in smokers of cigarettes treated with levulinic acid, particularly when applied to lower-yield and reduced-exposure products. Table 1 summarizes the effects of levulinic acid as a cigarette additive, and these effects are each described in turn below.

Alters sensory perception of smoke. R. J. Reynolds began evaluating the addition of levulinic acid to tobacco in an effort to address harshness issues encountered in the development of low-tar cigarettes. Researchers had observed that levulinic acid reduced throat irritation from cigarette smoke (Santambrogio, 1991). Subjective reports indicated that overall sensitivity to cigarette smoke constituents was decreased in the upper respiratory tract

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Table 1. Summary of effects of levulinic acid when used as an additive in cigarettes.

Potential effect	Measure used	Objective	Outcome
Sensory perception (Steele, 1989)	Subjective consumer panel testing of treated cigarettes	Offset harshness and irritation in development of low-yield cigarettes	"...physiological clues are being blocked, since people smoked the test cigarettes essentially the same as the control, even though more nicotine was obtained"
Smoke pH (Stewart & Lawrence, 1988)	Electrode-based measure of smoke pH of machine-smoked cigarettes	Offset harshness and irritation in development of low-yield cigarettes	Decreased smoke "pH" in Camel Light when used alone or added as nicotine levulinate
Nicotine delivery in smoke (Steele, 1989)	Puff profiles of smokers, followed by yield measures based on Human Mimic Smoking Machine	Increase smoke nicotine delivery of low-tar cigarettes relative to higher tar controls	Smoke nicotine delivery increased in a number of tested brands, including Camel Light, Vantage Ultra Light, and NOW
Plasma nicotine (Steele, 1989)	Plasma nicotine change from baseline measured comparing smokers of control and test cigarettes	Increase bioavailability of smoke nicotine in low-yield and low tar/nicotine cigarettes	Plasma nicotine for NOW about 6 ng/ml higher than the control (Winston King); for Winston Ultra Light, about 13 ng/ml higher than control
Tar/nicotine ratio (Steele, 1989)	Machine-measured smoke yields of tar and nicotine	Increase delivery of nicotine relative to tar in low-yield cigarettes	Levulinic acid alone had little effect; nicotine levulinate decreased tar and nicotine by half in Winston Ultra Light and NOW
Receptors in brain (Steele, 1989)	In vitro studies on binding of radiolabeled nicotine to pharmacological receptors in brain tissue	Determine whether levulinic acid affects nicotinic cholinergic receptors in the brain	Observed increased nicotine binding ranging from 20%–50%, with a mean value of around 30%; "...changes in receptor binding may lead to changes in physiological effects of nicotine..."

from the oropharynx to the trachea (R. J. Reynolds, 1990a). Consumer panel testing of levulinic acid treated cigarettes showed a reduction in harshness but also revealed a decrease in strength (impact), taste, and consumer preference (satisfaction; R. J. Reynolds, 1990b). At high levels (3%–5%), the application of levulinic acid resulted in products that were "very smooth" but had an off taste (R. J. Reynolds, 1991b). Adding nicotine levulinate instead of the acid precursor produced cigarettes that were much smoother than expected, without a measurable deterioration in taste (R. J. Reynolds, 1991b).

A series of internal studies was conducted to measure the effects of levulinic acid on neural response. These included psychophysical and respiratory response studies conducted with anosmic human subjects (i.e., those without a sense of smell), measurement of peripheral sensory response in the trigeminal and olfactory nerve endings of pigeons, and physiological experiments on portions of the upper respiratory tract in dogs (Walker, 1990). An incremental increase in nerve activity was shown with the addition of a small concentration (1 ppm) of levulinic acid. This increase in activity was greatest for the lowest nicotine concentration and decreased as the nicotine concentration was progressively increased, suggesting increasing overlap between the neurons activated by these two compounds (Guy, Jennings, Morgan, & Walker, 1992). Pretreatment with levulinic acid significantly reduced the olfactory response to nicotine concentrations, consistent with these findings (Walker, 1991). Figure 1 illustrates the effect of levulinic acid on the olfactory nerve response in an effort to modify perceptual responses to cigarette smoke.

The mechanism of action for these effects was a subject of some internal debate (Best, 1992). Some researchers speculated that levulinic acid may restrict chemoreceptor stimulation in the upper airway and thereby decrease the permeability of nicotine through the epithelia and nasal cavity, blocking the physiological clues for the delivery of nicotine (R. J. Reynolds, 1990a). Other researchers hypothesized that levulinic acid may alter olfactory responses to nicotine by lowering the pH of the mucus overlying the olfactory receptor sheet. This lower pH would reduce the proportion of free-base nicotine that is available to interact with receptor olfactory neurons (Jennings et al., 1992). Indeed, according to data taken from a separate study of nicotine transport, the addition of levulinic acid measurably reduced the amount of nicotine in the vapor phase of smoke, presumably making the nicotine less available to receptors that respond to irritating compounds in the throat or upper airways (Dufour, 1991).

Alters smoke pH. The tobacco industry has an established history of manipulating the pH levels of tobacco and smoke (Connolly, 1995; Hurt & Robertson, 1998; Pankow, 2001). Cigarette smoke pH is ordinarily slightly acidic (about 6), and as a result nicotine in smoke exists mainly in the salt

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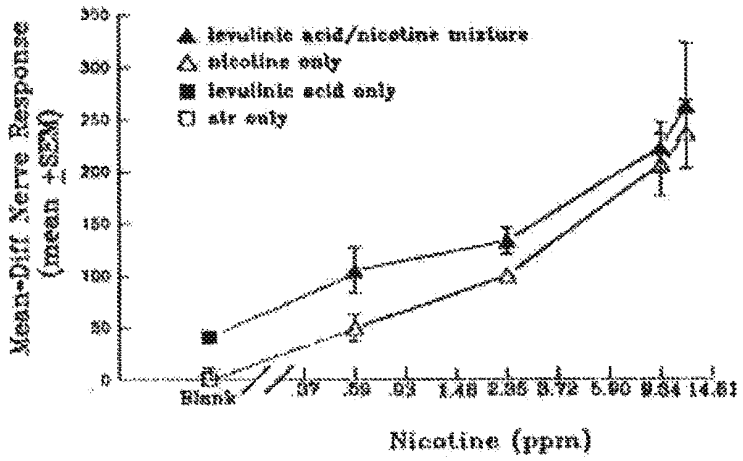


Figure 1. An illustration of the effect of levulinic acid on olfactory nerve activity for increasing levels of nicotine. From an R. J. Reynolds internal report, "Modification of olfactory nerve response to nicotine by levulinic acid experiment" (Jennings et al., 1992).

(protonated) form. When pH is elevated (7–12), nicotine moves to its free-base form, in which it is more readily absorbed into the lungs and provides a stronger sensory impact in the mouth and throat. Higher rates of free nicotine may increase the potential for addiction but also can be experienced as too harsh and having too strong an impact (Hale, Kroustalis, Lin, Raymond, & Spielberg, 1990b). Thus a reduction in smoke pH may be desirable for cigarettes exhibiting higher smoke delivery, whereas increased pH may compensate for reduced delivery.

As the level of levulinic acid in tobacco is increased (from 0% to 5%), the pH of tobacco smoke decreases, consistent with the acidic nature of the additive itself (Cook, 1987). In one series of studies, R. J. Reynolds researchers determined that a 3:1 molar ratio of levulinic acid to nicotine resulted in a decrease in the smoke pH of Camel Light 85 cigarettes from 6.25 to 5.38 (R. J. Reynolds, 1988a). Tests comparing combinations of added levulinic acid, nicotine levulinate, and a "soup" of levulinic acid and "SDK-22" tobacco essence indicated that levulinic acid decreased smoke pH values more than either nicotine salt preparation. But high doses of nicotine levulinate and the mixture of levulinic acid and tobacco essence were effective in decreasing smoke pH as well, lowering the pH value by 0.52 units and 0.74 units, respectively, from the control value of 6.12 (Figure 2; Stewart & Lawrence, 1988).

Increases smoke nicotine delivery and absorption. High-nicotine tobaccos treated with levulinic acid or nicotine levulinate delivered an increased dose of nicotine to the smoker across a range of experiments, including low-tar (Camel Light 85) and ultra-low-tar (Vantage Ultra Light 85) configurations, and across a variety of tobacco types (Montoya & Best, 1987; Perfetti, 1989; Powell, Redding, & Stewart, 1988). For example, smoke nicotine levels (as measured using a Human Mimic Smoke Machine, which adjusts for differences in inhalation behaviors) for the brand NOW 85 were doubled for test cigarettes treated with nicotine levulinate (0.77 mg/cigarette for control vs. 1.68 for the test; Steele, 1989). The smoke nicotine delivery from the treated (test) cigarettes was considered remarkably high: The study authors noted that 1.19 is generally the upper limit of full-flavor Winstons and Marlboros (Steele, 1989). Subsequent research confirmed that smokers could get the same nicotine from lower-tar products treated with levulinic acid as from higher-tar controls. A study completed in 1991 used low tar/nicotine (T/N) prototypes including Dakota Lights base blend with G7-1 reconstituted tobacco at 5 mg tar and 0.47 mg nicotine (J. H. Reynolds, 1991). When modified by additions of nicotine and levulinic acid, the nicotine yield ranged from 0.73 mg to 1.02 mg. Although the majority of internal studies on nicotine yield were conducted using nicotine levulinate as the additive, and nicotine levulinate increased yields significantly more than levulinic acid alone, the nicotine yields from G7-1 treated with levulinic acid also were increased (Perfetti, 1989).

One noted advantage of levulinic acid was its ability to offset the harshness usually associated with an increase in smoke nicotine delivery, particularly in lower-yield cigarette brands (Hale et al., 1990b; R. J. Reynolds, 1988b). Biobehavioral studies confirmed that the NOW 85 test and control cigarettes described previously were smoked almost identically, "even though T/N was low enough in the test cigarettes to make them 'almost unsmokable' without the nicotine levulinate" (Steele, 1989). However, an internal harshness threshold study

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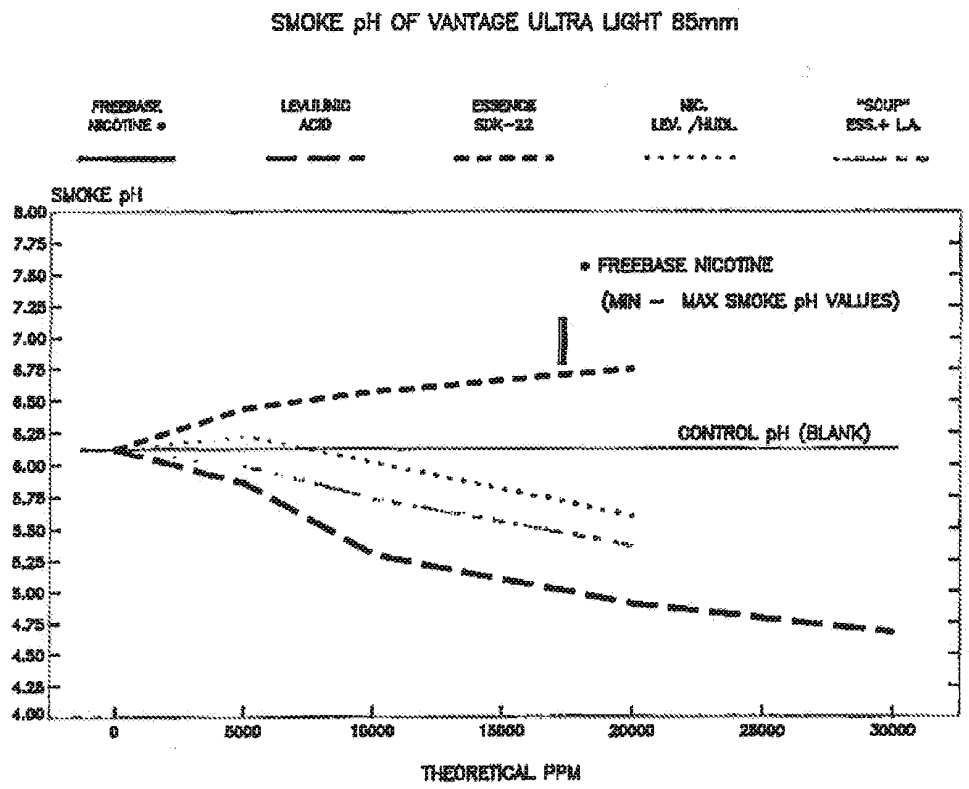


Figure 2. Effects of levulinic acid and other compound mixtures on smoke pH of experimental (Vantage Ultra Light) cigarette. From an R. J. Reynolds internal report on the development of Project XGT prototypes (Stewart & Lawrence, 1988).

demonstrated that for products with a high T/N ratio, levulinic acid can increase harshness (Perfetti & Wong, 1989). The authors cited further internal studies to suggest that a smoke aerosol high in organic acids and with low yields of nicotine is perceived as harsh, and will grow increasingly harsher following application of higher loads of the acid.

Increases peak plasma nicotine level. Higher smoke nicotine deliveries were ultimately reflected in plasma nicotine/cotinine changes from baseline among study subjects (R. J. Reynolds, 1990c). Researchers observed increased peak plasma levels of two times or greater in ultralight brands tested (R. J. Reynolds, 1987). The plasma nicotine for NOW 85 (treated with 10% nicotine levulinate) was approximately 6 ng/ml higher than for the control, whereas the Winston Ultra Light (5% nicotine levulinate) was about 13 ng/ml higher. In fact, the plasma nicotine levels for both brands proved higher than the Winston Full Flavor plasma nicotine rise (R. J. Reynolds, 1991b). This indicated that smokers had no problem inhaling smoke, even though the treated cigarettes contained higher nicotine and had lower T/N ratios. A separate document claimed that a 1- to 2-mg (nicotine) prototype had been developed internally that achieved higher blood nicotine levels than conventional 1- to 2-mg products (R. J. Reynolds, 1992).

Reduces tar/nicotine ratio. A primary goal in the design of lower-yield cigarettes is to increase the smoke delivery of nicotine relative to tar (Hale et al., 1990b). Although levulinic acid alone had little direct effect, nicotine levulinate proved particularly successful in reducing T/N levels (R. J. Reynolds, 1991b). When NOW 85s and Winston Ultra Lights were treated with nicotine levulinate (10% and 5%, respectively), FTC tar and carbon monoxide delivery were essentially unchanged for test and control cigarettes (Steele, 1989). But T/N ratios decreased by approximately one-half (9.1 and 4.97 for the control and test, respectively). Nicotine levulinate added to NOW 100s and Winston Ultra Light 100s was found to reduce T/N ratios (4–5) and to significantly increase mainstream smoke yields of nicotine, further corroborating these findings (R. J. Reynolds, 1990c).

Enhances binding of nicotine in brain. Although research had originally focused on the interactions of nicotine and levulinic acid at sensory receptor

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sites, scientists at R. J. Reynolds conducted experiments beginning in 1989 to assess potential pharmacological interactions affecting the nicotinic cholinergic receptors in the brain (Lippiello, Fernandes, Reynolds, & Hayes, 1989). It had already been determined that some compounds enhanced the binding of nicotine to its receptors in brain tissue (Lippiello et al., 1989), although nicotine salts per se had not been investigated. Evidence indicated, however, that levulinic acid might interact with cholinergic systems by virtue of its ability to reverse acetyl cholinesterase inhibition (Lippiello et al., 1989).

Inhibition binding assays were conducted in vitro to test the effects of levulinic acid and nicotine levulinate on the binding of nicotine to pharmacological receptors in membrane preparations derived from rat brain tissue (Lippiello et al., 1989). The high-affinity sites present in the tissue were saturated (i.e., >90%) by a concentration of radiolabeled nicotine (30 nM), and the level of binding was arbitrarily taken to be 100%. Nicotine binding was then plotted as a function of increased concentrations of an unlabeled competitive inhibitor (such as nicotine salicylate or nicotine levulinate). The study results showed that the levulinic compounds significantly increased the amount of nicotine bound to nicotinic receptors above the expected control level. In the case of nicotine levulinate, observed increases ranged from 20% to 50%, with a mean value of around 30%, whereas enhancement was similar although somewhat less in the case of levulinic acid alone (Lippiello et al., 1989). A graph modeling enhanced nicotine binding in the presence of levulinic acid is presented in Figure 3.

Lippiello et al. (1989) theorized that levulinic acid induces positive cooperativeness at an additional

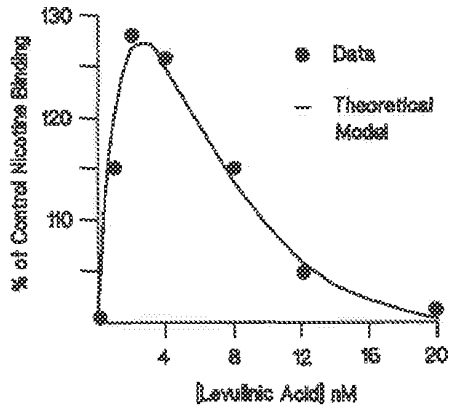


Figure 3. Theoretical curve for enhancement of [3H]-nicotine binding to nicotinic receptors. Cited in a 1989 R. J. Reynolds study on the effects of nicotine levulinate and levulinic acid on the binding of nicotine to nicotine receptors in rat brain tissue (Lippiello et al., 1989). nM, nanomoles per liter.

class of low-affinity receptor sites. Thus, in the presence of levulinic acid, nicotine binds to an additional set of receptors that would not ordinarily be responsive to the nicotine molecule. Although other organic acids were similarly tested, only levulinic acid demonstrated significant enhancement of nicotine binding, and it did so only in a narrow concentration range (Guy, 1990). At higher concentrations the effect was reversed, suggesting that levulinate also has a reasonable affinity for the nicotine binding sites and therefore eventually inhibits its own effect. Another study conducted at the University of Colorado using mouse brain tissue indicated a similar trend but with a lower magnitude of effect (i.e., maximum effect of approximately 10%–12%; as discussed in Steele [1989] and Lippiello et al. [1989]).

Application and smoke delivery of levulinic acid

Migration. Internal research suggests that use of levulinic acid may have produced unintended effects on product delivery and tobacco smoke exposure. For example, migration of levulinic acid within the cigarette was found to be a significant problem during toxicological tests conducted in 1989–1990, resulting in a significant change in the FTC tar and carbon monoxide values of test cigarettes. When levulinic acid was applied to the cigarette rod, it migrated heavily to the paper wrapper (50% after 4 months), regardless of wrapper type (Best, 1990), and not to the cellulose acetate filter (R. J. Reynolds, 1990d). The migration occurred radially, thereby decreasing the wrapper porosity. This in turn affected sidestream/mainstream ratios as well as the burn rate and puff count (R. J. Reynolds, 1989), and the amount of tobacco consumed during puff and smolder periods, resulting in more tobacco consumed during puffs (Best, 1990). These differences resulted in an increase in mainstream gases (particularly carbon monoxide and carbon dioxide) at the expense of sidestream gases. Process changes were used to arrest the migration in a later round of toxicological testing (Lloyd, 1992a), but internal analysis of these changes was not identified in the present study.

Mainstream and sidestream delivery. Levulinic acid has been reported in mainstream smoke at levels of 29–56 μg/cigarette and in sidestream smoke at 25–49 μg/cigarette (Kusama, Munakata, Ohsumi, Sakuma, & Sugawara, 1983). However, industry analysis of prototypes developed and tested internally demonstrated yields in some cases 10–100 times greater (J. H. Reynolds, 1991). Radiotracer studies performed at R. J. Reynolds found that 9% of the levulinic acid added to tobacco was transferred intact to mainstream smoke, with a further 3% transferred

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in mainstream smoke as pyrolysis products (R. J. Reynolds, 1990d). The transfer distribution between mainstream and sidestream vapor phases changed when using longer equilibration times or increasing application of levulinic acid to the wrappers, with mainstream smoke increasing and sidestream smoke decreasing (Best, 1990). Industry documents list a number of the pyrolysis products of levulinic acid and nicotine levulinate, including carcinogenic and toxic compounds such as styrene, trimethylbenzene, and naphthalene (Chung & Aldridge, 1990; Chung, Moore, & Aldridge, 1987). However, internal documents do not discuss the effects (actual or potential) of these products on the smoker.

Use of levulinic acid in commercial cigarette brands

In the late 1980s, R. J. Reynolds embarked on a series of research projects with the goal of developing a reduced-tar product with taste, impact, and satisfaction comparable with a higher delivery product (Table 2). Levulinic acid played a central role in this research. Physical, analytical, sensory, and behavioral effects were evaluated for levulinic acid, a nicotine extract ("KDN"), and various mixtures of the two, across a wide range of levels (R. J. Reynolds, 1991a). In addition to research conducted under projects targeting development of a successful ultralight brand, levulinic acid was incorporated into the development of the potentially reduced-exposure Premier prototype (R. J. Reynolds, 1990b). Internal research found that levulinic acid transferred to smoke from the Premier prototype substrate at a rate six to seven times greater, as measured by human smoking conditions, than with a standard FTC smoke-machine measure (Best, 1991).

Levulinic acid was included in a voluntary 1994 list of the 599 additives used by tobacco manufacturers in commercial cigarettes (Doull et al., 1994) and continues to be listed as an active ingredient on R. J. Reynolds's Web site (www.rjrt.com, accessed February 4, 2004). Although internal discussion of the use of additives in specific commercial brands is quite limited, the available evidence suggests that levulinic acid has been used at levels consistent with a significant role in cigarette design relative to other additives. For example, an internal commentary from 1991 noted, "Use of levulinic acid is proposed at levels which may place it within the top ten ingredients used by RJR" (Dube, 1991). The author observed the importance of obtaining further information "to identify potential concerns and defend its use" and recommended the development of a protocol for evaluation of use of this additive in commercial cigarettes. According to the list made publicly available by R. J. Reynolds's Web site, the current maximum level of levulinic acid used in any brand is 0.02%. This would equate to 200 µg in a typical (~1 g) cigarette. This level is greater than the amount common for most tobacco flavorants but below the levels typical of sugars, cocoa, licorice, and

Table 2. Series of R. J. Reynolds projects targeting use of levulinic acid.

Project	Objective	Use of levulinic acid	Outcome
Delta (Premier) (1986) (R. J. Reynolds, 1990b)	Develop cigarette that heats rather than burns tobacco (potential reduced-exposure product)	Explored ways to reduce harshness of cigarettes; organic acids evaluated for "smoothness"	Levulinic acid increased smoothness without off taste; suggests application in development of conventional (ultralight) brands considered
Project GT (1987) (R. J. Reynolds, 1990b, 1990e)	Develop product with reduced tar (ULT) comparable with full-flavor light	Explored the addition of nicotine levulinate to two ULT cigarettes, NOW and Winston Ultra Light 100s	Extremely low TN ratios, increased smoothness, low impact; no change in smoking behavior; increased nicotine delivery reflected in plasma concentrations
Project GTX (1990) (R. J. Reynolds, 1990b, 1990e)	Develop alternate methods/ sources for enhancing nicotine yields of low-tar products	Experimental nicotine levulinate sheet developed for sensory and biobehavioral testing	Concluded "ULT cigarettes with enhanced nicotine yields and good smoking characteristics can be produced"
Project XB (1991) (Lloyd, 1992b; R. J. Reynolds, 1990a, 1990e; Wilson, 1991)	Provide the taste and satisfaction of FFLT products at lower tar yields (1 mg)	"Breakthrough": when nicotine was added to levulinic acid to form nicotine levulinate, significant T/N reductions achieved with products much smoother than expected	Proposed further exploration of psychophysical and respiratory effects among normal and anosmic human subjects
KDN extract (1991) (Lloyd, 1992b; R. J. Reynolds, 1991c)	"need an in-process source of nicotine because we couldn't achieve a consumer acceptable low T/N ratio product using construction variables..."	KDN extract identified as a source of nicotine for the synthesis of nicotine levulinate, supporting use of nicotine levulinate in brand development	"Levulinic acid is what helps the KDN have a higher overall acceptance and closer subjective response to Marlboro Lights..."

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humectants. An internal file note from 1988 observed that "levulinic acid is currently used as a direct flavor additive in 12 RJRT brands at concentrations ranging from 0.040 to 154.8 µg/cigarette" (R. J. Reynolds, 1988b). Table 3 lists those cigarettes and their respective levels of levulinic acid (R. J. Reynolds, 1988c).

Discussion

Tobacco industry scientists generated considerable evidence that levulinic acid and nicotine levulinate decreased harshness and increased nicotine yield from tobacco smoke. Further, internal research demonstrated the capacity of levulinic acid to enhance the binding of nicotine in the brain, increasing its pharmacological effectiveness. The addition of levulinic acid also altered the composition of mainstream and sidestream smoke and introduced potentially toxic pyrolysis products to smoke. These combined effects could have significant implications for the increased addictiveness or toxicity of the cigarette and the progression of smoker behaviors including initiation and quitting. Measured increases in peak plasma nicotine levels among treated low-yield cigarettes confirm the importance of these internal findings in the assessment of brand deliveries.

Despite the potential health consequences, internal findings regarding the effects of levulinic acid as an additive were not reported to public health or other government agencies. Commercial products containing levulinic acid have been sold to smokers, but the relative amounts of the additive and its effects on smoke perception, behaviors, and bioavailability remain for the most part unknown. Based on recent internal industry projects, it seems likely that levulinic acid may have had particular impact in the development of so-called reduced-exposure products such as Premier and, later, Eclipse. Thus possible effects on smoker inhalation patterns or bioavailability of smoke constituents may present serious concerns regarding the evaluation of these nonconventional products, as well as conventional cigarettes. Although internal findings do not clearly indicate levels of the additive relevant for human exposure, they suggest the importance of further research in these areas.

Table 3. Levels of levulinic acid used in 12 commercial cigarettes.

Brand	Levulinic acid level (µg/cigarette)
More Light 100 Menthol Box	0.040
Salem Light 100 Custom Case Box	0.045
Century Light 100 Menthol	0.046
Salem Light 100	0.046
Vantage 85	1.407
Century 85	2.496
Magna 80 Box	2.565
Magna 85	2.584
Vantage Ultra Light 100	2.945
Winston Ultra Light 100	2.945
More 120	154.282
More Light 120	154.822

Source. R. J. Reynolds, 1988c.

Given the health risks of tobacco use and addiction, and the complicated array of additives commonly used in tobacco products, scientists and public health officials must continue to advance their knowledge of the function of additives and, ultimately, their effects. This investigation depends on adequate disclosure requirements and ongoing independent research. To date, the success of tobacco manufacturers at safeguarding the identity of the additives used in their products has prevented meaningful disclosure. Making this information available to appropriate regulatory agencies would allow researchers to assess interactions between additives and to evaluate their effects. Further, smokers would be given the opportunity to consider added chemicals and their byproducts inhaled in cigarette smoke.

A critical first step in the evaluation of the role of additives in tobacco products is the requirement of full and meaningful disclosure (by brand) to an appropriate regulatory agency, such as the U.S. Food and Drug Administration. In addition to questions of toxicity, the role of additives in controlling or altering pharmacological and sensory effects of smoke must be considered, particularly in the context of low-yield and reduced-exposure products. Future studies should include respiratory effects and bronchodilation, smoke perception, effects on absorption and receptor binding, and smoker topography. All internal toxicological and behavioral studies undertaken by manufacturers should be released to the public record, including methodologies used, data collected, and results. Finally, continuing independent public health research is needed, including product testing to identify and assess brand-specific design issues and to warn the public of potential harm.

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Numerical Simulation of the Effects of Dilution Level, Depth of Inhalation, and Smoke Composition on Nicotine Vapor Deposition During Cigarette Smoking

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A numerical model of an aerosol containing vaporizable nicotine depositing to the walls of a tube was developed and applied to simulate the vapor deposition of nicotine in a denuder tube and under conditions approximating those in the respiratory tract during mainstream cigarette smoke inhalation. The numerical model was validated by comparison to data for denuder tube collection of nicotine from the smoke of three types of cigarette differing in smoke acidity and nicotine volatility. Simulations predict that the absorption of water by aerosol particles inhibits nicotine vapor deposition to tube walls, and that increased temperature, decreased tube diameter, and increased dilution enhance nicotine vapor deposition rate. The combined effect of changing these four parameters to approximate the transition from conducting to gas exchange regions of the respiratory tract was a significant net increase in predicted nicotine vapor deposition rate. Comparisons of nicotine deposition rates between conditions in the conducting airways and those in the gas exchange region were informative with regard to reported nicotine retention measurements during human smoking. Reports that vaporizable nicotine can penetrate past the conducting airways, that nicotine can be retained at near 100% efficiency from mainstream smoke, and that cigarettes with differing acidity and nicotine volatility have similar nicotine uptake rates are all shown to be consistent with the results of the model simulations.

The uptake of nicotine during smoking and, in particular, the influence of mainstream cigarette smoke acidity on nicotine retention have been central issues in discussions of the relationship between cigarette design and smoking dependence. One view suggests that "smoke pH" can be manipulated by tobacco type and additive level, which in turn influences the rate of nicotine uptake during smoking and determines the addictive potential of a particular cigarette design (Pankow, 2001). An alternate perspective holds that although there is some support for a relationship between "smoke pH" and nicotine transfer rate in the basic chemistry of nicotine and considerations of aerosol dynamics, the suggestion of a direct dependence is a hypothesis that is problematic and not consistent with measurements of nicotine retention during human smoking (Ingebrethsen et al., 2001; Baker & Dixon, 2006). The experimental results that would most directly address and resolve this issue, specifically high time resolution nicotine deposition measurements on cigarette smoke in the human respiratory tract, are not available and disagreement on the issue remains. However, a number of replicated experimental findings regarding nicotine retention in smokers are available, as are numerical models of nicotine liquid/vapor equilibrium behavior in mainstream smoke (Ingebrethsen et al., 2001; Lipowicz & Piade, 2004) that accurately describe nicotine vapor deposition from smoke in denuder tube experiments, a system with fundamental similarities to smoke traveling in the respiratory tract. The objective of this study is to compare the predictions of one experimentally based numerical model of mainstream smoke aerosol dynamics with several observations regarding nicotine retention during smoking in an attempt to reconcile some apparent contradictions between experiment and theory. The present study does not address particle deposition directly (see Bernstein, 2004; Robinson & Yu, 2001) as the focus is on selective retention of nicotine versus particle retention, which is a result of vapor nicotine transport during smoking. Additionally, ammonia has been shown to be rapidly lost from smoke in denuder tubes (Ingebrethsen et al., 2001; Seeman et al., 2004), and by prediction in the upper airways, and its minimal effect on nicotine evaporation rate was not included in the present analysis.

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A number of studies are in agreement that nicotine is retained from mainstream smoke during human smoking more efficiently than bulk particulate matter: on the order of 60 to 80% for bulk particulate versus 90 to 100% for nicotine (Robinson & Yu, 2001; Baker & Dixon, 2006). This observation is consistent with enhanced deposition of nicotine, versus nonvolatile particulate matter, due to the vaporization of nicotine from smoke particles during inhalation followed by vapor deposition to respiratory tract surfaces. If one considers that for an inhaled nicotine vapor/air mixture, nicotine is almost completely retained in the upper airways (Bergstrom et al. 1995), and that nicotine in submicrometer smoke particles would be expected to rapidly achieve vapor equilibrium (Hinds, 1982), it might be expected that all potentially volatile nicotine in smoke would be removed in the conducting airways. Yet nicotine effectively reaches the gas exchange regions of the lung during mainstream smoke inhalation, indicating that there is some inhibitory process for nicotine vapor deposition from smoke in the upper airways.

A possible inhibitory influence on nicotine vapor deposition in the upper airways could result from a fraction of the total nicotine being present in a nonvolatile or protonated form in the smoke particulate. A partitioning of nicotine between volatile and nonvolatile forms is, in fact, implicit in the "smoke pH" nicotine retention hypothesis (Pankow, 2001). However, nicotine is observed to be almost completely retained from inhaled mainstream smoke at the same time that bulk particulate matter is retained to a significantly lower degree, suggesting that smoke particles can be completely stripped of nicotine during inhalation, presumably by evaporation. This observation suggests that all nicotine in smoke can potentially evaporate from the particles but that some process inhibits this evaporation in the conducting airways, allowing a substantial amount of nicotine to reach the gas exchange region of the respiratory tract.

Finally, results of diffusion denuder experiments (Ingebrethsen et al., 2001) suggest that vapor concentrations of nicotine in smoke can vary significantly with cigarette type. Smoke from more basic Burley cigarettes was found to deposit nicotine at a greater rate in denuder tubes than smoke from less basic Flue-cured and American blend cigarettes. If the rate of nicotine retention from inhaled smoke is dependent on the nicotine vaporization mechanism, then one would expect that nicotine uptake rates would depend to some degree on cigarette type in accordance with the volatility of nicotine in the smoke. This is in fact a key aspect of the hypothesis that nicotine "availability" can be controlled by alkaline tobacco additives that influence the volatility of nicotine in smoke (Pankow, 2001). However, nicotine is observed to be rapidly, and almost entirely, retained from inhaled smoke from all cigarettes, regardless of tobacco type or "smoke pH" (Baker & Dixon, 2006). It was observed in one study that, in contrast to oral absorption, the influence of "smoke pH" on lung absorption appears to be negligible (Schievelbien, 1982).

The results of the current analysis are found to provide a consistent description of nicotine retention that resolves, on a theoretical basis and within the limits of the assumptions employed, the questions just raised.

METHOD

The simulation of nicotine retention reported in this article proceeded through three stages. First, a numerical model was constructed that captured the properties and processes believed to be most important to nicotine vapor exchange from mainstream cigarette smoke. Next, the model was fitted to diffusion denuder measurements of nicotine collection for several cigarette types, and "best fit" values for adjustable model parameters were determined. Finally, the model was used to explore the effects of several physical parameters on nicotine vapor transport and to predict nicotine deposition for conditions approximating smoke inhalation in the human respiratory tract.

The description of the aerosol was a modification of that used in Ingebrethsen et al. (2001) and similar to that subsequently presented by Seeman et al. (2004), in which a particulate phase of adjustable number concentration, particle size, and composition contains nicotine in particle/vapor equilibrium. The particulate phase composition consisted of five components: nicotine; water; a water-soluble, generic acid; a water-soluble, generic base; and generic, water-soluble particulate matter. The only volatile species in the current treatment was nicotine, the vapor pressure for which was determined by its pure component vapor pressure, its mole fraction and state of protonation in the particulate solution, and an adjustable activity coefficient. The state of ionization of the nicotine in solution was determined from the pH of the solution, which was determined by the concentrations of the acid, base, and nicotine in the particles.

In Lewis et al. (1995) and in Ingebrethsen et al. (2001), volatile component deposition from a flowing aerosol in a tube was modeled by a summation of volume elements acting independently of each other and depositing volatile components as calculated from the Gormley–Kennedy equation. This approximation yielded reasonable limiting case predictions, but the assumption of independence of vapor exchange to tube walls from volume elements moving past each other in a laminar flow profile was believed to be weak. Lipowicz and Piade (2004) were able to arrive at an exact solution to a differential equation describing an evaporation/deposition process but with a simplifying assumption that did not allow for acid/base behavior in the particles. Seeman et al. (2004) did not consider flow in their treatment.

In the present study, mass transfer and wall deposition calculations were first performed with a discreet element model for a static aerosol in a tube. Estimates for a flowing aerosol were then made from the static tube results utilizing a simple, approximate relationship between static and laminar flow diffusion to the walls of a tube identified by comparing calculations for the respective cases for vapor only deposition. Solutions for transient diffusion removal of vapor nicotine from a static gas to the walls of an infinite cylinder (Incropera & DeWitt, 1990) were calculated from the exact equation summed to 100 terms. The

static case results were compared to Gormley–Kennedy type equation calculations for vapor nicotine deposition to the walls of a tube from a laminar flow. Based on average residence time of a volume element, the static case yielded a removal rate of nicotine almost exactly two times greater than for the laminar flow case. Consequently, nicotine deposition calculated for the static case approximately equaled that calculated for the flowing case at twice the residence time of the static case calculation. A transformation of the time variable by a factor of 2 yielded nicotine deposition versus time curves for the static and flowing cases that were very similar, differing by a maximum of less than 5% and an average of 2% of the total nicotine present over the time range of interest, that is, that up to 99.5% nicotine deposited.

The simulation of nicotine deposition from a static aerosol to the walls of a cylindrical tube was accomplished by dividing the tube into annular cells, usually 20 cells of equal radial width, containing a specified initial particle concentration and composition of the model aerosol. An initial equilibrium vapor nicotine concentration was calculated based on the calculated vapor pressure of nicotine over the particles and available gas volume. The particle composition and vapor composition was iteratively adjusted for the loss of nicotine to the vapor to determine the initial equilibrium conditions. After the initial conditions were determined, the diffusion of vapor nicotine between cells and removal of nicotine to the tube wall, treated as a perfect sink, was calculated for a time step. New vapor nicotine and particle compositions in each cell were then calculated based on the new value of total nicotine available in the cell after diffusion of vapor nicotine into and out of the cell. The total amount of nicotine deposited to the walls of the tube was calculated as the sum of that deposited for each time step. For each set of initial conditions, simulations were performed at a series of decreasing cell dimensions and time increment sizes to the point at which further decrease in either value did not change the numerical results. Equilibrium constants, nicotine vapor pressures, and physical constants used in the model were the same as those given in Ingebrethsen et al. (2001).

The data for diffusion denuder nicotine collection reported in Ingebrethsen et al. (2001) were used to determine adjustable parameters of the model for smoke from three types of cigarettes that differed significantly with respect to the fraction of total nicotine collected in the denuder tubes. The "diluted case" data (Figure 9 of Ingebrethsen et al., 2001) for Burley, Flue-cured, and American blended cigarettes were compared to the current model predictions. The total nicotine content of the smoke and particulate mass concentration were known for each cigarette type from experimental data. The composition parameters adjusted to fit the model to the data were the generic acid concentration, generic base concentration, and the activity coefficient for nicotine.

The aerosol model with parameters that best described the denuder data for each cigarette type was used to predict respiratory-tract nicotine deposition. The conducting airways were modeled as laminar-flow diffusion denuders collecting nicotine diffusing from the flowing aerosol. Total nicotine deposited for laminar tube flow collection is dependent on the ratio of tube length to volumetric flow rate, L/Q, and is independent of tube diameter when tube length and volumetric flow are specified. The Weibel model of respiratory-tract structure was used to calculate a summation through generation 16 of L/Q for an inhalation flow of 250cm^3/s. This calculation yielded a summed L/Q of about 107 s/cm^2 corresponding to an average residence time of about 0.7 s at the specified flow rate. Calculations were then made for removal of nicotine from the static aerosol in a tube for the appropriate residence time, and the identified correlation between static and flowing removal rates already described was applied to yield the estimate of removal in the conducting airways. The alveoli removal was modeled as deposition from a static aerosol in a 0.035 mm diameter cylindrical tube.

RESULTS

The aerosol model was used to explore the effects of several physical parameters expected to influence nicotine deposition rate during smoke inhalation. Figure 1 shows the predicted denuder tube nicotine deposition curves and illustrates the effects of smoke concentration, particulate water content, temperature, and tube diameter. The bold solid line in Figure 1 is the theoretical prediction that best fits the measurements of nicotine collection in a denuder tube for the smoke from a blended cigarette (Ingebrethsen et al., 2001). The measured data points are also shown as circles in Figure 1. The light dashed lines in Figure 1 show the independent effects on nicotine deposition of a 10-fold increase in particulate water content, a 10-fold dilution of particle number concentration, an increase in temperature from 20°C to 37°C, and a decrease in tube diameter from 0.250 cm to 0.125 cm. Also shown as a bold dashed line is the predicted curve for all four parameter adjustments imposed simultaneously.

Figure 2 shows the model predictions for conducting airway and alveolar deposition for the three cigarette types studied. The nicotine deposition curves for the conducting airways in Figure 2 assumed that the fresh smoke was not diluted and was thermally and aqueously unequilibrated as it passed the conducting airways. Specifically, the conditions for the conducting airway simulations were: zero dilution level of the smoke, that is, fresh smoke concentration; temperature 25°C; and zero additional water condensation to particles. The predictions of alveoli deposition assumed dilution of the smoke into the alveoli space and thermal and aqueous equilibrium of the aerosol. Specifically, the conditions for the alveoli simulations were: 60 times dilution of the particle number concentration corresponding to a 50-ml puff diluted into 3000 ml lung volume; temperature 37°C; condensation of water to the particles equal to 10 times the initial mass of the particles; and a tube diameter of 0.35 mm.

In fitting the predictions of the aerosol model to the denuder tube data, the influence of the acidity of the particle solution could be counterbalanced with changes in the nicotine activity coefficient, and, as a result, multiple sets of adjustable

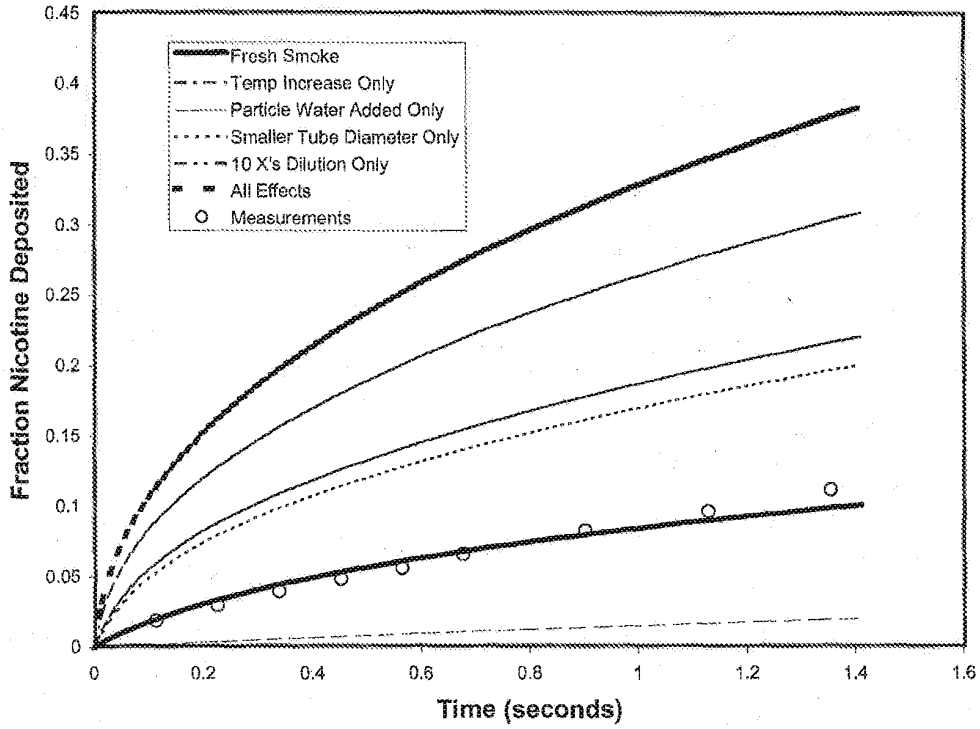


FIG. 1. Fraction nicotine in blended-cigarette smoke deposited in denuder tube: measured (points) and predicted by model (curves) for fresh smoke and increased temperature, increased particle water content, smaller tube, higher dilution, and all effects combined.

parameters over a limited range of values could be determined that described the data equally well. Although the aqueous particle solution properties are not uniquely determined, the changing vapor concentrations of nicotine that drive the vapor deposition process are well predicted by the model as confirmed by the agreement with the denuder data. The details of the particle solution used in the model are one simplified description that predicts the correct nicotine vapor pressure for smoke, but are not presented as a realistic representation of cigarette smoke particulate matter from which other particle properties can be deduced.

DISCUSSION

As fresh mainstream smoke is inhaled it is warmed, humidified, diluted, and introduced into successively smaller airways. The numerical model predicts the effects of these changes in state on nicotine vapor deposition rate as isolated and as combined effects as illustrated in Figure 1. The warming of the aerosol raises the vapor pressure of nicotine over the particles and speeds the vapor deposition relative to the room temperature smoke. The condensation of water into the particle solution lowers the nicotine vapor pressure over the particles by reducing the concentration of nicotine in the particles, resulting in a reduced nicotine vapor deposition rate. The reduced diameter tube simulations demonstrate the expected higher vapor deposition rate for smaller diffusion distances in more narrow tubes. Dilution of the smoke increases the fractional deposition rate of nicotine, that is, the deposition rate as a percentage of available nicotine, relative to fresh smoke, an effect that has been identified and discussed previously (Lewis et al., 1995; Ingebrethsen et al., 2001). Reduced particle concentration increases the concentration gradient between the particle surface and the gas phase due to the reduced number of particles per unit gas volume acting as evaporation sources of nicotine as the tube wall adsorbs vapor. More concentrated smoke will deposit a greater absolute amount of nicotine to the tube walls than more dilute smoke under the same conditions, but the more concentrated smoke will deposit a smaller fraction of total nicotine per unit volume versus less concentrated smoke. Finally, when the four physical parameters just discussed are changed in the direction expected to occur during inhalation, the combined effect is a significant increase in nicotine vapor deposition rate, as illustrated in Figure 1.

The conducting airway simulation results shown in Figure 2 are based on the assumption that the smoke travels as a bolus through the conducting airways without thermal and water vapor equilibration or volume dilution. These conditions are considered a reasonable approximation for comparative purposes with the recognition that some minimal equilibration and dilution of an inhaled bolus of smoke can take place in the conducting airways. The changing airway diameter in the conducting airways is accounted for in the calculations through the summation of

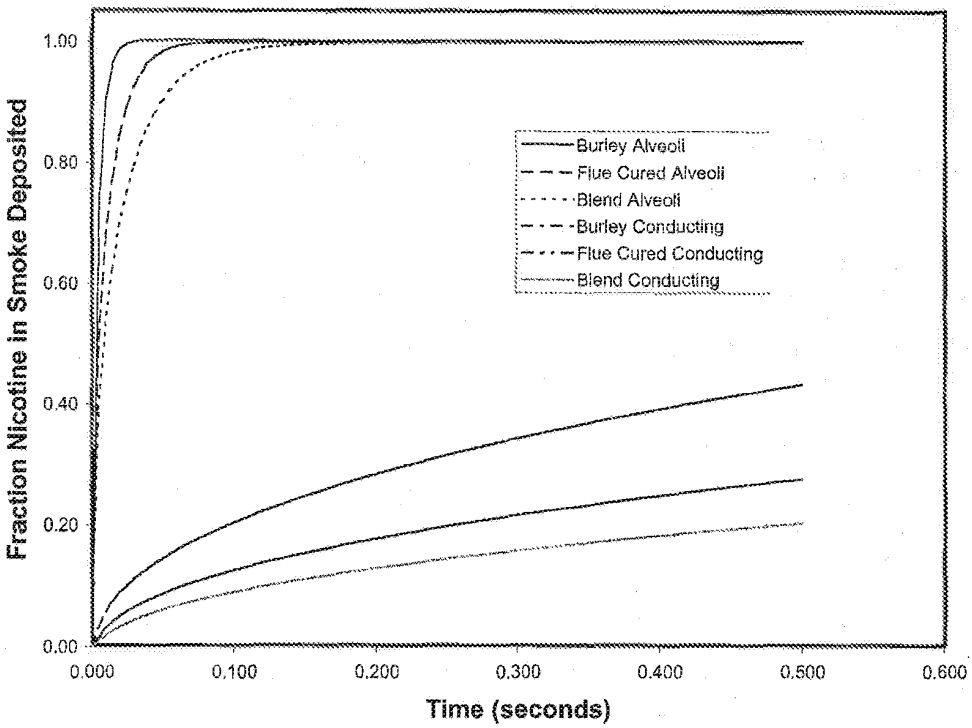


FIG. 2. Predicted nicotine vapor deposition from smoke of three types of cigarettes in the conducting and in the alveolar region.

L/Q based on the Weibel model. The alveoli simulations assume full thermal and water vapor equilibration and full dilution as described earlier.

The present analysis does not take into account the direct deposition of particles during the inhalation process. It would be expected that an overall deposition of 60–80% of the particulate matter (Baker & Dixon, 2006), weighted to the gas exchange region, would result in a small contribution to the dilution level relative to the dilution of the smoke into the lung gas volume, in fact enhancing the observed effects of dilution in the alveolar region. The net effects indicated by the simulations for nicotine vapor deposition calculated with constant particle concentration would be little changed by this degree of particle deposition.

The net result of the changing conditions during inhalation is that, for a given type of smoke, nicotine vapor deposition is significantly slower and less efficient in the conducting airways than in the gas exchange region of the respiratory tract. In the alveolar region, the inhibition of nicotine vapor deposition by water condensation is a smaller effect than the enhancement of deposition by the higher dilution, higher temperature, and smaller tube dimensions. Additionally, Figure 2 illustrates that the differences in nicotine deposition rates observed among the cigarette types in the denuder measurements are also observed in the airway simulations.

Revisiting the questions raised in the introduction, we see that the fact that nicotine in smoke, that is free to vaporize, is able to pass through the conducting airways without depositing is shown to be the result of the inhibition of nicotine vapor deposition by high particle number concentration. The high particle concentration of the smoke in the conducting airways reduces nicotine vapor deposition rate, allowing a substantial fraction of nicotine, which can potentially evaporate and deposit, to remain in the particulate phase until it is diluted into the alveolar region where it rapidly evaporates.

With regard to the near complete retention of nicotine during human smoking discussed in the introduction, we observe the following. In the current model, nicotine in the particulate phase is in acid/base equilibrium between nonvolatile and volatile species in a manner that yields a nicotine vapor pressure in agreement with the denuder measurements. Although the aqueous solution approach is certainly an oversimplification, the model, as employed, predicts nicotine vapor pressure in agreement with experimental data. The experimentally validated nicotine vapor pressures coupled with the very high predicted deposition rates of nicotine under the alveolar conditions results in a prediction of near complete depletion of nicotine from the particles under alveolar conditions for all cigarettes studied (despite the decreasing particle pH, and associated decreasing nicotine vapor pressure, as the particles are depleted of nicotine), in agreement with the human smoking observations. The results of these simulations also point to the dominant role of nicotine evaporation from particles in the overall nicotine deposition from smoke, which is consistent with prior findings (Lewis et al., 1995; Ingebrethsen et al., 2001; Lipowicz & Piade, 2004).

Finally, the simulations provide a reasonable explanation for the absence of experimental observations of differences in nicotine uptake rate for cigarettes differing in smoke acidity. High-pH smoke from Burley cigarettes is predicted to deposit nicotine at a higher rate in the upper respiratory tract than lower pH smoke, consistent with the sensory perception of high pH cigarettes as being very harsh on the throat and cigar-like. High-pH smoke is also predicted to deposit nicotine in the alveolar region at a higher rate than lower pH smoke, but even for low-pH smoke the deposition in the alveolar region is predicted to be rapid and nearly complete on the time scale of a few tenths of a second, rendering differences among the smoke types experimentally inaccessible. This latter prediction is consistent with the experimental observations discussed earlier that nicotine in inhaled smoke from all cigarette types, regardless of "smoke pH," appears in the blood very rapidly and is retained in the respiratory tract at near 100% efficiency.

In summary, observations of nicotine retention in smokers are shown to be consistent with an experimentally based, quantitative aerosol dynamics simulation of nicotine vapor deposition in the respiratory tract. The near complete retention of nicotine from inhaled smoke, the penetration of volatile nicotine past the conducting airways, and the absence of differences in nicotine uptake rate for different acidity levels of smoke are seen to be consistent with the description of the nicotine vapor exchange process presented.

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Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Robert E. Bolcome III
Attorney Docket Number:	52210-501C03US / 713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	850	850
		Total in USD ($)		**1550**

Electronic Acknowledgement Receipt

EFS ID:	31116118
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Robert E. Bolcome III
Filer Authorized By:	
Attorney Docket Number:	52210-501C03US / 713.302
Receipt Date:	04-DEC-2017
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Time Stamp:	14:04:05
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Payment Type	DA
Payment was successfully received in RAM	$1550
RAM confirmation Number	120517INTEFSW00000316500311
Deposit Account	500311
Authorized User	Alejandro Alvarez

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		52210_501C03US_Amendment_Reply.pdf	43301 563e68b79d2c69a2ce846229f511b0e7acae0ef1	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Applicant Arguments/Remarks Made in an Amendment	5	8
	Claims	2	4
	Response After Final Action	1	1

Warnings:					
Information:					
2	Request for Continued Examination (RCE)	52210_501C03US_Request_for_Continued_Examination.pdf	1366251 6b1f993ad954427a5415555af9e5bf1621320a1a	no	3
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4	Miscellaneous Incoming Letter	52210_501C03US_Exhibit_A.pdf	7699305 becefab90f879598511aadc75e026c6ceaf4f267	no	64
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Information:					
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Claim Status

Upon entry of these amendments, claims 26-42 are pending. Claims 1, 4-7, 9, 24, and 25 have been cancelled without prejudice or disclaimer. Claims 26-42 have been added.

Support for new claims 26, 30, 31, 32, 36, 38, and 42 may be found in the subject application as filed, *e.g.*, at [0002], [0006], [0055], [0059], [0061], [0062], [0063], [0068], [0078], and [0079], as well as FIG. 1.

Support for new claims 27, 33, and 39 may be found in the subject application as filed, *e.g.*, at [0062].

Support for new claims 28, 34, and 40 may be found in the subject application as filed, *e.g.*, at [0071] and [0077].

Support for new claims 29, 35, and 41 may be found in the subject application as filed, *e.g.*, at [0059].

Support for new claim 37 may be found in the subject application as filed, *e.g.*, at [0002], [0006], [0055], [0059], [0061], [0062], [0063], [0068], [0071], [0072], [0078], and [0079].

No new matter has been added by the amendments filed herein.

With respect to any claim amendments or cancellations, Applicant has not dedicated to the public or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejection and/or objection made by the U.S. Patent and Trademark Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuing application(s).

Claim Rejections

Rejections under 35 U.S.C. § 112(a)

Claims 24 and 25 are rejected under 35 U.S.C. § 112(a), as allegedly failing to comply with the written description requirement. *See* Office Action at pages 2-3.

Applicant respectfully disagrees. Nonetheless, in an effort to expedite prosecution, Applicant has cancelled claims 24 and 25 without prejudice or disclaimer.

Accordingly, the rejections under 35 U.S.C. § 112(a) are moot.

Rejections under 35 U.S.C. § 103

Claims 1, 4, 5, and 7 are rejected under 35 U.S.C. § 103 as allegedly unpatentable over Sebastian et al. (U.S. Patent Publication No. 2014/0000638) hereinafter "Sebastian." *See* Office Action at pages 4-9. Claim 9 is rejected under 35 U.S.C. § 103 as unpatentable over Sebastian in view of Gonda (U.S. Patent Publication No. 2014/0261474) hereinafter "Gonda." *See* Office Action at pages 6-9.

Applicant respectfully disagrees. However, for the sole purpose of advancing prosecution and without conceding correctness of the Examiner's position, Applicant has canceled claims 1, 4, 5, 7, and 9 without prejudice or disclaimer.

Accordingly, the rejections under 35 U.S.C. § 103 are moot.

Claims 26-42 have not been considered by the Office. However, in the interest of advancing prosecution, Applicant notes that these claims are nonobvious over the cited art.

The Declaration of Adam Bowen (previously submitted with Applicant's April 20, 2017 Response to the December 20, 2016 Office Action) explains that "those of skill in the art believed that vaporized nicotine did not result in an effect on heart rate comparable to that seen with a traditional cigarette." *See* the Declaration of Adam Bowen at paragraph (7). The subject application states: "It has been unexpectedly discovered herein that certain nicotine salt formulations provide satisfaction in an individual superior to that of free base nicotine, and more comparable to the satisfaction in an individual smoking a traditional cigarette." *See* Specification at [0051].

Applicant discovered, *inter alia*, that the combination of an effective organic acid, such as benzoic acid, and nicotine results in a rapid onset peak increase in heart rate relative to the absence of the effective acid. *See, e.g.,* FIG. 1 of the subject application. Prior to this discovery, a person having ordinary skill in the art would have had no reason to form an aerosol with a liquid nicotine formulation as specified in the claims, and no reasonable expectation of successfully doing so. In fact, a person having ordinary skill in the art would have expected that a basic nicotine formulation would lead to superior absorption results when compared to an acidic nicotine formulation. *See, e.g.,* the Declaration of Bradley Ingebrethsen, which was previously submitted in connection with U.S. Serial No. 14/512,311 (the "Ingebrethsen Declaration"; filed herewith as Exhibit A).

Nicotine is a diprotic organic base that can exist in three different forms: a deprotonated form, a monoprotonated form, and an electrically neutral free base form. *See, e.g., id.* at paragraph (4). The Ingebrethsen Declaration states that "Of these three forms the electrically neutral, free base form is known in the art to be the form that is most readily absorbed across cell membranes, and has been widely and commonly assumed over a long time period to be the form that will be most readily and rapidly absorbed from cigarette smoke into the blood upon inhalation." *Id.* Given that free base nicotine was assumed to be the most readily and rapidly absorbed form of nicotine, a person having ordinary skill in the art would not have combined nicotine with benzoic acid as claimed with a reasonable expectation of success.

None of the cited art suggests or describes a liquid nicotine formulation comprising nicotine and benzoic acid, much less an effective amount of benzoic acid such as the 1:1 molar ratio of benzoic acid to nicotine at a nicotine concentration of about 4% (w/w) to about 12% (w/w) as set forth in the pending claims.

The link between effective acids such as benzoic acid and their ability to increase a physiological effect of nicotine such as an increase in heart rate was unknown before Applicant's invention. For example, benzoic acid invokes a stronger physiological response than, *e.g.*, citric acid. *See, e.g.*, paragraph (8) of the Ingebrethsen Declaration.

Even if the cited art generally suggested that an organic acid could invoke a rapid onset peak increase in heart rate (which it did not), the claimed invention would still be nonobvious. None of the cited art provides any teaching that would lead a person having ordinary skill in the art at the relevant time to select a specific effective acid, such as ***benzoic acid***, over any other acid. There is also no suggestion to select any particular efficacious amount of benzoic acid, such as the specific amount required by the instant claims (*e.g.*, the level of benzoic acid required in light of the recited amount of nicotine together with the specified molar ratio).

Accordingly, the pending claims are nonobvious.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration is respectfully requested. This application should now be in condition for allowance; a notice to this effect is respectfully requested.

If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

Except for the issue fees payable under 37 C.F.R. § 1.18, the Commissioner is authorized to charge any fees that may be due in connection with the filing of this paper, or to credit any overpayment thereof, to Deposit Account No. 50-0311 referencing the above-identified attorney docket number.

Dated: December 4, 2017

Respectfully submitted,

Electronic signature: /Robert E. Bolcome III/
Kenneth E. Jenkins, Ph.D., J.D.
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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed.

Listing of Claims

1.-25. (Cancelled)

26. (New) An electronic cigarette cartridge comprising:

a nicotine liquid formulation, the nicotine liquid formulation comprising nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine liquid formulation is about 1:1.

27. (New) The electronic cigarette cartridge of claim 26, wherein the nicotine concentration is about 4% (w/w).

28. (New) The electronic cigarette cartridge of claim 26, wherein the nicotine liquid formulation further comprises a flavorant.

29. (New) The electronic cigarette cartridge of claim 26, which is configured to serve as a mouthpiece and a reservoir that holds the nicotine liquid formulation.

30. (New) The electronic cigarette cartridge of claim 26, wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

31. (New) An electronic cigarette comprising:

the electronic cigarette cartridge of claim 26; and

a battery.

32. (New) A method of providing nicotine to a user, the method comprising

(i) heating a nicotine liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine liquid formulation comprises nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine liquid formulation is about 1:1, and

(ii) inhalation of the aerosol by the user.

33. (New) The method of claim 32, wherein the nicotine concentration is about 4% (w/w).

34. (New) The method of claim 32, wherein the nicotine liquid formulation further comprises a flavorant.

35. (New) The method of claim 32, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine liquid formulation.

36. (New) The method of claim 32, wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

37. (New) An electronic cigarette cartridge comprising:

a nicotine liquid formulation, the nicotine liquid formulation comprising nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol;

(c) the molar ratio of benzoic acid to nicotine in the nicotine liquid formulation is about 1:1;

(d) the nicotine liquid formulation comprises a flavorant; and

(e) the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine liquid formulation.

38. (New) A method of vaporizing a nicotine liquid formulation comprising heating the nicotine liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine liquid formulation comprises nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine liquid formulation is about 1:1.

39. (New) The method of claim 38, wherein the nicotine concentration is about 4% (w/w).

40. (New) The method of claim 38, wherein the nicotine liquid formulation further comprises a flavorant.

41. (New) The method of claim 38, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine liquid formulation.

42. (New) The method of claim 38, wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on December 4, 2017.

MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO pc

By: /Alejandro Alvarez/

PATENT
Attorney Docket No.: 52210-501C03US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: Dionne W. MAYES

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION DATED JUNE 2, 2017

By EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

This paper is submitted in response to the Final Office Action mailed June 2, 2017 (the "Office Action") in the above-referenced application. A Petition for a Three-Month Extension of Time is submitted herewith along with the required fee. With the extension of time, a response to the Office Action is due on or before December 4, 2017 (since December 2, 2017 falls on a Saturday). Accordingly, this response is being timely filed.

Applicant submits this paper in conjunction with a Request for Continued Examination under 37 C.F.R. § 1.114 and the required fee under 37 C.F.R. § 1.17(e). This paper constitutes a proper submission in accordance with 37 C.F.R. § 1.114(c).

Amendments to the Claims begin on page **2** of this paper.

Remarks begin on page **5** of this paper.

Document code: WFEE

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **12/04/2017**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 17	Minus	** 23	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***3	= 1	X $210 =	210
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**210**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
ROSALIND BALL

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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Used in Lieu of PTO/SB/08A/B
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/925,961
				Filing Date	October 28, 2015
				First Named Inventor	Adam Bowen
				Art Unit	1747
(Use as many sheets as necessary)				Examiner Name	D. W. Mayes
Sheet	1	of	10	Attorney Docket Number	052210-501C03US

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
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				First Named Inventor	Adam Bowen
				Art Unit	1747
				Examiner Name	D. W. Mayes
Sheet	2	of	10	Attorney Docket Number	052210-501C03US

	AQ	US-8,910,641	12-16-2014	Hon	
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	BM	US-9,687,025	06-27-2017	Cyphert et al.	
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Sheet	3	of	10	Attorney Docket Number	052210-501C03US

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
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	B	WO-0028842-A1	05-25-2000	Reemtsma H F & Ph		
	C	WO-03056948-A1	07-17-2003	Japan Tobacco Inc		
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	E	WO-2012120487-A2	09-13-2012	Chong Corp		
	F	WO-2013044537-A1	04-04-2013	Joyetech (changzhou) Electronics Co., Ltd		
	G	WO-2015042412-A1	03-26-2015	Nicotine Technology Inc E		
	H	WO-2015066136-A1	05-07-2015	Reynolds Tobacco Co R		
	I	WO-2015073975-A1	05-21-2015	Vmr Products, LLC		
	J	WO-2015157893-A1	10-22-2015	Kimree Hi Tech Inc		
	K	WO-2015157901-A1	10-22-2015	Kimree Hi Tech Inc		
	L	WO-2015165067-A1	11-05-2015	Kimree Hi Tech Inc		
	M	WO-2016041114-A1	03-24-2016	Huizhou Kimree Technology Co., Ltd		
	N	WO-2016041140-A1	03-24-2016	Huizhou Kimree Technology Co.,ltd		
	O	WO-2016050247-A1	04-07-2016	Fertin Pharma As		
	P	WO-2016058189-A1	04-21-2016	Huizhou Kimree Technology Co., Ltd		
	Q	WO-2016065606-A1	05-06-2016	Huizhou Kimree Technology Co.,ltd		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO				Complete if Known	
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Sheet	4	of	10	Attorney Docket Number	052210-501C03US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	"A Randomised Placebo-Controlled Trial of a Nicotine Inhaler and Nicotine Patches for Smoking cessation," 5 pages, available at http://www.otago.ac.nz/wellington/otago047634.pdf.	
	B	"How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attibutable Disease," U.S. Department of Health and Human Services, 2010.	
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
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				Art Unit	1747
				Examiner Name	D. W. Mayes
Sheet	5	of	10	Attorney Docket Number	052210-501C03US

	S	Caldwell, B., et al., "A Systematic Review of Nicotine by Inhalation: Is There a Role for the Inhaled Route?," Nicotine & Tobacco Research, pp.1-13 (2012).	
	T	Callicutt, C.H., "The role of ammonia in the transfer of nicotine from tobacco to mainstream smoke," Regulatory Toxicology and Pharmacology, 46, 2006.	
	U	Caponnetto, Pasquale, et al. "EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study." PloS one 8.6 (2013): e66317.	
	V	Caponnetto, Pasquale, et al. "The emerging phenomenon of electronic cigarettes." Expert review of respiratory medicine 6.1 (2012): 63-74.	
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	X	Cig Buyer.com 2013 Inside E-Cigarette Liquids and Vapor	
	Y	Cisternino, S., et al., "Coexistence of Passive and Proton Anitporter-Mediated Processes in Nicotine Transport at the Mouse Blood-Brain Barrier," The AAPS Journal, Vol. 15, No. 2, April 2013.	
	Z	Dawkins, Lynne, et al. "The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition." Addictive behaviors 37.8 (2012): 970-973.	
	AA	Dawkins, Lynne, et al., "Acute electronic cigarette use: nicotine delivery and subjective effects in regular users," Psychopharmacology, 2013.	
	AB	Dawkins, Lynne, John Turner, and Eadaoin Crowe. "Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers." Psychopharmacology 227.3 (2013): 377-384.	
	AC	Definition of "aerosol", Merriam-Webster Dictionary, [online], no date, retrieved from the Internet, [retrieved 6/8/2017], <URL: https://www.merriam-webster.com/dictionary/aerosol>.	
	AD	Dezelic, M., et al., "Determination of structure of some salts of nicotine, pyridine and N-methylpyrrolidine on the basis of their infra-red spectra," Spectrochimica Acta, Vol. 23A, 1967.	
	AE	Dixon, M., "On the Transfer of Nicotine from Tobacco to the Smoker. A Brief Review of Ammonia and "pH" Factors," Contributions to Tobacco Research, Vol. 19, No. 2, July 2000.	
	AF	Dong, J.Z., et al., "A Simple Technique for Determining the pH of Whole Cigarette Smoke," Contributions to Tobacco Research, Vol. 19, No. 1, April 2000.	
	AG	Drummond, M. Bradley, et al., "Electronic cigarettes. Potential harms and benefits." Annals of the American Thoracic Society 11.2 (2014): 236-242.	
	AH	Effros, R., et al., "The In Vivo pH of the Extravascular Space of the Lung," The Journal of Clinical Investigation, Vol. 48, 1969.	
	AI	Eissenberg, Thomas. "Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration." *Tobacco control* 19.1 (2010): 87-88.	
	AJ	Etter, Jean-François, et al., "Analysis of refill liquids for electronic cigarettes." Addiction 108.9 (2013): 1671-1679.	
	AK	Etter, Jean-François. "Levels of saliva cotinine in electronic cigarette users." Addiction 109.5 (2014): 825-829.	
	AL	Farsalinos, Konstantinos E., et al. "Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers." *International journal of environmental research and public health* 11.4 (2014): 4356-4373.	

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/925,961
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				First Named Inventor	Adam Bowen
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				Examiner Name	D. W. Mayes
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	AM	Farsalinos, Konstantinos E., et al. "Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking." Substance abuse: research and treatment 7 (2013): SART-S12756.	
	AN	Farsalinos, Konstantinos E., et al. "Impact of flavour variability on electronic cigarette use experience: an internet survey." *International journal of environmental research and public health* 10.12 (2013): 7272-7282.	
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	AR	Gonda, I., et al. "Smoking cessation approach via deep lung delivery of 'clean'nicotine." *RDD Europe* (2009): 57-61.	
	AS	Goniewicz, Maciej L., et al., "Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications." Addiction 109.3 (2014): 500-507.	
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	AW	Hurt, R., et al., "Prying Open the Door to the Tobacco Industry's Secrets About Nicotine," The Journal of the American Medical Association, Vol. 280, 1998.	
	AX	Keithly, Lois., et al., "Industry research on the use and effects of levulinic acid: A case study in cigarette additives," Nicotine & Tobacco Research Volume 7, No. 5, 761-771, 2005.	
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	AZ	Lauterbach, J.H, "COMPARISON OF MAINSTREAM CIGARETTE SMOKE pH WITH MAINSTREAM E-CIGARETTE AEROSOL pH" Tob. Sci. Res. Conf., 2013, 67, abstr. 78. 2013.	
	BA	Lauterbach, J.H., "A Critical Assessment of Recent Work on the Application of Gas/Particle Partitioning Theories to Cigarette Smoke," Contributions to Tobacco Research, Vol. 19, No.2, July 2000.	
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Sheet	7	of	10	Attorney Docket Number	052210-501C03US

	BE	Lee, L.-Y., et al., "Airway irritation and cough evoked by inhaled cigarette smoke: Role of neuronal nicotinic acetylcholine receptors," Pulmonary Pharmacology & Therapeutics, Vol. 20, 2007.	
	BF	Leffingwell, J., et al., "Tobacco Flavoring for Smoking Products," R.J. Reynolds Tobacco Company, 1972.	
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	BI	Lux, J.E., et al., "Subjective Responses to Inhaled and Intravenous Injected Nicotine," American Society for Clinical Pharmacology and Therapeutics, 1988.	
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	BL	McQueen, Amy, et al., "Interviews with "vapers": implications for future research with electronic cigarettes." Nicotine & Tobacco Research 13.9 (2011): 860-867.	
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	BO	Oldendorf, W., et al., "Blood-brain barrier penetration abolished by N-methyl quaternization of nicotine," Proc. Natl. Acad. Sci, Vol. 90, pp. 307-311, 1993.	
	BP	Oldendorf, W., et al., "pH Dependence of Blood-Brain Barrier Permeability to Lactate and Nicotine," Stroke, Vol. 10, No. 5, 1979.	
	BQ	Omole, Olufemi Babatunde, et al., "Review of alternative practices to cigarette smoking and nicotine replacement therapy: how safe are they?." South African Family Practice 53.2 (2011): 154-160.	
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	BS	Pankow, et al., "Conversion of Nicotine in Tobacco Smoke to Its Volatile and Available Free-Base form Through the Action of Gaseous Ammonia," Eniron. Sci. Technol. 31 (8), 1997.	
	BT	Pankow, James F. "A consideration of the role of gas/particle partitioning in the deposition of nicotine and other tobacco smoke compounds in the respiratory tract." *Chemical research in toxicology* 14.11 (2001): 1465-1481.	
	BU	Perfetti, T., "Investigation of Nicotine Transfer to Mainstream Smoke I. Synthesis of Nicotine Salts," 1978.	
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	BW	Polosa, Riccardo, et al. "A fresh look at tobacco harm reduction: the case for the electronic cigarette." Harm reduction journal 10.1 (2013): 19.	

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	BX	Polosa, Riccardo, et al. "Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study." BMC public health 11.1 (2011): 786.	
	BY	Polosa, Riccardo, et al. "Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal." International journal of environmental research and public health 11.5 (2014): 4965-4977.	
	BZ	Polosa, Riccardo, et al. "Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study." Internal and emergency medicine 9.5 (2014): 537-546.	
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	CC	Provisional Application 61/856,286, filed July 19, 2013.	
	CD	Provisional Application 61/856,374, filed July 19, 2013.	
	CE	Provisional Application 61/891,626, filed on October 16, 2013.	
	CF	Provisional Application 61/969,650, filed March 24, 2014.	
	CG	Provisional Application 61/971,340, filed March 27, 2014.	
	CH	Riggs, et al., "The Thermal Stability of Nicotine Salts," R.J. Reynolds Tobacco Company, 2000.	
	CI	Robertson, C., et al., "In their own words: an epoch of deceit and deception," Chapter 5 (find out from which book)	
	CJ	Rose, J., "Nicotine and nonnicotine factors in cigarette addiction," Psychopharmacology, 184:274-285, 2006.	
	CK	Rose, J., "Pulmonary Delivery of Nicotine Pyruvate: Sensory and Pharmacokinetic Characteristics," Expermimental and Clinical Psychopharmacology, Vol. 18, No. 5, 2010.	
	CL	Sahu, S.K., et al., "Particle Size Distribution of Mainstream and Exhaled Cigarette Smoke and Predictive Deposition in Human Repiratory Tract," Aerosol and Air Quality Research, 13: 324-332, 2013.	
	CM	SCENIHR, "Addictiveness and Attractiveness of Tobacco Additives," Scientific Committee on Emerging and Newly Identified Health Risks, November 12, 2010.	
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	CP	SEEMAN, et al., "The form of nicotine in tobacco. Thermal transfer of nicotine and nicotine acid salts to nicotine in the gas phase," J Aric Food Chem, 47(12), pp/ 5133-5145. December 1999.	
	CQ	Seeman, J., "Possible Role of Ammonia on the Deposition, Retention, and Absorption of Nicotine in Humans while Smoking," Chemical Research in Toxicology, 20, 2007.	
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	CS	Seeman, J., et al., "On the Deposition of Volatiles and Semivolatiles from Cigarette Smoke Aerosols: Relative Rates of Transfer of Nicotine and Ammonia from Particles to the Gas Phase," Chemical Research in Toxicology, 17, 2004.	

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	CT	Seeman, J., et al., "The possible role of ammonia toxicity on the exposure, deposition, retention, and the bioavailability of nicotine during smoking," Food and Chemical Toxicology, 46, 2008.	
	CU	Sensabaugh, A.J., et al., "A New Technique for Determining the pH of Whole Tobacco Smoke," Tobacco Science.	
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	CW	Snowdon, Christopher. "Harm reduction and tobacco: a new opportunity or a step too far?." Drugs and Alcohol Today 13.2 (2013): 86-91.	
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	CY	Teague, "Implications and Activites Arising from Correlation of Smoke pH with Nicotine Impact, Other Smoke Qualities and Cigarette Sales," 1983.	
	CZ	Tomar, S., et al., "Review of the evidence that pH is a determinant of nicotine dosage from oral use of smokeless tobacco," Tobacco Control, 6:219-225, 1997.	
	DA	Torrie, B., "Nicotine inhaler gives instant 'hit'," 2 pages (2013), available at http://www.stuff.co.nz/national/health/8822875/Nicotine-inhaler-gives-instant-hit.	
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	DC	Trehy, Michael L., et al. "Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities." Journal of Liquid Chromatography & Related Technologies 34.14 (2011): 1442-1458.	
	DD	Uchiyama, Shigehisa, et al. "Determination of carbonyl compounds generated from the E-cigarette using coupled silica cartridges impregnated with hydroquinone and 2, 4-dinitrophenylhydrazine, followed by high-performance liquid chromatography." Analytical sciences 29.12 (2013): 1219-1222.	
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	DH	Weiss, G., "The Effect of pH on Nicotine-Induced Contracture and Ca45 Movements in Frog Sartorius Muscle," The Journal of Pharmacology and Experimental Therapeutics, Vol. 154, No.3, 1966.	
	DI	World Health Organization, "Health Effects of Interations Between Tobacco Use and Exposure to Other Agents," Environmental Health Criteria 211, 83 pages (1999), available at http://www.inchem.org/documents/ehc/ehc/ehc211.htm.	
	DJ	Wynn III, William P., et al. "The pharmacist "toolbox" for smoking cessation: a review of methods, medicines, and novel means to help patients along the path of smoking reduction to smoking cessation." Journal of pharmacy practice 25.6 (2012): 591-599.	

Used in Lieu of PTO/SB/08A/B
(Based on PTO 11-07 version)

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	DK	Zenzen, Volker, et al. "Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 2: Smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior." Regulatory Toxicology and Pharmacology 64.2 (2012): S11-S34.	
	DL	Zhang, Yaping, et al., "In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns." Nicotine & Tobacco Research 15.2 (2012): 501-508.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	32014024
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Robert E. Bolcome III/shae jackson
Filer Authorized By:	Robert E. Bolcome III
Attorney Docket Number:	52210-501C03US / 713.302
Receipt Date:	12-MAR-2018
Filing Date:	28-OCT-2015
Time Stamp:	16:22:04
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Tomar-Review_of_the_evidence_that_pH_is_a_determinant.pdf	1024524 aef068e153c6693a3cb3337177cd1724d7796b73	no	8

Warnings:

Information:					
2	Non Patent Literature	Torrie-Nicotine_inhaler.pdf	146913 c7b60f7036fc4aaf1436b6559dd8a036bb57b8aa	no	2
Warnings:					
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3	Non Patent Literature	Travell_Influence_of_the_hydrogen_ion_concentration.pdf	1290540 5777e6d39b97ee2a10b9a2a18428a160914a4f3d	no	13
Warnings:					
Information:					
4	Non Patent Literature	Trehy-Analysis_of_Electronic_cigarette_cartridges.pdf	597531 aa8b2cd22b579582c33d165a24abeaf602e78d58	no	17
Warnings:					
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5	Non Patent Literature	Uchiyama-Determination_of_Carbonyl_Compounds_Generated_from_the_E-cigarette.pdf	1830223 6a24db7f094a97e56093b34183bea7665c93c5eb	no	4
Warnings:					
Information:					
6	Non Patent Literature	Vansickel-Electronic_Cigarettes_Effective_Nicotine_Delivery_After_Acute_Administration.pdf	432947 ca552f414096d842ad8908d85298aa6fe7da54fb	no	4
Warnings:					
Information:					
7	Non Patent Literature	Wayne_Brand_differences_of_free-base_nicotine_delivery_in_cigarette_smoke_2006.pdf	374730 f41f95c43cd5ef0d064005ee796611b52d23c1e6	no	11
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8	Non Patent Literature	Weiss_Effect_of_pH_on_nicotine-induced_contracture_and.pdf	1129401 3b678fa05854720ef5f64690cd5044811968a2a7	no	8
Warnings:					
Information:					

9	Non Patent Literature	WHO-Health_effects_Of.pdf	564244 3c8ddc3f9fe9e25345164174ef1b88ee3d1e1e04	no	12
Warnings:					
Information:					
10	Non Patent Literature	Wynn-The_pharmacist_toolbox.pdf	112048 4bad5725c57714e76e2de7ec01ce98dfec43be94	no	9
Warnings:					
Information:					
11	Non Patent Literature	Zenzen-Reduced_exposure_evaluation_of_an_Electrically_Heated_cigarette_Part2.pdf	1107929 e4132b94a669c11c1098a84c5b3c1d59ff62e53f	no	24
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Information:					
13	Non Patent Literature	Vansickel-A_clinical_laboratory_model_for_evaluating_the_acute.pdf	354778 66a0a10ec9dd1a81ea53522dbc8af7dfdec82141	no	10
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Information:					
14		052210-501C03US-Information_disclosure_statement_and_SB08.pdf	339618 6f80661a106e8428ad1057d4b7ba4522841e7546	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	12

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 052210-501C03US/713.302
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: D. W. Mayes

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

FILED VIA EFS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114 (37 C.F.R. § 1.97(b)(4)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with

37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-0311, under Order No. 052210-501C03US/713.302 from which the undersigned is authorized to draw.

Dated: March 12, 2018

Respectfully submitted,

Electronic signature: /Robert E. Bolcome III/
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Electronic Acknowledgement Receipt

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First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	EP2110033A1.pdf	605487 5ec40ca5d5dbdac08eaaab29d74331036cd6c62b	no	11
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2	Foreign Reference	WO0028842A1.pdf	1450321 3baabaf3bedec5f6eca889e827a68ff299b3d81a	no	29
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3	Foreign Reference	WO03056948A1.pdf	614327 b482e13e58d81f6c35ee390d2e20b162814ae950	no	16
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4	Foreign Reference	WO2006004646A1.pdf	2177206 fc6dd4cc8b5104d16113015e2535cfac260d4cba	no	44
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5	Foreign Reference	WO2012120487A2.pdf	2840080 0f50a260b95bedc234fdb93f99478e7a4b3a7463	no	71
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6	Foreign Reference	WO2013044537A1.pdf	901290 f505b4188beeda87da1a5646edf786ef37fce190	no	26
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7	Foreign Reference	WO2015042412A1.pdf	7162264 4e9d619d2b4accbdd8b42cb0325043722325e805	no	129
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14	Foreign Reference	WO2016041140A1.pdf	1438684 c7c39f950c39a3c374a1f7894e58062006a0be96	no	29
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18	Non Patent Literature	61826318-App.pdf	571486 af37a0ade1b9594c0face729bb6bf8e76481052b	no	14
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22	Non Patent Literature	61969650-App.pdf	1857545 0b26ef3f4c7bb37ba1d2005edea6e93c735450d9	no	43
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24	Non Patent Literature	A_Randomized_Placebo-Controlled_trial.pdf	231478 de1e183118bfe0d7edf52a30c8aef67c4ef28890	no	5
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25	Non Patent Literature	Adam-Investigation_of_tobacco_pyrolysis_gases_and_puff-by-puff.pdf	4986226 cf7fb41989d047a0b082da766a7705961f8167f6	no	24
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26	Non Patent Literature	aerosol.pdf	35199 9484b6a42acae86ca8d0c57885b24eff117a7513	no	1
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27	Non Patent Literature	Baker_Effect_of_tobacco_ingredients_on_smoke_chemistry_Part_II_Casing_ingredients_2004.pdf	602284 20d9f1c31b0fde606efe1fab06380650bfef1bba	no	14
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28	Non Patent Literature	Baker_Overview_of_effects_of_tobacco_ingredients_on_smoke_chemistry_and_toxicity_2004.pdf	1253167 7654c457ef66b4d86a24c0d0f4083a2906384a09	no	31
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29	Non Patent Literature	Bao-An_improved_headspace_solid-phase.pdf	359318 0c4930e60b9d755dfe39ec20b7f87021d50b6d6b	no	6
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31	Non Patent Literature	Bates_Tobacco_Additives__cigarette_engineering_and_nicotine_addiction_London__ASH_UK_Report_1999.pdf	1345417 8f3daa592827d71066db2ea41ad4f42855ed597c	no	36
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32	Non Patent Literature	Bertholon-Comparison_of_electronic_cigarette.pdf	580523 96159ffd28bf0a1ac744044583b7291ac7435e0d	no	6
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33	Non Patent Literature	Bertholon-Electronic_Cigarettes_a_short_review.pdf	232262 d0aa04637b9165ab273b6b4f95a3221ff97a4bac	no	6
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34	Non Patent Literature	Brown_Caffeine_and_Cigarette_Smoking_1988.pdf	720468 168dd1152fcc051f770d536508753f76e2730f5f	no	6
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35	Non Patent Literature	Brown-Electronic_ciagrettes_product_characterisation.pdf	2387747 96972bf9cdddc6a989e45e1a8e890e1c175f70a9	no	8
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36	Non Patent Literature	Bullen-Effect_of_electronic_nicotine_delivery.pdf	186461 c3fdfeec540567155d511599cc5208af4f1db604	no	6
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38	Non Patent Literature	Burch-Effect_of_pH_on_Nicotine.pdf	436153 eefd5c3cd138edcc609df18255c6ffa4e3fd9972	no	8
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39	Non Patent Literature	Cahn-Electronic_cigarettes_as_a_harm_reduction_strategy_for_tobacco_control.pdf	248040 be482dffa7ef5a38dedd669c5fd1cd950cb64a62	no	16
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40	Non Patent Literature	Caldwell-A_systematic_review_of_nicotine.pdf	145842 521b5e4e53d7f86e93bd46301b126b78c8031889	no	13
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42	Non Patent Literature	Caponnetto-EffiCiency_and_safety_of_an_eLectronic.pdf	867735 57c519b008d583b150ba1dfe98488d5f1364b6e4	no	12
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43	Non Patent Literature	Caponnetto-The_Emerging_phenomenon_of_electronic_cigarettes.pdf	10697326 6b8f388789b24c8b9d5b1c186e3e852d769822bd	no	13
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44	Non Patent Literature	CDC_How_Tobacco_Smoke_Causes_Disease_2010.pdf	12140866 2a61cf2df74cf306e418bdf42537a23db7a0fd7d	no	727
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45	Non Patent Literature	Cheng-Chemical_evaluation_of_electronic_cigarettes.pdf	314154 6be2daa24df6212b47517eef3d2c653a7832a115	no	8
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46	Non Patent Literature	Cisternino_Coexistence_of_Passive_and_Proton.pdf	271183 4c267b0cae3caafeb7c53409c59a82a3f993cbf6	no	9
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47	Non Patent Literature	Cigbuyer.pdf	260472 7372e4528a490da7832482b4250c8d380f16e4b8	no	7
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48	Non Patent Literature	Dawkins-Acute_electronic_cigarette_use.pdf	240578 b49792acafbc2bd1cea03205ffb06ff4cd03acf5	no	7
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49	Non Patent Literature	Dezelic_Determination_of_structure_of_some_salts.pdf	409538 88379ad472f4fe088ba0932832c4097bd9b29275	no	5
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50	Non Patent Literature	Dixon_2000_Beitr_Ammonia_review.pdf	179397 0d984105663a58c7e44e456478ba2c1110ccaa04	no	11
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51	Non Patent Literature	Dong_A_simple_technique_for_determining_the_pH_of_whole_cigarette_smoke_2000.pdf	263529 a2f6c9a146c87485fe3c642dabc447c989e8e2db	no	16
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52	Non Patent Literature	Drummond-Electronic_cigarettes_potential_harms_and_benefits.pdf	297525 f9480ed7ccb4f53ccdad56827b3d0852e754bbc4	no	7
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53	Non Patent Literature	Effros_TheIn_Vivo_pH_of_the_Extravascular_Space_of_the_Lung_1969.pdf	2337735 39b120a2e0a3add8901cc6d2d97b99e10355377a	no	14
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54	Non Patent Literature	Eissenberg-Electronic_Nictoine_Delivery_Devices.pdf	189549 0f235740eae0fcdbb611dcf456abb5964863b72e	no	3
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55	Non Patent Literature	Etter-Analysis_of_refill_liquids.pdf	326369 cad7f3791b01d69c29d3df4b49708f5ee78f55c6	no	9
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56	Non Patent Literature	Etter-Levels_of_salvia_cotinine.pdf	99340 b607369bdb74b44d1c69125c278abc5c195e0de6	no	5
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Information:					
57	Non Patent Literature	Farsalinos-Characteristics_perceived_side_effects.pdf	301375 d5fb2e2c0b34225a78b991fb926398acac267db6	no	18
Warnings:					
Information:					

58	Non Patent Literature	Farsalinos-Evaluating_Nicotine_Levels_Selection_and_.pdf	3204200 f6067c0237cd333dfc8789c0299a0217190c3a66	no	8
Warnings:					
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59	Non Patent Literature	Dawkins-Nicotine_derived_from_the_electronic_cigarette_improves.pdf	188601 968bf06a667319d17a5ceda856483c909f86f86b	no	8
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60	Non Patent Literature	Dawkins-The_electronic-cigarette_effects_on_desire_to_smoke.pdf	235403 442bbc6ec5d2aed6e3619c93da346f3c135271a9	no	4
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Electronic Acknowledgement Receipt

EFS ID:	32013972
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Robert E. Bolcome III/shae jackson
Filer Authorized By:	Robert E. Bolcome III
Attorney Docket Number:	52210-501C03US / 713.302
Receipt Date:	12-MAR-2018
Filing Date:	28-OCT-2015
Time Stamp:	16:21:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Farsalinos-Impact_of_flavour_variability.pdf	244541 ed193882ad5f9cf26f20f9b7d0f74a9cd07ef131	no	11

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2	Non Patent Literature	Farsalinos-Nicotine_absorption_from_electronic_cigarette_use_comparison_between_first.pdf	796166 4fc52deecc1ff7dd56e35f06c232660020c51b84	no	7
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3	Non Patent Literature	Farsalinos-Safety_Evaluation_and_Risk_Assessment.pdf	990802 655132c0ebda8efb6609cd8a1fc0a270dc30619a	no	20
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4	Non Patent Literature	Fournier_2001_Heterocycles.pdf	921396 32169c0f3649590a5d4c526587d10283c30bf6d4	no	16
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5	Non Patent Literature	Gonda-Smoking_cessation_approach_via_deep.pdf	471110 1810cb4e8ca2e632acd4d034098c9dafe00445f2	no	6
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6	Non Patent Literature	Goniewicz-Nicotine_content_of_electronic_cigarettes_its_release.pdf	523750 638d921d1b6692d037f60968e6ca45bddae65c35	no	8
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7	Non Patent Literature	Goniewicz-Nicotine_levels_in_electronic_cigarettes.pdf	992760 5d2aa219b524ba1e492651aa0480d62631defe87	no	9
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8	Non Patent Literature	Grotenhermen-Developing_Science-based.pdf	863170 9d7ce03431a5ef8416de7cf50e21f78fe3356138	no	49
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9	Non Patent Literature	Harris-Warning_cigarettes.pdf	1139835 5a3d0d63506da4a8c39f302bc228163608fa0942	no	4
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10	Non Patent Literature	Heyder_Alveolar_deposition_of_inhaled_particles_in_humans_2010.pdf	238825 dba0e20b925a7c018c6f50f0db7e135774758094	no	4
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11	Non Patent Literature	Keithly-Industry_research_on_the_use_and_effects.pdf	399501 46a2aaea1e957ef01478e64629313fc9e8790248	no	11
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12	Non Patent Literature	Lauterbach_A_critical_assessment_of_recent_work_on_the_application_of_.pdf	331532 074d800d71c6f0b77d629e220757ed3a81b74658	no	19
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13	Non Patent Literature	Lauterbach_Comment_on_gas_particle_partitioning_of_two_acid.pdf	635850 c4ca3ce2a67977552a4ccca7dbcd767a97a9c527	no	2
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14	Non Patent Literature	Lauterbach_Comparison_of_mainstream_cigarette_smoke_pH_with.pdf	1750702 0b1b02175d3bf29ceba88ead067a356d4ed73b07	no	23
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15	Non Patent Literature	Lauterbach_GC-MS_analysis_of_e-liquids_taken_from_e-cigarettes.pdf	927809 8cdd2c27ac49f5518e5085847e70fa1488a85e01	no	17
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16	Non Patent Literature	Lee_Airway_irritation_and_cough_evoked_by_inhaled_cigarette_smoke_2007.pdf	340590 6b9419378880c4e73cbc8a4fd1ef151d64f7d971	no	10
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17	Non Patent Literature	Leffingwell_Tobacco_Flavoring_Book.pdf	4218129 42cb6f2b46a89b2ace52be7eea0f3d997e397bb9	no	74
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18	Non Patent Literature	Lim-Inhallation_of_e-cigarette_cartridge_solution.pdf	275093 627b1e6eed48823c33b8a42640d99aa687954eb5	no	6
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19	Non Patent Literature	Lippiello_Enhancement_of_nicotine_binding_to_nicotinic_receptors.pdf	1294982 a0e23e44ecc75718c7e0a2d8f3b4e00ed17e01f7	no	27
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20	Non Patent Literature	Lux_Generation_of_a_Submicrometre_nicotine_aerosol_for_inhalation_1988.pdf	1512507 afe5d2e7a267b5d0807380edda91d7d948acab75	no	3
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21	Non Patent Literature	Lux_Subjective_responses_to_inhaled_and_intravenous_injected_nicotine_1988.pdf	113284 bf8388773446387f8113b1ef1a1b1a50f60e9c35	no	1

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22	Non Patent Literature	MacDougall_Selective_Cardiovascular_Effects_of_Stress_and_Cigarette_Smoking_1983.pdf	1213982 b802cb5f61d54f102bc0a7971ffbdf283a7b7a8a	no	10
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23	Non Patent Literature	McQueen-Interviews_with_vapers_implications_for_future_research_with_electronic_cigarettes.pdf	905262 6e0cb9f222e29e157c9eaed6ed59030f580303cb	no	8
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24	Non Patent Literature	McRobbie-Electronic_cigarettes_for_smoking_cessation.pdf	3689327 4f0984bea579d1798c7fa677fcd5bfca4ae267a0	no	61
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25	Non Patent Literature	Oldendorf_Blood-brain_barrier_penetration_abolished_by_N-methyl_quaternization_of_nicotine_1992.pdf	1003033 d58f434e97ee52201cdd4f8e5efeec021f3caf9d	no	5
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26	Non Patent Literature	Olendorf_pH_Dependence_of_Blood-Brain_Barrier_Permeability_to_Lactate_and_Nicotine_1979.pdf	692587 62c1917bfe4095745340fed89526aca46b27577d	no	6
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27	Non Patent Literature	Omole-Review_of_alternative_practives_to_cigarette_smoking.pdf	3310761 9452a517bdb2b04b77f0a83093e39c4f5b761330	no	8
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28	Non Patent Literature	Pankow_Conversion_of_nicotine_in_tobacco_smoke_to_its_volatile.pdf	709249 114ada892733cbd839eacd01dd8301fce4b5a65e	no	17
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31	Non Patent Literature	Perfetti_Investigation_of_Nicotine_Transfer_ot_Mainstream_Smoke.pdf	849636 13418271de20656d0cd153edde17e2fa6672f277	no	17
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32	Non Patent Literature	Perfetti_Transfer_of_nicotine_from_nicotine_salts_to_mainstream_smoke_2000.pdf	1978334 f5423dbb04a885e38821ee6883b8fcd608ad92c9	no	36
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33	Non Patent Literature	Perfetti-Structural_study_of_nicotine_salts.pdf	651919 62811edff1512345cf31a1ed66260418b6191e84	no	12
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34	Non Patent Literature	Polosa_Effect_of_an_electronic_nicotine_delivery_device_e-Cigarette.pdf	816195 229944000be8d28eb53981d214f2bc83ab6d1b42	no	12
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36	Non Patent Literature	Polosa_Effectiveness_and_tolerability_of_electronic_cigarette_in_real-life_2013.pdf	327479 aae9c944b15dabc6ad750dbfe99da2ce51fed850	no	10
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37	Non Patent Literature	Polosa-A_fresh_look_at_tobacco_harm_reduction_the_case_for_the_electronic_cigarette.pdf	585320 9efbe81b7d496b9779a5ad4333eaaced0ccdbfaa	no	11
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38	Non Patent Literature	Riggs-Thermal_stability_of_nicotine_salts.pdf	681003 824fa9887bdee46c65a7c8f9b7b9afdca8e1a385	no	14
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39	Non Patent Literature	RJ_Reynolds_Nicotine_salts_1990.pdf	89813 86a506e8f589d93c6e422192720e6a4f66684597	no	6
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40	Non Patent Literature	Robertson__Hurt_In_their_own_words__an_epoch_of_deceit_and_deception_2010.pdf	2675792 4d2f4d13f1217d33372abb2aa7a41e0c91d548bb	no	35
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41	Non Patent Literature	Rose_Nicotine_and_nonnicotine_factors_in_cigarette_addiction_2006.pdf	210789 081e8643d881d79303b1448aab92957703abb085	no	12
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43	Non Patent Literature	Sahu_Particle_Size_Distribution_of_Mainstream_and_Exhaled_Cigarette.pdf	392563 fb50da4d1e32b3eebe126069ca31c4c02c97d952	no	9
Warnings:					
Information:					
44	Non Patent Literature	SCENHIR_Addictiveness_and_Attractiveness_of_Tobacco_Additives_2010.pdf	1691604 a23632e11849d93ea8a5c36297e1e32685a001d3	no	119
Warnings:					
Information:					
45	Non Patent Literature	Schripp-Does_e-cigarette_consumption_cause_passive_vaping.pdf	1149202 397ae39ba82414dc643ce54465759cc36c22a7fd	no	7
Warnings:					
Information:					
46	Non Patent Literature	Schroeder-Electornic_cigarettes_and_nicotine_clinical_pharmacology.pdf	287471 8dce888eceece9218bc350fa056675aedb032387	no	7
Warnings:					
Information:					
47	Non Patent Literature	Seeman-on_the_deposition.pdf	289535 96d899f16171194ce946f7027b80b8a6f48ab9c0	no	18
Warnings:					
Information:					
48	Non Patent Literature	Seeman-Possible_role_of_ammonia.pdf	751357 59d6b677fa72ac4cd778f0fff051501e90084949	no	18
Warnings:					
Information:					
49	Non Patent Literature	Seeman-Role_of_ammonia_on_toxiticy.pdf	903740 d135bd8a22616bb0e273b29fa22ae3858d555980	no	19
Warnings:					
Information:					

50	Non Patent Literature	Seeman-the_form_of_nicotine_in_tobacco.pdf	1637221 5315fcdfa033120faa58e1794bc204606b88fff9	no	13
Warnings:					
Information:					
51	Non Patent Literature	Seeman-using_basic_principles.pdf	157957 e7b5ca3b8cf0b6a17e2ed3521a868a1d94e23631	no	7
Warnings:					
Information:					
52	Non Patent Literature	Sensabaugh_A_new_technique_for_determining_the_pH_of_whole_tobacco_smoke_1995.pdf	406787 d62c8fba36b7b78f38ebae136833bd2d4d3d0de5	no	6
Warnings:					
Information:					
53	Non Patent Literature	Shahab-Novel_Delivery_Systems_for_Nicotine_Replacement_Therapy.pdf	417551 04ecde6dc1d0cf2818a452079cbba14e56e4e4ae	no	13
Warnings:					
Information:					
54	Non Patent Literature	Snowdon-Harm_reduction_and_tobacco.pdf	115593 c10a64daff4f5ae6e6c4439a9fb74cc3b368b6bd	no	6
Warnings:					
Information:					
55	Non Patent Literature	Stevenson-The_secret_and_soul_of_marlboro.pdf	600269 124800221ed49a531b3b17aeaad5dd838af6db08	no	11
Warnings:					
Information:					
56	Non Patent Literature	Teague_Implications_and_activities_arising_from_correlation.pdf	830094 076faebca4bfb2a594a962ab07f69203a35b0f19	no	22
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					

57	Non Patent Literature	Hurt_Prying_open_the_door_to_the_tobacco_industrys_secrets_about_nicotine_1998.pdf	1321457 2c27452bddadc20023d29983277d0ab53a17997f	no	9
Warnings:					
Information:					
58	Non Patent Literature	kosmider-Electronic-cigarette-a_safe_substitue_english.pdf	11546205 560011ad75573dd12747fc41b08a18674839d8c4	no	45
Warnings:					
Information:					
59	Non Patent Literature	Lauterbach-Free_base_nicotine_in_tabacco_products.pdf	604088 50570a38f1d17e6d1a0613f9775c84eb63f28215	no	19
Warnings:					
Information:					
60	Non Patent Literature	Prignot-Electronic_Nicotine_delivery_systems_English.pdf	2423312 63e94517eb8bb9ce827ade78d095d8d57abfbb99	no	20
Warnings:					
Information:					
		Total Files Size (in bytes):	68768302		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: R46C.REQ
Document Description: Request under 37 CFR 1.46(c) to correct, update or change the applicant.

PTO/AIA/41 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST TO CORRECT OR UPDATE THE NAME OF THE APPLICANT UNDER 37 CFR 1.46(c)(1), OR CHANGE THE APPLICANT UNDER 37 CFR 1.46(c)(2) (FOR USE ONLY IN APPLICATIONS FILED ON OR AFTER SEPTEMBER 16, 2012)		
	Application Number	14/925,961
	Filing Date	October 28, 2015
	First Named Inventor	Adam Bowen
	Art Unit	1747
	Examiner Name	D. W. Mayes
	Practitioner Docket Number	052210-501C03US

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby **requests that the name of the applicant be corrected or updated under 37 CFR 1.46(c)(1), or that the applicant be changed under 37 CFR 1.46(c)(2),** in the above-identified application. **Requests under 37 CFR 1.46(c)(1) or (c)(2) cannot be submitted after payment of the issue fee or if the application has been patented.**

Please check the applicable box(es) below.

[x] 1.This request is to **correct or update the name of the applicant** (**under 37 CFR 1.46(c)(1)**) and includes:

[x] An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). A Corrected Web-based ADS may be used.

Note: Requests under 37 CFR 1.46(c)(1) may be filed to correct typographical errors in the name of the § 1.46 applicant, or for updating the name of the § 1.46 applicant (*i.e.,* where there is no change in the applicant itself but just in the applicant's name). See the Manual of Patent Examining Procedure (MPEP) section 605.01.

[ ] 2. This request is to **change the applicant** (**under 37 CFR 1.46(c)(2)**) and includes:

[ ] An application data sheet (ADS) in accordance with 37 CFR 1.76(c) that identifies the changes with proper markings (underlining for insertions and strikethrough for deletions). A Corrected Web-based ADS may be used.

[ ] A Statement Under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent). See MPEP 325.

I am the

[ ] applicant* [x] attorney or agent of record Registration number 56,239 [ ] attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Erin Weinlick/

Typed or printed name Erin Weinlick

Date April 25, 2018

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

[ ] ** Total of 1 forms are submitted.

77256714v.1

Corrected Application Data Sheet

Applicant Information

Applicant Number::	1
Applicant Type::	Assignee
Organization Name::	~~PAX Labs, Inc~~ JUUL Labs, Inc.
Street of mailing address::	660 Alabama Street, Second Floor
City of mailing address::	San Francisco
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94110

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Erin Weinlick/	Date (YYYY-MM-DD)	2018-04-25
Name	Erin Weinlick	Registration Number	56,239

77256612v.1

Electronic Acknowledgement Receipt

EFS ID:	32444173
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Erin E. Weinlick/Emily Rogers
Filer Authorized By:	Erin E. Weinlick
Attorney Docket Number:	52210-501C03US / 713.302
Receipt Date:	25-APR-2018
Filing Date:	28-OCT-2015
Time Stamp:	18:01:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	Request_Change_Applicant.pdf	210141 954cd4b139ff6bd344c3db688a2d59d99c089b71	no	1
Warnings:					

Information:					
2	Application Data Sheet	Corrected_ADS.pdf	92467 78ddccf8a6e688aebcb3ea3b36c5c351fc39d1d4	no	1
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
			Total Files Size (in bytes):	302608	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/925,961	10/28/2015	1747	2260	52210-501C03US / 713.302	23	3

CONFIRMATION NO. 1528

CORRECTED FILING RECEIPT

148514
Mintz/JUUL/PAX
One Financial Center
Boston, MA 02111



Date Mailed: 04/30/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Adam BOWEN, San Francisco, CA;
Chenyue XING, San Francisco, CA;

Applicant(s)

JUUL Labs, Inc., San Francisco, CA;

Assignment For Published Patent Application

PAX Labs, Inc., San Francisco, CA

Power of Attorney: The patent practitioners associated with Customer Number 64046

Domestic Priority data as claimed by applicant

This application is a CON of 14/271,071 05/06/2014 ABN
which claims benefit of 61/820,128 05/06/2013
and claims benefit of 61/912,507 12/05/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/09/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/925,961**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

Preliminary Class

131

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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Used in Lieu of PTO/SB/08A/B
(Based on PTO 11-07 version)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/925,961
				Filing Date	October 28, 2015
				First Named Inventor	Adam Bowen
				Art Unit	1747
(Use as many sheets as necessary)				Examiner Name	D. W. Mayes
Sheet	1	of	1	Attorney Docket Number	052210-501C03US/713.302

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A	US-20020043554-A1	04-18-2002	White et al.	
	B	US-20060196518-A1	09-07-2006	Hon	
	C	US-20120261286-A1	10-18-2012	Holloway et al.	
	D	US-20120273589-A1	11-01-2012	Hon	
	E	US-20130276802-A1	10-24-2013	Scatterday	
	F	US-20130284190-A1	10-31-2013	Scatterday et al.	
	G	US-20130284191-A1	10-31-2013	Scatterday et al.	
	H	US-20130313139-A1	11-28-2013	Scatterday et al.	
	I	US-20130319440-A1	12-05-2013	Capuano	
	J	US-20140209105-A1	07-31-2014	Sears et al.	
	K	US-7,374,048	05-20-2008	Mazurek	
	L	US-7,766,013	08-03-2010	Wensley et al.	
	M	US-8,464,867	06-18-2013	Holloway et al.	
	N	US-8,596,460	12-03-2013	Scatterday	
	O	US-8,794,245	08-05-2014	Scatterday	
	P	US-8,794,434	08-05-2014	Scatterday et al.	
	Q	US-8,905,040	12-09-2014	Scatterday et al.	
	R	US-8,931,492	01-13-2015	Scatterday	
	S	US-9,319,865	04-19-2016	Van Phan et al.	
	T	US-9,420,829	08-23-2016	Thorens et al.	
	U	US-9,717,279	08-01-2017	Hon	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	33593490
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Robert E. Bolcome III/shae jackson
Filer Authorized By:	Robert E. Bolcome III
Attorney Docket Number:	52210-501C03US / 713.302
Receipt Date:	30-AUG-2018
Filing Date:	28-OCT-2015
Time Stamp:	17:49:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		052210-501C03US-Information_Disclosure_Statement_SB08.pdf	250304 46698e0d6d3a4bc63f7b74b7d5989f053fe77a09	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	3
Warnings:			
Information:			
	Total Files Size (in bytes):	250304	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 052210-501C03US/713.302
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: D. W. Mayes

INFORMATION DISCLOSURE STATEMENT (IDS)

FILED VIA EFS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114 (37 C.F.R. § 1.97(b)(4)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted.

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be

an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this paper. However, if a fee is due, please charge our Deposit Account No. 50-0311, under Order No. 052210-501C03US/713.302 from which the undersigned is authorized to draw.

Dated: August 30, 2018

Respectfully submitted,

Electronic signature: /Robert E. Bolcome III/
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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	52210-501C03US / 713.302	1528

148514 7590 09/28/2018

Mintz/JUUL/PAX
One Financial Center
Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
09/28/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN et al.	
	Examiner DIONNE W MAYES	Art Unit 1747	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/4/2017.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 26-42 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 26-42 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 4, 2017 has been entered.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

6. Claims 26-42 are rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638) in view of Lindell et al (US. Pat. App. Pub. 2007/0163610).

Regarding independent claim 26, and dependent claim 27, Sebastian et al discloses an electronic smoking article (corresponding to the claimed "an electronic cigarette cartridge") that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which can contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed "An electronic cigarette cartridge comprising: a nicotine liquid formulation, the nicotine liquid formulation comprising nicotine and…acid in a liquid carrier").

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor. The nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1) (see para. [0059]).

The aerosol precursor composition may include glycerol and/or propylene glycol. Further, Sebastian et al discloses that, as a non-limiting example, an aerosol precursor composition may include nicotine in an amount of about 0.1-5.0% (para. [0061]). This would motivate one of ordinary skill to undergo routine experimentation to find the optimal amount of nicotine to add to the precursor composition and, in doing so, selected

the high end of this range, i.e. 3-5%, after determining that such nicotine concentration provided for superior flavor, sensation and organoleptic properties for the user (Note: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (corresponding to the claimed "(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w); (b) the liquid carrier comprises glycerol and propylene glycol; and (c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1"; the "wherein the nicotine concentration is about 4% (w/w)" recitation of claim 27).

As stated above, Sebastian et al teaches that organic acids can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference teaches that benzoic acid can be used, in addition to a myriad of other organic acids (like pyruvic), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Hence, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid,

as an organic acid to combine with the nicotine in the liquid formulation of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for… administration to a user in liquid form (corresponding to the claimed “nicotine liquid formulation comprising nicotine and benzoic acid”).

Regarding claim 28, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed “wherein the nicotine liquid formulation further comprises a flavorant”).

Regarding claim 29, as evident from Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “which is configured to serve as a mouthpiece and a reservoir that holds the nicotine formulation”).

Regarding claims 30, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already

been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed “wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid”).

Regarding claim 31, the heating element (50 can be powered by an electrical power source, such as a battery (40)(see para. [0078] and Fig. 1)(corresponding to the claimed “the electronic cigarette cartridge of claim 26; and a battery”).

Regarding claim independent claim 32, and dependent claim 33, Sebastian et al discloses an electronic smoking article that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which can contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed “A method of providing nicotine to a user, the method comprising: (i) heating a nicotine liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine comprises nicotine and…acid in a liquid carrier”).

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that

the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor. The nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1) (see para. [0059]).

The aerosol precursor composition may include glycerol and/or propylene glycol. Further, Sebastian et al discloses that, as a non-limiting example, an aerosol precursor composition may include nicotine in an amount of about 0.1-5.0% (para. [0061]). This would motivate one of ordinary skill to undergo routine experimentation to find the optimal amount of nicotine to add to the precursor composition and, in doing so, selected the high end of this range, i.e. 3-5%, after determining that such nicotine concentration provided for superior flavor, sensation and organoleptic properties for the user (Note: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (corresponding to the claimed "(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w); (b) the liquid carrier comprises glycerol and propylene glycol; and (c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1, and (ii) inhalation of the aerosol by the user").

As stated above, Sebastian et al teaches that organic acids can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference teaches that benzoic acid can be used, in addition to a myriad of other organic acids (like pyruvic), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Hence, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the liquid formulation of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for… administration to a user in liquid form (corresponding to the claimed "nicotine liquid formulation comprising nicotine and benzoic acid"; the "wherein the nicotine concentration is about 4% (w/w)" recitation of claim 33).

Regarding claim 34, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed "wherein the nicotine liquid formulation further comprises a flavorant").

Regarding claim 35, as evident from Fig. 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine liquid formulation”).

Regarding claims 36, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed “wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid”).

Regarding independent claim 37, Sebastian et al discloses an electronic smoking article (corresponding to the claimed “an electronic cigarette cartridge”) that provides for delivery of aerosolized components of

an aerosol precursor liquid composition, which can contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed “An electronic cigarette cartridge comprising: a nicotine liquid formulation, the nicotine liquid formulation comprising nicotine and…acid in a liquid carrier”).

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor. The nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1) (see para. [0059]).

The aerosol precursor composition may include glycerol and/or propylene glycol. Further, Sebastian et al discloses that, as a non-limiting example, an aerosol precursor composition may include nicotine in an amount of about 0.1-5.0% (para. [0061]). This would motivate one of ordinary skill to undergo routine experimentation to find the optimal amount of nicotine to add to the precursor composition and, in doing so, selected the high end of this range, i.e. 3-5%, after determining that such nicotine concentration provided for superior flavor, sensation and organoleptic properties for the user (Note: “[W]here the general conditions of a claim

are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (corresponding to the claimed "(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w); (b) the liquid carrier comprises glycerol and propylene glycol; and (c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1").

Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed "wherein the nicotine liquid formulation further comprises a flavorant").

As evident from Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed "which is configured to serve as a mouthpiece and a reservoir that holds the nicotine formulation").

As stated above, Sebastian et al teaches that organic acids can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention

"benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference teaches that benzoic acid can be used, in addition to a myriad of other organic acids (like pyruvic), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Hence, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the liquid formulation of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for… administration to a user in liquid form (corresponding to the claimed "nicotine liquid formulation comprising nicotine and benzoic acid").

Regarding claim independent claim 38, and dependent claim 39, Sebastian et al discloses an electronic smoking article that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which can contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed "A method of vaporizing a nicotine liquid formulation comprising heating the nicotine liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine liquid formulation comprises nicotine and…acid in a liquid carrier").

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor. The nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1) (see para. [0059]).

The aerosol precursor composition may include glycerol and/or propylene glycol. Further, Sebastian et al discloses that, as a non-limiting example, an aerosol precursor composition may include nicotine in an amount of about 0.1-5.0% (para. [0061]). This would motivate one of ordinary skill to undergo routine experimentation to find the optimal amount of nicotine to add to the precursor composition and, in doing so, selected the high end of this range, i.e. 3-5%, after determining that such nicotine concentration provided for superior flavor, sensation and organoleptic properties for the user (Note: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (corresponding to the claimed "(a) the nicotine concentration in the nicotine liquid formulation is from about 4% (w/w) to about 12% (w/w); (b) the liquid carrier comprises glycerol and

propylene glycol; and (c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1, and (ii) inhalation of the aerosol by the user").

As stated above, Sebastian et al teaches that organic acids can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference teaches that benzoic acid can be used, in addition to a myriad of other organic acids (like pyruvic), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Hence, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the liquid formulation of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for… administration to a user in liquid form (corresponding to the claimed "nicotine liquid formulation comprising nicotine and benzoic acid"; the "wherein the nicotine concentration is about 4% (w/w)" recitation of claim 39).

Regarding claim 40, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice

(see para. [0053])(corresponding to the claimed “wherein the nicotine liquid formulation further comprises a flavorant”).

Regarding claim 41, as evident form Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine liquid formulation”).

Regarding claims 42, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed “wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid”).

Response to Applicant's Arguments

7. Applicant's arguments filed April 20, 2017 have been fully considered but are moot because of the new grounds of rejection, presented above, which were necessitated because of the newly amended claims filed with the RCE on December 4, 2017.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE WALLS MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Thursdays, and alternate Monday and Tuesdays, from 7:30a - 4:00a.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael H Wilson can be reached on 571-270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE W. MAYES/
Examiner, Art Unit 1747

Notice of References Cited	Application/Control No. 14/925,961	Applicant(s)/Patent Under Reexamination BOWEN et al.	
	Examiner DIONNE W MAYES	Art Unit 1747	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20070163610-A1	07-2007	Lindell et al	A61K31/465	131/271
*	B	US-20140000638-A1	01-2014	Sebastian et al	A24F47/008	131/328
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC - Searched*		
Symbol	Date	Examiner
A24F47/008	1/11/2016	DWM
updated above	6/11/2016	DWM
updated above	5/25/2017	DWM
updated above	09/25/2018	DWM

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM
Inventor Search updated	6/11/2016	DWM
Inventor Search updated	09/25/2018	DWM

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Used in Lieu of PTO/SB/08A/B
(Based on PTO 11-07 version)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/925,961
				Filing Date	October 28, 2015
				First Named Inventor	Adam Bowen
				Art Unit	1747
(Use as many sheets as necessary)				Examiner Name	D. W. Mayes
Sheet	1	of	1	Attorney Docket Number	052210-501C03US/713.302

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A	US-20020043554-A1	04-18-2002	White et al.	
	B	US-20060196518-A1	09-07-2006	Hon	
	C	US-20120261286-A1	10-18-2012	Holloway et al.	
	D	US-20120273589-A1	11-01-2012	Hon	
	E	US-20130276802-A1	10-24-2013	Scatterday	
	F	US-20130284190-A1	10-31-2013	Scatterday et al.	
	G	US-20130284191-A1	10-31-2013	Scatterday et al.	
	H	US-20130313139-A1	11-28-2013	Scatterday et al.	
	I	US-20130319440-A1	12-05-2013	Capuano	
	J	US-20140209105-A1	07-31-2014	Sears et al.	
	K	US-7,374,048	05-20-2008	Mazurek	
	L	US-7,766,013	08-03-2010	Wensley et al.	
	M	US-8,464,867	06-18-2013	Holloway et al.	
	N	US-8,596,460	12-03-2013	Scatterday	
	O	US-8,794,245	08-05-2014	Scatterday	
	P	US-8,794,434	08-05-2014	Scatterday et al.	
	Q	US-8,905,040	12-09-2014	Scatterday et al.	
	R	US-8,931,492	01-13-2015	Scatterday	
	S	US-9,319,865	04-19-2016	Van Phan et al.	
	T	US-9,420,829	08-23-2016	Thorens et al.	
	U	US-9,717,279	08-01-2017	Hon	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/DIONNE W. MAYES/	Date Considered	09/25/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	3364	(A24F47/008).cpc.	US-PGPUB; USPAT	ADJ	ON	2018/09/25 15:32
L4	4	"27760379".FMID.	US-PGPUB; USPAT; FPRS	ADJ	OFF	2018/09/25 15:41
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	ADJ	ON	2015/01/20 15:28

			IBM_TDB			
S14	2	("131"/$ or "128"/$).ccls. and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:51
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15	US-PGPUB;	ADJ	ON	2015/01/20

		(seconds or secs)	USPAT; USOCR			16:48
S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:59
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or	US-PGPUB; USPAT;	ADJ	ON	2015/05/14 16:08

		liquid or solvent) and benzoic	USOCR			
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or	US-PGPUB;	ADJ	ON	2015/05/14

		"514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	USPAT; USOCR			18:31
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or	US-PGPUB; USPAT;	ADJ	ON	2015/09/17 14:48

		liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	USOCR			
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	("14925961").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30
S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33
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S81	1	("14925961").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/13 15:38
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S83	1595	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/12/14 13:14
S84	1	("9215895").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/14 13:23
S85	1998	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/05/25 21:46
S86	2	(adam near3 bowen).in. and (nicotine and liquid formulation and benzoic).clm.	US-PGPUB; USPAT	ADJ	OFF	2018/09/23 19:40
S87	4	(adam near3 bowen).in. and (nicotine and liquid and formulation and benzoic).clm.	US-PGPUB; USPAT	ADJ	OFF	2018/09/23 19:54
S88	4	(adam near3 bowen).in. and (benzoic).clm.	US-PGPUB; USPAT	ADJ	OFF	2018/09/23 22:05
S89	529	131/$.ccls. and (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 13:19
S90	209	131/$.ccls. and nicotine and (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 13:19
S91	58	131/$.ccls. and nicotine near50 (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 13:42
S92	91	131/$.ccls. and nicotine near50 liquid and (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 14:20
S93	1	(14/925961).APP.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/09/24 14:40
S94	0	(2014/0000638).CCLS.	US-PGPUB; USPAT;	OR	OFF	2018/09/24 18:36

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S96	1	("7726320").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/09/24 18:43
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9/25/2018 3:59:25 PM
C:\Users\dmayes\Documents\EAST\Workspaces\14925961.wsp

Bibliographic Data

Application No: 14/925,961

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: _____ _____

Examiner's Signature | Initials

Title: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/28/2015	131	1747	52210-501C03US / 713.302
RULE			

APPLICANTS

JUUL Labs, Inc., San Francisco, CA,

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Adam BOWEN San Francisco, CA, UNITED STATES

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CONTINUING DATA

This application is a CON of 14271071 05/06/2014

14271071 has PRO of 61912507 12/05/2013

14271071 has PRO of 61820128 05/06/2013

FOREIGN APPLICATIONS

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	Q	WO-2016065606-A1	05-06-2016	Huizhou Kimree Technology Co.,ltd		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	09/25/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
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	BO	Oldendorf, W., et al., "Blood-brain barrier penetration abolished by N-methyl quaternization of nicotine," Proc. Natl. Acad. Sci, Vol. 90, pp. 307-311, 1993.	
	BP	Oldendorf, W., et al., "pH Dependence of Blood-Brain Barrier Permeability to Lactate and Nicotine," Stroke, Vol. 10, No. 5, 1979.	
	BQ	Omole, Olufemi Babatunde, et al., "Review of alternative practices to cigarette smoking and nicotine replacement therapy: how safe are they?." South African Family Practice 53.2 (2011): 154-160.	
	BR	Pachke, T., et al., "Effects of Ingredients on Cigarette Smoke Composition and Biological Activity: A Literature Overview," Contributions to Tobacco Research, Vol. 20, No. 2, Aug. 2002.	
	BS	Pankow, et al., "Conversion of Nicotine in Tobacco Smoke to Its Volatile and Available Free-Base form Through the Action of Gaseous Ammonia," Eniron. Sci. Technol. 31 (8), 1997.	
	BT	Pankow, James F. "A consideration of the role of gas/particle partitioning in the deposition of nicotine and other tobacco smoke compounds in the respiratory tract." *Chemical research in toxicology* 14.11 (2001): 1465-1481.	
	BU	Perfetti, T., "Investigation of Nicotine Transfer to Mainstream Smoke I. Synthesis of Nicotine Salts," 1978.	
	BV	Perfetti, Transfer of Nicotine salts to mainstream smoke (2000) https://www.industrydocumentslibrary.ucsf.edu/tobacco/docs/#id=rzwp0187	
	BW	Polosa, Riccardo, et al. "A fresh look at tobacco harm reduction: the case for the electronic cigarette." Harm reduction journal 10.1 (2013): 19.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

Used in Lieu of PTO/SB/08A/B
(Based on PTO 11-07 version)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/925,961
				Filing Date	October 28, 2015
				First Named Inventor	Adam Bowen
				Art Unit	1747
				Examiner Name	D. W. Mayes
Sheet	8	of	10	Attorney Docket Number	052210-501C03US

	BX	Polosa, Riccardo, et al. "Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study." BMC public health 11.1 (2011): 786.	
	BY	Polosa, Riccardo, et al. "Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal." International journal of environmental research and public health 11.5 (2014): 4965-4977.	
	BZ	Polosa, Riccardo, et al. "Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study." Internal and emergency medicine 9.5 (2014): 537-546.	
	CA	Prignot, J., "Electronic Nicotine Delivery Systems (Electronic Cigarettes, Cigars, Pipes)," Louvain Medical, V. 132, No. 10, December 2013. [including English language translation thereof]	
	CB	Provisional Application 61/826,318, filed May 22, 2013.	
	CC	Provisional Application 61/856,286, filed July 19, 2013.	
	CD	Provisional Application 61/856,374, filed July 19, 2013.	
	CE	Provisional Application 61/891,626, filed on October 16, 2013.	
	CF	Provisional Application 61/969,650, filed March 24, 2014.	
	CG	Provisional Application 61/971,340, filed March 27, 2014.	
	CH	Riggs, et al., "The Thermal Stability of Nicotine Salts," R.J. Reynolds Tobacco Company, 2000.	
	CI	Robertson, C., et al., "In their own words: an epoch of deceit and deception," Chapter 5 (find out from which book)	
	CJ	Rose, J., "Nicotine and nonnicotine factors in cigarette addiction," Psychopharmacology, 184:274-285, 2006.	
	CK	Rose, J., "Pulmonary Delivery of Nicotine Pyruvate: Sensory and Pharmacokinetic Characteristics," Expermimental and Clinical Psychopharmacology, Vol. 18, No. 5, 2010.	
	CL	Sahu, S.K., et al., "Particle Size Distribution of Mainstream and Exhaled Cigarette Smoke and Predictive Deposition in Human Repiratory Tract," Aerosol and Air Quality Research, 13: 324-332, 2013.	
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	CP	SEEMAN, et al., "The form of nicotine in tobacco. Thermal transfer of nicotine and nicotine acid salts to nicotine in the gas phase," J Aric Food Chem, 47(12), pp/ 5133-5145. December 1999.	
	CQ	Seeman, J., "Possible Role of Ammonia on the Deposition, Retention, and Absorption of Nicotine in Humans while Smoking," Chemical Research in Toxicology, 20, 2007.	
	CR	Seeman, J., "Using 'Basic Principles' to Understand Complex Science: Nicotine Smoke Chemistry and Literature Analogies," Journal of Chemical Education, Vol. 82, No. 10, 2005.	
	CS	Seeman, J., et al., "On the Deposition of Volatiles and Semivolatiles from Cigarette Smoke Aerosols: Relative Rates of Transfer of Nicotine and Ammonia from Particles to the Gas Phase," Chemical Research in Toxicology, 17, 2004.	

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				Art Unit	1747
				Examiner Name	D. W. Mayes
Sheet	9	of	10	Attorney Docket Number	052210-501C03US

	CT	Seeman, J., et al., "The possible role of ammonia toxicity on the exposure, deposition, retention, and the bioavailability of nicotine during smoking," Food and Chemical Toxicology, 46, 2008.	
	CU	Sensabaugh, A.J., et al., "A New Technique for Determining the pH of Whole Tobacco Smoke," Tobacco Science.	
	CV	Shahab, L., et al., "Novel Delivery Systems for Nicotine Replacement Therapy as an Aid to Smoking Cessation and for Harm Reduction: Rationale, and Evidence for Advantages over Existing Systems," CNS Drugs, 27: 1007-1019, 2013.	
	CW	Snowdon, Christopher. "Harm reduction and tobacco: a new opportunity or a step too far?." Drugs and Alcohol Today 13.2 (2013): 86-91.	
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	CY	Teague, "Implications and Activites Arising from Correlation of Smoke pH with Nicotine Impact, Other Smoke Qualities and Cigarette Sales," 1983.	
	CZ	Tomar, S., et al., "Review of the evidence that pH is a determinant of nicotine dosage from oral use of smokeless tobacco," Tobacco Control, 6:219-225, 1997.	
	DA	Torrie, B., "Nicotine inhaler gives instant 'hit'," 2 pages (2013), available at http://www.stuff.co.nz/national/health/8822875/Nicotine-inhaler-gives-instant-hit.	
	DB	Travell, J., "The Influence of the Hydrogen Ion Concentration on the Absorption of Alkaloids from the Stomach," The Journal of Pharmacology, January 1940.	
	DC	Trehy, Michael L., et al. "Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities." Journal of Liquid Chromatography & Related Technologies 34.14 (2011): 1442-1458.	
	DD	Uchiyama, Shigehisa, et al. "Determination of carbonyl compounds generated from the E-cigarette using coupled silica cartridges impregnated with hydroquinone and 2, 4-dinitrophenylhydrazine, followed by high-performance liquid chromatography." Analytical sciences 29.12 (2013): 1219-1222.	
	DE	Vansickel, Andrea R., et al. "A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects." Cancer Epidemiology and Prevention Biomarkers 19.8 (2010): 1945-1953.	
	DF	Vansickel, Andrea Rae, et al., "Electronic cigarettes: effective nicotine delivery after acute administration." Nicotine & Tobacco Research 15.1 (2012): 267-270.	
	DG	Wayne, G., et al., "Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents," Tobacco Control, 15:189-198, 2006.	
	DH	Weiss, G., "The Effect of pH on Nicotine-Induced Contracture and Ca45 Movements in Frog Sartorius Muscle," The Journal of Pharmacology and Experimental Therapeutics, Vol. 154, No.3, 1966.	
	DI	World Health Organization, "Health Effects of Interations Between Tobacco Use and Exposure to Other Agents," Environmental Health Criteria 211, 83 pages (1999), available at http://www.inchem.org/documents/ehc/ehc/ehc211.htm.	
	DJ	Wynn III, William P., et al. "The pharmacist "toolbox" for smoking cessation: a review of methods, medicines, and novel means to help patients along the path of smoking reduction to smoking cessation." Journal of pharmacy practice 25.6 (2012): 591-599.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

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Substitute for form 1449/PTO				Complete if Known	
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				Filing Date	October 28, 2015
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				Art Unit	1747
(Use as many sheets as necessary)				Examiner Name	D. W. Mayes
Sheet	10	of	10	Attorney Docket Number	052210-501C03US

	DK	Zenzen, Volker, et al. "Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 2: Smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior." Regulatory Toxicology and Pharmacology 64.2 (2012): S11-S34.	
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Examiner Signature	/DIONNE W. MAYES/	Date Considered	09/25/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	03/27/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 23	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/SHAREILL A COLES/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 Confirmation No.: 1528

Filed: October 28, 2015 Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF Examiner: Dionne W. MAYES

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

By EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This paper is filed in response to the Non-Final Office Action dated September 28, 2018 in the above-identified application. The shortened statutory period for reply expired December 28, 2018. With this response, Applicant requests a three-month extension of time, and submits the requisite fee. Accordingly, this response is timely filed. Please amend the application as set forth below, and consider the following remarks:

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **6** of this paper

Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Jeffery C. Giering
Attorney Docket Number:	52210-501C03US/713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
		Total in USD ($)		**700**

Electronic Acknowledgement Receipt

EFS ID:	35547053
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Angela Olivos
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	52210-501C03US/713.302
Receipt Date:	27-MAR-2019
Filing Date:	28-OCT-2015
Time Stamp:	17:00:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$700
RAM confirmation Number	032819INTEFSW00004221500311
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		052210-501C03US_Response.pdf	5609638 239615638e73cc585ca716a0f83af21f1904b529	yes	94

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	17	94
	Applicant Arguments/Remarks Made in an Amendment	6	16
	Claims	2	5
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30978 1ed31b5ef7b0cf365fb02a174918a67c6226908b	no	2

Warnings:

Information:

Total Files Size (in bytes):	5640616

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

APPENDIX A

The SECRET and SOUL of Marlboro

Phillip Morris and the Origins, Spread, and Denial of Nicotine Freebasing

Terrell Stevenson, BA, and Robert N. Proctor, PhD

Philip Morris and other tobacco companies have been using ammonia in their manufacturing for more than half a century, and for a variety of purposes: to highlight certain flavors, to expand or "puff up" the volume of tobacco, to prepare reconstituted tobacco sheet ("recon"), to denicotinize (reduce the amount of nicotine in) tobacco, and to remove carcinogens.

By the early 1960s, however, Philip Morris had also begun using ammonia to "freebase" the nicotine in cigarette smoke, creating low-yield (reduced-tar or -nicotine) cigarettes that still had the nicotine kick necessary to keep customers "satisfied" (i.e., addicted). We show that Philip Morris discovered the virtues of freebasing while analyzing the impact of the ammoniated recon used in Marlboro cigarettes.

We also show how Marlboro's commercial success catalyzed efforts by the rest of the tobacco industry to discover its "secret," eventually identified as ammonia technology, and how Philip Morris later exploited the myriad uses of ammonia (e.g., for flavoring and expanding tobacco volume) to defend itself against charges of manipulating the nicotine deliveries of its cigarettes. (*Am J Public Health.* 2008;98:1184–1194. doi:10.2105/AJPH.2007.121657)

AMMONIA OCCURS NATURALLY in cured tobacco leaf, from close to 0% in some varieties up to about 1% (by weight) in the leaves used in some higher-quality cigars.[1] The compound is also commonly used as a tobacco additive, either in its native form as a clear, pungent gas (NH_3, an ingredient in smelling salts) or as an aqueous or solid ammonium salt (NH_4^+). Although toxic in large doses, ammonia is relatively easy to remove from processed tobacco leaves; the gaseous form is quite volatile, and the salt is easily neutralized by the addition of an acid.[2] The tobacco industry has for many years used ammonia as a relatively innocuous additive to augment certain flavors, to economize on costs by expanding or "puffing" the cured leaf, to denicotinize (reduce the amount of nicotine in) tobacco, and even to reduce some of the carcinogens in tobacco smoke.

By the early 1960s, however, Philip Morris scientists had discovered that ammonia could also be used to increase the free nicotine in cigarette smoke, providing a more powerful nicotine kick than the milder low-pH tobaccos traditionally used in American-blend cigarettes. The discovery seems to have come about by accident, in the course of exploring the properties of the ammoniated tobaccos used in the preparation of reconstituted tobacco sheet ("recon").

This freebased version of Marlboro cigarettes was one of the greatest triumphs in the history of modern drug design and one reason the brand became the world's most popular cigarette. Yet to this day, Philip Morris denies it has ever deliberately freebased tobacco to boost nicotine yields. The company recalls only the many innocuous uses of ammonia—as a "flavorant" or binder required for the manufacture of recon, for example. The industry reminds us that ammonia is naturally found in foods, fertilizers, and the very air we breathe.

We have analyzed internal documents of the tobacco industry to show that Philip Morris discovered ammonia's freebasing ability while attempting to understand

the impact of the ammoniated tobacco sheet used in its Marlboro cigarettes. The archival record shows that ammonia technology eventually spread throughout the industry, but only after diligent efforts to reverse engineer the chemistry of Marlboros to discover their "secret." Philip Morris later exploited the alternate uses of ammonia—in flavoring, expanding, reconstituting, and denicotinizing tobacco—to defend itself against charges of having manipulated the nicotine in cigarettes. The tobacco industry is notorious for having manipulated science; it is now in the process of renarrating the history of science to defend itself against charges of having deliberately taken paths that led to massive death and disease.[3]

THE OMNIPRESENT ADDITIVE

Ammonia's capacity to improve tobacco smoke flavor has been recognized at least since the early 1950s, when Claude E. Teague Jr, an RJ Reynolds chemist who later became the company's director of research, found that ammonia gave smoke a richer, smoother, "chocolate-like" taste reminiscent of a burley blend, the most alkaline of the common varieties of tobacco leaf.[4] Philip Morris scientists also recognized this relationship between alkalinity and burley's rich taste, and in the late 1950s and early 1960s began using a range of bases, including ammonia, diammonium phosphate (DAP), and various ethanolamines and carbonates to "improve smoke flavor."[5]

In these early years, tobacco manufacturers were not sure why ammonia—most often regarded as an irritant—improved the taste of tobacco smoke. They eventually came to understand that there was a threshold level beyond which further additions of the compound would no longer improve flavor. In 1971, Philip Morris experimented on competitors' brands and found that ammonia added at 0.25% concentration created a taste that was "milder, more aromatic, sweeter, less harsh, and more like a Marlboro," whereas ammonia added at 0.50% concentration created an "off taste."[6] RJ Reynolds scientists later hypothesized that ammonia might improve tobacco smoke flavor by reacting with sugars to produce heterocyclic ring compounds known as pyrazines. Because pyrazines were already known for their vibrant flavors, RJ Reynolds scientists hypothesized (in documents marked "secret") that amino-sugars such as pyrazines might be the key to ammonia's ability to improve tobacco.[7]

Ammonia has also been used in a number of cost-saving processes, including the production of expanded or "puffed" tobacco. Increasing tobacco's volume was a priority in the 1970s, when tobacco companies first recognized that expanding a given volume of tobacco could increase its "filling power," thereby reducing the mass of leaf required to fill a cigarette of some fixed length and circumference. The reduced mass of tobacco per cigarette encouraged customers to smoke more to get their desired amount of "satisfaction," the industry's euphemism for nicotine.

There are a number of ways to expand tobacco. The most common today is the dry ice expanded tobacco (DIET) process, which uses carbon dioxide (CO_2) in solid form to freeze-dry and "puff up" the tobacco. In 1973, however, Philip Morris patented a puffing procedure that used ammonia in conjunction with CO_2. The cured leaf was treated with dry ice and ammonia—in liquid or gaseous form, as a hydroxide with CO_2 or as a carbonate or bicarbonate—followed by applications of heat.[8] This method was soon discontinued in favor of the DIET process,[9] apparently because of cost concerns. According to confidential Philip Morris records, it took 143 pounds of ammonia to make 2000 pounds of expanded tobacco[10]; dry-ice methods, by contrast, were relatively cheap.

Reconstituted tobacco has been a more enduring use of ammonia. Essentially a paper-making process, recon was developed in the 1930s and 1940s as part of an effort to salvage more of the tobacco leaf, including the stems or mid-ribs formerly thrown away as waste. To make these waste parts smokable, however, and to increase sheet strength, required the addition of a substance "to release the pectins in tobacco stems so they may form a gel which becomes the binder in the blended leaf sheet."[11] In the 1950s Philip Morris had begun exploring the use of diammonium phosphate (DAP) in recon and found it to be a successful pectin releaser and a potent flavor enhancer, masking the unpleasant taste of stem.[12] The company set up its first pilot plant for ammoniating tobacco (with DAP) in 1961, and 6 years later patented the "diammonium phosphate–blended leaf" (DAP-BL) process after realizing diammonium

"This freebased version of Marlboro cigarettes was one of the greatest triumphs in the history of modern drug design and one reason the brand became the world's most popular cigarette. Yet to this day, Philip Morris denies it has ever deliberately freebased tobacco to boost nicotine yields."

phosphate's ability to increase free nicotine "delivery" in cigarettes.[13] The patent, interestingly, contains nothing about DAP's ability to freebase nicotine, citing only its importance as a pectin releaser.[14]

The tobacco industry also uses ammonia to remove nicotine from tobacco. The procedure is simple: Tobacco leaves are exposed to gaseous ammonia, which replaces nicotine in the salts that bind the alkaloid to the leaf. The ammonia and resulting nicotine are then removed by steam. This method of nicotine reduction gives tobacco manufacturers a degree of control over the amount of nicotine in a given tobacco blend.[15]

CANCER PREVENTION?

In the 1990s, Philip Morris and the other tobacco companies often mentioned these relatively innocuous uses of ammonia—in flavoring, expanding, and denicotinizing tobacco and in making reconstituted tobacco sheet—when defending themselves against charges of having used ammonia to freebase tobacco. Essentially, their argument was, how could we have done something insidious and underhanded with a molecule like ammonia that is so commonplace, public, and patented for use in so many different kinds of manufacturing processes?[16] Typical was a February 24, 1998, letter to the *New York Times* from Philip Morris's director of external relations that claimed that the company's use of ammonia in cigarette manufacturing "does not increase the amount of nicotine delivered to the smoker, does not increase the amount of nicotine absorbed in the lungs of the smoker, and does not affect the form of nicotine delivered to the smoker's brain."[17] The company was responding to a *New York Times* exposé on the industry's widespread use of ammonia technology.[18]

Prior even to the discovery of ammonia's ability to increase nicotine availability, however, tobacco companies were using the reagent in confidential experiments to reduce carcinogens in cigarettes. Throughout the 1950s and 1960s, industry scientists were researching the idea that certain ammonium salts, such as ammonium sulfamate and ammonium chloride, could reduce the levels of benzpyrene,[19] one of the forty carcinogens in cigarette smoke named by Helmut Wakeham, Philip Morris's director of research and development, in 1961.[20] This research on reducing benzpyrene was part of Philip Morris's Project 0107, the purpose of which was to develop cigarettes with "less tendency to cause lung cancer in smokers."[21] The Celanese Corporation in 1964 patented a tobacco substitute "in which ammonia salts are used to inhibit benz-a-pyrene formation,"[22] and in 1967 British American Tobacco researchers reported similar reductions with potassium carbonate.[23]

THE "SECRET" (AND SOUL) OF MARLBORO

Marlboro began in the 1920s as a women's cigarette. Advertisements called it "mild as May," and it was taken off the market during World War II because of a sales slump. In the mid-1950s, however, with growing public concerns about the link between smoking and lung cancer, Philip Morris decided to reintroduce the brand with a new and improved filter, a flip-top box, and a new masculine image.[24] This new version of Marlboro sold surprisingly well, and for an unanticipated reason.

Philip Morris researchers discovered that the reconstituted tobacco they were using to cut costs—the DAP-BL—had some fortunate side effects. Diammonium phosphate, which breaks down into ammonia when a cigarette is burned, improved the flavor of the smoke, giving it that smooth, "chocolate-like" taste, while also increasing the availability of nicotine in the smoke.[25] Soon thereafter Philip Morris began using diammonium phosphate and other forms of ammonia in its other cigarettes, including its health-conscious (low-tar) Merit brand. Merits were introduced in 1976 and within 3 years accounted for about 20% of Philip Morris's cigarette sales.[26]

How, though, did diammonium phosphate freebase the nicotine in cigarettes? Freebasing entered public consciousness in the mid-1980s, when a cheaper street version of cocaine known as "crack" came on the scene.[27] In point of fact, however, a kind of folk freebasing has been widely used in different parts of the world for many centuries. Archaeologists have found evidence of the use of lime or wood ash to freebase botanicals such as pituri (*Duboisia hopwoodii*), a nicotine-containing plant used by Australian aborigines to help them endure the harsh desert climate. Folk freebasing can also be found among traditional chewers of coca leaves, betel nuts, and tobacco.[28]

The chemistry of freebasing is not complex. A base, such as ammonia, accepts a proton from a positively charged nicotine carboxylic acid salt (e.g., a malate or a tartrate) found in tobacco. The ammonia (NH_3) is thereby transformed into a cation (NH_4^+), and the positively charged nicotine acid salt is deprotonated to become neutral. This neutral, deprotonated

nicotine is "free" in that it is no longer bound to another molecule (or anion) in the form of a salt. Free nicotine is more volatile; James F. Pankow, of Oregon Health and Science University, stresses that "increasing the proportion of the particle-phase nicotine that is in the freebase form will . . . tend to drive more nicotine into the gas phase."[29] Gas-phase nicotine is able to deposit quickly and easily in the respiratory tract and, because of its freebase form, crosses the blood–brain barrier more readily ("moves easily into fatty tissues"[30]), making the nicotine more "available" to the smoker and therefore more potent.

Ammoniation increases nicotine's volatility. There is not universal agreement on whether ammoniation also increases the *rate* of nicotine delivery, but freebasing is widely thought to increase the *impact* of nicotine by increasing its efficiency of extraction during the smoking process.[31] Many tobacco industry documents mention augmentation of nicotine impact, and many of those also reveal a conviction that ammoniation was increasing the rate of nicotine delivery, causing a more immediate and profound "kick" to a smoker's central nervous system (Figure 1). Philip Morris admitted the increased rate of nicotine delivery in a 1989 interoffice memo, noting that "the CNS [central nervous system] effects obtained using the NC [nicotine citrate] cigarettes were approximately half the magnitude of those obtained with FB [freebase nicotine] and unextracted cigarettes."[33]

Many different terms have been used within the tobacco industry to describe this augmented impact, including *volatile nicotine, pH effect, amelioration, extractable nicotine, burley impact,* and *increased satisfaction* or *augmentation.*[34]

Channing Robertson, a Stanford chemical engineer, was barred from using the term *freebase nicotine* in his 1998 testimony for the plaintiffs in *Minnesota v. Philip Morris*, so he testified instead about what he called "crack nicotine."[35] Crucial for the tobacco industry, however, was that this augmented "kick" provided by ammoniation could offset declining levels of tar and nicotine in

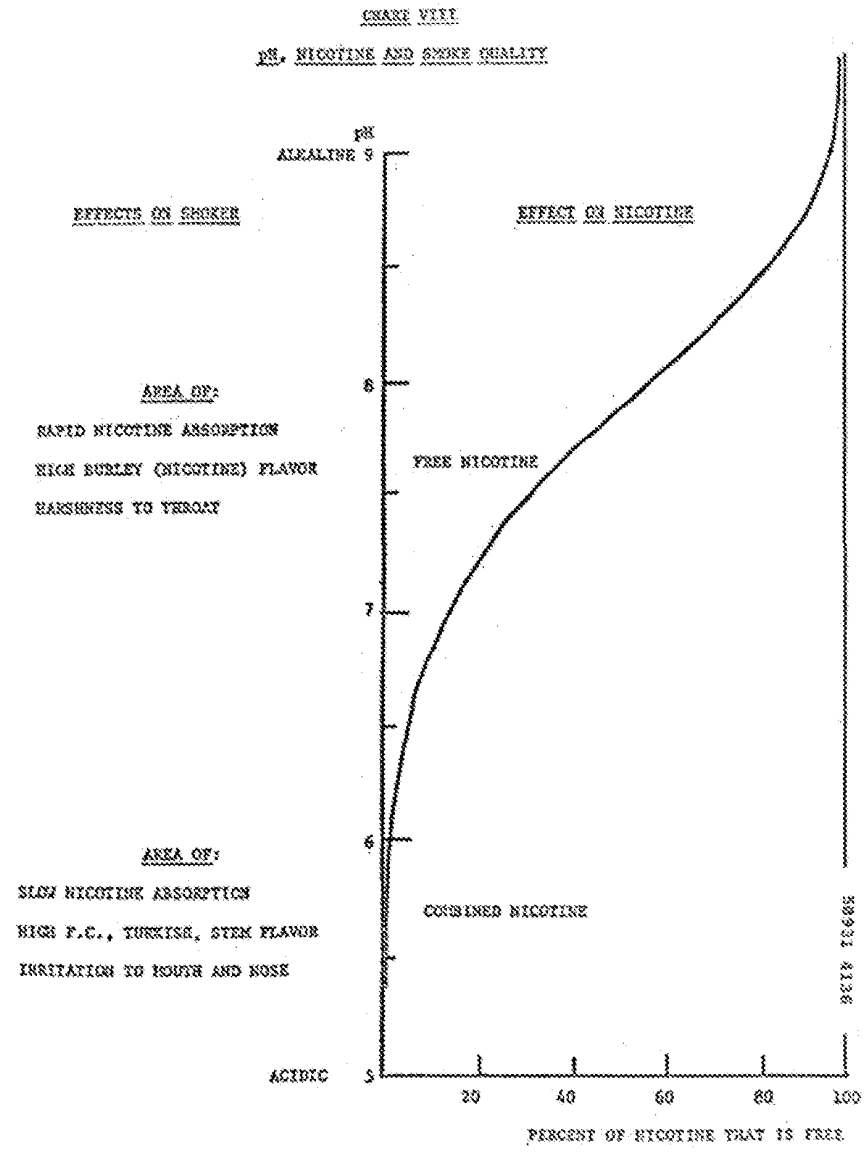


FIGURE 1—The chemistry of freebasing. The tobacco industry has long appreciated the importance of smoke pH for boosting nicotine's impact. This page, from a 1973 report by Claude E. Teague Jr of RJ Reynolds (*Implications and Activities Arising From Correlation of Smoke pH With Nicotine Impact*), shows how the freebase form of nicotine in smoke increases with increasing alkalinity. Although pH is a good indicator of relative freebase availability, it tends to underestimate the actual amount available. Other industry methods for measuring free nicotine—such as oil versus water partitioning or studies of nicotine volatility—reveal free nicotine levels much higher than those predicted from pH alone.[32]

Summary of Progress in 1971 on Project TE-5001

Title: DEVELOPMENT OF A CIGARETTE WITH INCREASED SMOKE pH

Prepared by: Robert K. Williams — Section: Organic

Date: December 16, 1971 — Checked by: [illegible]

Notebook Ref. No.: PO-92A — Approved by: [illegible]

CHRONOLOGY

May-June - Tobacco treated with $Ca(OH)_2$ to increase smoke pH showed increased tobacco pH but no increase in smoke pH in handmade L+M cigarettes.

July-August - Tobacco treated with $Ca(OH)_2$ showed an increase in smoke pH if the cigarette was of the unfiltered type.

September-October - Sample cigarettes were made in the factory adding three levels of $Ca(OH)_2$. The project was turned over to Physical Section.

SUMMARY OF PROGRESS

Increasing the pH of a medium in which nicotine is delivered increases the physiological effect of the nicotine by increasing the ratio of free base to acid salt form, the free base form being more readily transported across physiological membranes. We are pursuing this project with the eventual goal of lowering the total nicotine present in smoke while increasing the physiological effect of the nicotine which is present, so that no physiological effect is lost on nicotine reduction.

Source. Reference 36.

FIGURE 2—The Industry's Rationale for Freebasing. Liggett and Myers in 1971 explained the rationale behind the company's experiments to increase the proportion of "freebase" nicotine as part of its multiyear "Project TE-5001."

cigarettes, which fell by more than half from the 1950s through the 1980s as the industry sought to reassure worried smokers. Freebasing meant you could maintain a high nicotine impact while lowering reported tar and nicotine levels. As one 1971 Liggett document states, "there could be a reduction in total nicotine in the smoke without a reduction in the physiological satisfaction associated with nicotine"[36] (Figure 2).

THE ORIGINS AND SPREAD OF AMMONIA TECHNOLOGY

Long before the widespread use of freebasing, tobacco industry scientists knew that nicotine deliveries were sensitive to pH manipulation (by adding acids or bases). Several documents from the 1930s and 1940s discuss how to *reduce* the amount of free nicotine in tobacco by adding an organic acid, which would combine with the free nicotine base to form a (bound) nicotine salt.[37] Free (vs "combined") nicotine in those early years was often characterized as "toxic,"[38] which made sense at a time prior to the push to reduce tar and nicotine in the "filter wars" and "tar derby" of the 1950s and 1960s. Many other industry documents from this earlier period describe the well-known art of denicotinization, which often used a base (such as ammonia) and steam to remove the offending alkaloid from tobacco. Denicotinization involves some of the same processes as freebasing, although the desired outcomes are different. Denicotinization involves the application of gaseous ammonia so that, upon addition of steam, the nicotine can be removed; freebasing impregnates tobacco with a salt (such as DAP) so that ammonia is released when the cigarette is lit, making nicotine more available to the smoker.

Tobacco chemists knew enough to freebase nicotine as early as the 1930s and 1940s,[39] but there was little reason then to manipulate cigarettes in this manner. Smoking was not yet widely accepted as a cause of lung and heart disease,[40] and most people still smoked cigarettes yielding very high levels of tar and nicotine. Only beginning with the "health scare" of the 1950s, and with increasing urgency in the 1960s and 1970s, did Philip Morris and the other manufacturers scramble to appease a rattled public by marketing cigarettes with lower levels of tar and nicotine, which is where the value of ammoniation came in.

It is difficult to say whether Philip Morris scientists expected diammonium phosphate to increase the availability of free nicotine in its new version of Marlboro,

introduced in the mid-1950s. After all, the compound was largely being used as a pectin releaser and flavorant in reconstituted tobacco. Philip Morris chemists were, however, experts in pH manipulation, as were chemists more generally. Freebasing was not an unknown phenomenon, but there was not yet a practical need for it in the cigarette business.

In 1962, a Philip Morris study found diammonium phosphate products delivering 0.57 mg of nicotine per cigarette versus 0.44 mg in untreated tobaccos.[41] Keenly aware of the increasing demand for cigarettes low in nicotine,[42] Philip Morris later used its patented DAP-BL process to give its "low-yield" Merit brand an edge over its competitors. Merit cigarettes boasted a total nicotine yield (measured by Federal Trade Commission machines) only half of that found in Marlboros, but still managed to make available the same amount of free nicotine to smokers (about 0.33 mg in both instances). Brown and Williamson scientists reflected on this in 1980, commenting that "in theory a person smoking these cigarettes [Merit and Marlboro] would not find an appreciable difference in the physiological satisfaction from either based on the amount of free nicotine delivered."[43]

This was not the first time Brown and Williamson had pondered the value of freebasing. Its parent company, British American Tobacco, in the mid-1960s had recognized along with Philip Morris that the "strength" or "impact" of a cigarette was related not to the total nicotine content of the smoke but rather to the amount of "extractable" or "free" nicotine, which varied significantly with smoke pH.[44] Brown and Williamson in 1971 had given the code name UKELON to urea, an ammonia source that the company recognized as "a way of achieving normal impact from low tar cigarettes."[45] The same company's "Project LTS" (low "tar" satisfaction) acknowledged that free (unprotonated) nicotine was "more readily absorbed and thus has a decidedly satisfying effect on the smokers' taste receptors." The goal of LTS was a cigarette containing "greater levels of 'free' nicotine" in "an enhanced alkaline environment."[46] By 1980, the company had concluded that "we have sufficient expertise available to 'build' a lowered mg tar cigarette which will deliver as much 'free nicotine' as a Marlboro, Winston or Kent without increasing the total nicotine delivery above that of a 'Light' product."[47]

Apart from DAP-BL recon, Philip Morris experimented with other kinds of ammonia technology. As early as 1957, for example, the company came up with the economically unfeasible "New Idea No. 46"[48] to "soak stems in liquid ammonia," imparting to them greater "protein-like" material and "those properties now being produced by the aqueous NaOH, by virtue of its basic nature."[49] The ammonia was difficult to recycle, however, and the idea was quickly abandoned. A 1966 progress report on "nicotine and smoke pH" discussed the results of adding ammonium carbonate and oxalic acid to tobacco and concluded that nicotine deliveries could be "controlled via filler or smoke pH adjustment."[50] Throughout this time, from the mid-1960s through the 1970s and 1980s, the company kept a close eye on the pH levels of its major brands.[51]

THE STAMPEDE TO KEEP UP WITH THE MARLBORO MAN

Although some historians maintain that Philip Morris's rise to the top of the tobacco industry in the mid-1970s was because of its ingenious Marlboro ad campaign, featuring a ruggedly handsome cowboy in the beautiful and equally rugged West[52]—"Marlboro Country"—the makers of competitor brands could justifiably disagree. In the 1960s, with Philip Morris brands streaking ahead of the pack, RJ Reynolds, American Tobacco, Lorillard, Liggett, and Brown and Williamson all began investigations into what would later be called "the secret"[53] and eventually "the soul" of Marlboro.[54] All discovered the virtues of freebasing, but this didn't happen overnight.

Brown and Williamson and its parent, British American Tobacco, were apparently the first (after Philip Morris) to realize the importance of ammonia in increasing nicotine availability, but American Tobacco[55] and the other companies were not far behind. RJ Reynolds incorporated ammoniated sheet into Camel filters in 1974, allowing them to deliver 36 mg of ammonia per cigarette in the mainstream smoke.[56] Five years later, the company began using ammoniated sheet in its popular Winston brand.[57] Teague, in a 1973 report marked "secret," noted that Marlboro, in comparison with RJ Reynolds's own Winston, showed

> 1) higher smoke pH (higher alkalinity), hence increased amounts of "free" nicotine in smoke, and higher immediate nicotine "kick", 2) less mouth irritation, less stemmy taste and less Turkish and flue-cured flavor, and 4) [sic] increased burley flavor and character.[58]

Teague then went on to point out that cigarettes with rising sales, especially Philip Morris brands, all showed evidence of pH manipulation. Another RJ Reynolds document from 1973 (aimed at targeting the youth market) stated that "for public relations reasons it would be impossible to go back all the way to the 1955 type cigarettes"—high in tar and nicotine—but took comfort from the fact that "still, with an old style filter, any desired *additional* nicotine 'kick' could be easily obtained through pH regulation."[59]

Sometime during the 1980s, Lorillard caught up with Philip Morris and began using ammonia technology in its own cigarettes, by which time British American Tobacco had initiated Project AMTECH to investigate "the potential benefits of ammonia technology."[60] By the end of the 1980s, five of the "big six" of the industry (all but Liggett, which had researched but apparently never commercialized a freebase concept using calcium hydroxide)[61] were using a total of 10 million pounds of ammonia per annum, amounting to about 10 mg per cigarette. RJ Reynolds alone released 900 000 pounds of ammonia in 1989 from its factory in North Carolina.[62]

British American Tobacco and Brown and Williamson held the first of several ammonia technology conferences in the spring of 1989 to enhance "rapid commercial application" of ammonia technologies and to provide a forum to discuss "research strategies and priorities." Here we find an acknowledgment that ammonia technology was "the key to competing in smoke quality with [Philip Morris] worldwide"[63]; we also find a discussion of the different ways ammonia was being used to achieve the freebasing effect. Philip Morris was using DAP recon and urea; RJ Reynolds was using ammonia gas; American and Lorillard were using DAP recon; and Brown and Williamson itself was using DAP recon and urea, code-named QUELAR and UKELON.[64] At the second Annual Ammonia Technology Conference one year later, the opening statement affirmed that "ammonia technologies have been developed in the group to the stage where US blended products can be manufactured with comparable smoking quality to Marlboro."[65] A Brown and Williamson strategy document from 1991 concluded that ammonia technology was "the key factor" and "critical to the taste, character and delivery of Marlboro."[66]

Of course, the joy felt by Brown and Williamson and the other tobacco companies after uncovering "the secret of Malrboro" was matched by disappointment at Philip Morris, which had enjoyed this advantage over its competitors for years. William A. Farone, director of Applied Research at Philip Morris from 1976 to 1984, recalls that "when Winston started increasing their level of ammonia we had, you know—the roof fall down on us from [corporate headquarters in] New York City."[67]

THE OUTSIDE WORLD LEARNS THE TRUTH

Philip Morris's use of ammonia to freebase nicotine remained essentially a company secret until the 1970s and an industry secret until the 1990s. With access to documents produced in litigation, however, groups outside the industry began to catch on. Alix M. Freedman broke the story in a Pulitzer Prize–winning article for the *Wall Street Journal* in 1995,[68] based partly on documents unearthed through Commissioner David Kessler's investigations at the FDA. In 1996, in its regulations restricting the sale and distribution of cigarettes, the FDA noted that "compounds in free or unbound forms are vaporized more readily than compounds bound together in salts," giving both nicotine and cocaine as examples. The FDA went on to note that cigarette manufacturers had provided no evidence to rebut charges that "the conversion of nicotine from its bound form to its free form increases the transfer of nicotine to smoke."[69] One year later, James F. Pankow published a paper describing how ammonia increased nicotine volatility and availability in cigarette smoke, comparing this to the "immediate and intense high" produced by the freebasing involved in the making of crack cocaine.[70]

The industry's response was quick and characteristically dismissive. In 1998, Philip Morris lawyers deposed Pankow, questioning not just the details of his experimental design but also his professional ethics.[71] The company also criticized his assertion of a similarity between the tobacco industry's use of ammonia and the freebasing of cocaine.[72] Philip Morris lawyers also used the 1979 surgeon general's report to help them debunk the charge of freebasing. According to this report, produced under Surgeon General Julius B. Richmond, "the percentage of nicotine present as the free base is .40 at pH 5.35, 1.7 at pH 6, 15 at pH 7, 64 at pH 8, and 85 at pH 8.6."[73] Philip Morris maintained that because its cigarettes had a pH of about 6, nearly 99% of its nicotine was in the form of a protonated salt. So whatever effect ammonia might be having on the percentage of freebase nicotine, and thus the rate of nicotine "delivery," would be trivial.

From experiments performed by other companies, however, we know that even very slight increases in pH can have a significant effect on the availability of freebase nicotine in smoke. Recall Brown and Williamson's 1980s demonstration that Merit cigarettes had only half the total nicotine of Marlboro cigarettes while still delivering the same amount of free nicotine, thanks to only a 0.5 increase in pH. The companies were also aware that pH provides only an imperfect estimate of free nicotine availability.[74] Wayne, Connolly, and Henningfield have reviewed the industry's internal documents on freebasing and shown that free nicotine levels of Philip Morris's and other companies' cigarettes were significantly higher than those predicted from pH values alone.[32]

Company officials also argued that while ammonia might well increase the rate of nicotine delivery, the same total amount of nicotine was delivered nonetheless. Rate of nicotine delivery, though, is a key aspect of addiction. That is one reason nicotine gums and patches usually cannot deliver the same "satisfaction" as smoking: lung deliveries are far more intense, and freebasing only heightens this effect. A 1994 draft report on experiments conducted at Philip Morris's secret research center (INBIFO) in Cologne, Germany, conceded that when subjects inhaled the same amount of nicotine at different pH levels, those who inhaled at higher alkalinity experienced faster rates of entry of nicotine into the bloodstream.[75]

DISGUISING THE USE OF AMMONIA AS A FREEBASING AGENT

In their attempts to defend against charges of freebasing, Philip Morris and the other companies took advantage of ammonia's innocuous uses to draw attention away from its freebasing ability. Tobacco executives argued: how could ammonia, a natural compound found in tobacco, food, fertilizer, pesticides, and many other everyday products, have this secret ability to control nicotine levels? In a 1994 Tobacco Institute response to FDA Commissioner David Kessler we find such arguments, along with the claim that ammonia's most important use was in reconstituted tobacco, "so the blended leaf sticks together."[76] This same document suggests that the idea of the FDA regulating tobacco was ludicrous, making no more sense than the FDA regulating coffee or beer. (Philip Morris has since reversed course and now argues in favor of FDA regulation, hoping this regulation will help preserve its position as the nation's number one cigarette maker.)

There are many other industry pronouncements from the 1990s that attempt to draw attention away from ammonia's freebasing function. A 1994 Brown and Williamson document (prepared for use in public relations or litigation) points out that ammonia and its many derivatives are found in everyday foods: ammonium bicarbonate in baked goods; ammonium hydroxide in cured pork; diammonium phosphate in dough, ice cream, and gelatin; and ammonium sulfide in baked goods and meats. And ammonia itself is found in human breath.[77] An RJ Reynolds document insists that the industry's uses of ammonia "are similar to many of the applications commonly used in the food industry."[78]

Philip Morris has also tried to exonerate ammonia by emphasizing its roles as a flavorant and pectin-releaser.[79] In *Iron Workers v. Philip Morris*, Harold G. Burnley Jr, the company's former vice president of operations, was asked, "Is it true that Philip Morris uses ammonia for the purpose of increasing a nicotine kick?" He answered, "No, sir . . . it was used really initially in BL [blended leaf] to hold the sheet together, and it was used as a flavorant in RL [reconstituted leaf]."[80] In 1997, Philip Morris lawyers interrogated their company's former director of applied research about his claim that ammonia was used to increase nicotine availability, asking, in so many words: how do you know it's not just a flavor thing?[81] Pankow was questioned along similar lines in *Washington v. American Tobacco Co*, with lawyers for the defense asking how he could be sure that the increase in nicotine delivery was from the ammonia added and not the ammonia already present in the tobacco.[82] Similar rationalizations were put forward at the industry's second Annual Ammonia Technology Conference, where we hear that ammonia simply "enhances processes that occur *naturally* during tobacco and cigarette aging and during combustion."[83]

Philip Morris and the other tobacco companies also split chemical hairs by denying they had ever used gaseous ammonia to achieve any kind of freebasing effect.[84] A small truth here hides a larger deception, because it is true that the freebasing effect is not ordinarily achieved by using ammonia in gaseous form. The more usual practice is to use nitrogen-containing compounds such as proteins and amino acids (e.g., lysine) and ammonium salts such as DAP and ammonium tartrate, carbonate, and citrate along with ammonium hydroxide and urea, all of which readily transform into ammonia upon the addition of heat (as when a cigarette is lit). Tobacco manufacturers have also freebased using weakly basic substances that, when heated, convert into more-alkaline compounds (sodium carbonate produces sodium oxide, for example, which turns into sodium hydroxide in the presence of water).[85] Philip Morris in 1994 claimed that even if it *had* been adding ammonia (in a volatile gaseous form) to cigarettes the compound would simply evaporate away, reducing the pH to its normal level before the cigarette was even shipped.[86] That, however, is why most companies use nonvolatile ammonium salts such as DAP as their freebasing reagents: ammonium salts break down into ammonia, increasing the pH of the tobacco and deprotonating the nicotine in the process, but only after the cigarette has been lit.

CRACK NICOTINE?

In the mid-1990s, FDA Commissioner Kessler was using the tobacco companies' recently discovered manipulation of nicotine to argue for the regulation of tobacco.[87] The industry knew that any admission of using ammonia to increase the availability of nicotine would be an admission that nicotine is the addictive sine qua non of smoking, and tobacco manufacturers did not want to have cigarettes compared to crack cocaine. (According to Farone, the industry made a conscious effort in the 1980s and 1990s to avoid the term *freebasing* in any documents or statements because it didn't want to be associated with cocaine.[88]) With so much at stake, it is not surprising that the industry attempted to cover up its use of ammonia as a freebasing reagent.

It is important to keep in mind that the ammonia cover-up is only one of dozens of similar cover-ups, part of the industry's calculated disregard for human health.[89] The industry has tried to efface the truth in depositions and even in internal documents, but the facts are clear: Philip Morris by the early 1960s had realized ammonia's ability to augment the potency of nicotine and then used this knowledge to develop cigarettes that were nominally low in tar and nicotine while still having a powerful nicotine kick. Sales of Philip Morris products skyrocketed as a result, spiking the company to the top of the market charts. And the other manufacturers took notice: RJ Reynolds, American Tobacco, Brown and Williamson, Liggett, and Lorillard all worked hard to figure out Marlboro's secret and by the 1970s and 1980s had developed their own versions of ammonia technology, which all but Liggett implemented commercially.

It should also be noted that freebasing represented a reversal of a decades-old effort to make cigarettes "milder." The first major US cigarette brand, Camel, introduced in 1913, succeeded on the basis of its use of a flavored blend of oriental, burley, and flue-cured Virginia tobaccos, producing a milder and more inhalable smoke than previous generations of tobacco products. Flue-cured "bright" tobacco blends were less alkaline and therefore easier to inhale than traditional varieties, notably those used in the pipe and

cigar trade, where tobaccos were typically high in pH (circa 8) but generally too harsh to inhale. Cigarette makers modified the chemistry of tobacco throughout the 1930s and 1940s, seeking to produce an ever-milder smoke that could be inhaled without stimulating coughing. When demand for lower-tar and lower-nicotine cigarettes arose in the 1950s and 1960s, however, the industry realized there were limits to how low nicotine levels could go without "weaning"[90] smokers from their habit. Cigarette manufacturers worried about producing an "emasculated"[91] cigarette devoid of flavor and missing the grip of addiction. Freebasing solved a big part of this problem, because tar and nicotine levels could now be lowered—up to a point—without the risk of losing customers. Teague at Reynolds in 1973 summarized the achievement: "As a result of its higher smoke pH, the current Marlboro, despite a two-thirds reduction in smoke 'tar' and nicotine over the years, calculates to have essentially the same amount of 'free' nicotine in its smoke as did the early WINSTON."[92]

It is not yet clear to what extent manufacturers in other parts of the world—for example, China and Japan—use ammonia in the manufacture of their cigarettes; this topic deserves further study. Diammonium phosphate is not legal for use in cigarettes in Austria, Germany, or Spain;[93] does this mean that freebasing is achieved by other means? Nicotine yields of American cigarettes have risen steadily over the past few years[94]: could this mean a retreat from the practice of ammoniation in favor of other methods of nicotine manipulation?

What is not in doubt is that the continued pull of nicotine has generated a global epidemic of lung and heart disease. Tobacco has become the world's single largest preventable cause of premature death, accounting for about 5 million fatalities per annum, a number expected to grow to about 10 million per year over the next couple of decades.[95] There is also tragedy, though, in the fact that so many scholars have helped to perfect and enhance this terrible technology of mortality. Tens of billions of dollars have been spent by the industry on tobacco chemistry[96] in the decades since British and American scientists followed the Germans in proving that smoking could cause lung cancer and heart disease.[97] Cigarettes are among the most carefully (and craftily) designed small objects on the planet, but they also cause more death and disease than any other invention since humans first learned how to spark fire from stone and metal. We should not be so surprised that the industry has manipulated cigarette chemistry to keep people smoking; what is surprising, though, is how easily they have gotten away with it. ■

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APPENDIX B

11746

Influence of pH on Absorption of Nicotine from Urinary Bladder and Subcutaneous Tissues.

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It has been shown that the pH plays an important rôle in the absorption of alkaloids from the stomach.[1] So far as we know, no studies are available as to the influence of this factor on the absorption of these compounds from the urinary bladder. It seemed likely, however, that this membrane might behave like the gastrointestinal mucosa and absorb alkaloids quite rapidly from alkaline solutions. Nicotine was selected for the study because of the possibility that its reabsorption from the urinary bladder may be a source of poisoning in heavy tobacco smokers when the urine becomes alkaline.[2]

Experiments were carried out, therefore, to determine the influence of the pH on the absorption of nicotine from the urinary bladder. Under light ether anesthesia the ureters were ligated in 10 cats and a cannula inserted in the urethra for injection. The bladder was washed with physiological salt solution, and nicotine was injected in a buffered solution. Phthalates, phosphates and sodium bicarbonate were used as buffers. The volume of fluid injected in each experiment was 5 cc per kg. The pH of the solution injected into the bladder and of that recovered from the bladder 4 hours later or at death was determined electrometrically (glass electrode).

The results are shown in Table I. Figures are given for the time of onset and duration of the advancement of the nictitating membrane; the duration of this effect parallels closely the degree of nicotine poisoning. It may be seen that at pH levels of about 4.5 to 6.0, doses of 10 and 20 mg of nicotine produced no effects. Similar doses at pH levels of about 7.0 to 7.9 produced fairly marked poisoning; advancement of the nictitating membrane appeared in 20 to 30 minutes after injection and was present for an average of 53 minutes. At pH levels of about 8.0 to 9.0, 10 mg caused very severe

* With the assistance of Charles Salzman, B.S.

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2 Travell, J., Bodansky, O., and Gold, H., *J. Pharm. and Exp. Ther., Proc.*, 1940, **69**, 307.

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TABLE I.
Influence of pH on Absorption of Nicotine from Ligated Urinary Bladder.

Cat No.	pH of solution injected into bladder	pH of solution recovered from bladder*	Dose of nicotine injected into bladder† mg per kg	Advancement of nictitating membrane: onset, min	Advancement of nictitating membrane: duration, min	Degree of nicotine poisoning	Calculated concentration of undissociated nicotine base in solution injected
1	4.6	4.7	10	—	0	None	1:1,250,000
2	5.4	5.8	20	—	0	"	1:83,000
3	7.2	7.0	10	24	19	Moderate	1:3,300
4	7.9	7.4	10	21	50	Marked	1:1,000
5	7.0	6.8	20	30±	54	"	1:2,500
6	7.9	7.0	20	20	90	"	1:520
7	8.6	8.1	10	5	180	Very marked	1:630
8	8.7	8.1	10	10	148	" "	1:590
9	9.0	9.0	20	5	—	Fatal 17 min	1:270
10	9.0	8.9	20	6	—	" 40 "	1:270

*4 hours after injection or at death.
†Injected in a volume of 5 cc per kg.

nicotine poisoning; advancement of the nictitating membrane appeared much sooner and persisted for a much longer period of time, 2½ to 3 hours. At these latter pH levels 20 mg proved fatal. These results indicate that nicotine may be absorbed by the urinary bladder and that within a certain range the higher the pH, the more rapid is its absorption.

In Table I a correlation is shown between the degree of nicotine poisoning and the concentration of undissociated nicotine base. The latter was calculated in accordance with the formula which we have previously derived,[1] taking the dissociation constant of nicotine[3] as 9×70^{-7}.† At the pH values used in these experiments, the percent of total alkaloid present as undissociated base varied through a wide range: approximately 0.04% at pH 4.5, 0.2% at pH 5.0, 1% at pH 6.0, 10% at pH 7.0, 52% at pH 8.0, and 92% at pH 9.0. Taking into account the dissociation and the dose of nicotine and the volume of the solution, the concentration of undissociated nicotine base in the solution injected into the bladder was found to range from 1:1,250,000 in Cat 1 to 1:270 in Cats 9 and 10. At the lowest concentrations of undissociated base, 1:83,000 or lower, no nicotine effects were observed. At concentrations of about 1:3,000 to 1:1,000, moderate to marked poisoning occurred; the average duration of advancement of the nictitating membrane was 41 minutes. At a concentration of about 1:600, nicotine effects were more

[3] Craig, L. C., and Hixon, R. M., *J. Am. Chem. Soc.*, 1931, **53**, 4367.

† Thus, $\frac{[\text{Undissociated nicotine}]}{[\text{Nicotine ions}]} = \frac{1 \times 10^{-14}}{(9 \times 10^{-7})\ (1 \times 10^{-\text{pH}})}$

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marked and the average duration of the nictitating membrane advancement was 139 minutes. At a concentration of 1:270, death occurred. These results indicate that the rate of absorption of nicotine from the urinary bladder depends to a large extent on the concentration of undissociated nicotine base.

Two experiments were reported[1] in which nicotine was injected into the ligated stomach of the cat. Twenty-four hours after the injection of 50 mg per kg in acid solution (pH 1.2), the pH of the gastric fluid was 4.2, and nicotine effects had not been observed. Injected at a pH of 8.6, 20 mg per kg was fatal in 41 minutes. In these experiments the volume of fluid was 15 cc per kg, and the calculated concentration of undissociated nicotine base in the solution injected was approximately 1:15,000,000 in the case of the acid medium, and 1:900 in the case of the alkaline medium. As we have seen, concentrations of the base of about 1:500 to 1:1,000 injected into the urinary bladder caused severe poisoning, but did not prove fatal. However, if allowance is made for the greater absorbing surface of the stomach as compared with that of the bladder, the rates of absorption of nicotine by the membranes of these 2 organs appear to be of the same order.

The influence of the hydrogen ion concentration on the speed of absorption of an alkaloid from the subcutaneous tissues has not heretofore been studied directly, but Moore and Row[4] found nicotine base to be 5 times as active as its hydrochloride when injected subcutaneously in the frog. Haag and Neale[5] more recently reported that the toxicity of nicotine‡ injected subcutaneously in mice was only slightly greater than that of nicotine sulfate or salicylate. We have found that when nicotine is injected subcutaneously (within the inguinal fold of skin) in cats in a buffered solution in a constant volume of fluid, 5 cc per kg as employed in the bladder, the pH plays a rôle in the speed of absorption as indicated by the interval to death, and by the M.L.D. (Table II). When the pH was reduced from an alkaline to an acid value and at the same time the dose of nicotine was increased by 33%, the average interval to death was prolonged from 32 minutes to 102 minutes. When the pH was similarly reduced from 9.0 to 4.8 but the dose of nicotine increased by 66%, the average interval to death was the same, namely, 32 minutes at the acid and alkaline pH. The dose of nicotine which proved fatal in the majority of animals when injected at an alkaline

[4] Moore, B., and Row, R., *J. Physiol.*, 1897, **22**, 273.

[5] Haag, H. B., and Neale, R. C., *J. Pharm. and Exp. Ther., Proc.*, 1940, **69**, 289.

‡ We have determined that a 1% solution of nicotine in the form of the base has a pH of about 10.1, and in the form of the sulfate, a pH of about 4.3.

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TABLE II.
Influence of pH on Absorption of Nicotine from Subcutaneous Tissues.

Dose of nicotine* mg per kg	pH of solution injected	No. cats	No. died	Avg time injection to death, min
6	9.0	6	0	—
7.5	9.0	6	0	—
9	9.0	6	5	32 (25-36)
9	4.8	6	0	—
12	4.8	6	2	102 (50-304)
12	6.4	6	3	
15	4.8	6	4	32 (24-50)

*Injected in a volume of 5 cc per kg.

pH was 9 mg per kg, and at an acid pH was 15 mg per kg; 9 mg per kg injected at an acid pH was fatal in none. Thus within a certain critical range of pH and dosage both the M.L.D. of nicotine and the interval to death may be materially increased by lowering the pH of the solution injected. The use of a buffer in our experiments might explain the apparent discrepancy between these results and those of Haag and Neale.[5]

These experiments indicate that the absorption of nicotine is greater from subcutaneous tissues than from the urinary bladder, when injected at similar pH values and in the same volume of fluid. In the case of the urinary bladder, the amount of fluid injected remained unchanged, and hence as nicotine was absorbed, its concentration necessarily decreased. This fact would result in a diminishing rate of absorption, and provided the initial concentration was not high enough to cause death, nicotine effects would disappear while appreciable amounts of nicotine still remained in the bladder. When given by the subcutaneous route, the fluid was rapidly absorbed; this fact would tend to maintain the original concentration of nicotine, to prevent the slowing down of absorption and to insure virtually complete absorption of the alkaloid. That in the latter case there may actually be a rising curve of absorption is shown by the fact that in one experiment 20 mg per kg injected subcutaneously at a pH of 7.0 caused death after as long as 5 hours. In this case the increasing rate of absorption could scarcely be explained by a changing pH. It is obvious that owing to the number of variable factors a comparison cannot be made as to the influence of the pH alone on the speed of absorption of nicotine from subcutaneous tissues and that from the urinary bladder.

Summary. These experiments show that the hydrogen ion con-

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centration plays an important rôle in the absorption of nicotine from both the urinary bladder and the subcutaneous tissues. The toxicity of nicotine given by these routes is appreciably decreased when the pH of the solution is reduced within a certain range. At similar pH levels nicotine is absorbed from the urinary bladder and from the stomach at essentially similar rates. Absorption of nicotine from the subcutaneous tissues is greater than from the urinary bladder when the alkaloid is injected at similar pH values, but the impossibility of controlling the factors which influence absorption from the subcutaneous tissues precludes direct comparison as to the rôle of the pH alone.

A correlation is shown between the rate of absorption of nicotine from the urinary bladder and the calculated concentration of undissociated nicotine base in the solution injected.

The ligated urinary bladder provides a technic for the study of factors influencing absorption which is in some respects more satisfactory than the ligated stomach or intestinal loop, owing to the greater ease of controlling in the bladder certain variable factors such as the volume of fluid and the pH.

11747

Effect of N′-Dodecanoylsulfanilamide and of Sulfapyridine on Experimental Tuberculosis in Rabbits.*

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N′dodecanoylsulfanilamide was synthesized by Crossley, Northey, and Hultquist[1] and proposed as a possible chemotherapeutic agent against tuberculous infections. Climenko[2] has recently shown it to be capable of inhibiting the growth of human tubercle bacilli *in vitro*. He also reported that it exerts an inhibitory effect against the development of experimental tuberculosis in guinea pigs infected with

* This study was aided by a gift from the late Mr. George L. Bourne. The dodecanoylsulfanilamide and the sulfapyridine used in this experiment were supplied by the Calco Chemical Company through the courtesy of Dr. D. A. Bryce.

1 Crossley, M. L., Northey, E. H., and Hultquist, M. E., *J. Am. Chem. Soc.*, 1939, **61**, 2950.

2 Climenko, D. R., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 624.

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APPENDIX C

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M.D., Ph.D.

The official journal of the International Society for Aerosols in Medicine

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Deposition, Clearance, and Effects in the Lung

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Deposition, Clearance, and Effects in the Lung

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Effect of pH on Nicotine Absorption and Side Effects Produced by Aerosolized Nicotine

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ABSTRACT

Nicotine aerosol could prove to be a useful aid to smoking cessation. In previous studies, subjects complained of unpleasant side effects that seemed to be due to local irritation from the inhaled aerosol. The purpose of the current study was to compare nicotine absorption and side effects from inhalation of nicotine aerosols of varying pH. Ten healthy smokers inhaled aerosols made from nicotine solutions with a pH of 11, 7.5, or 5.6. The measured particle size was 8.5 μm MMAD. We measured serial plasma nicotine concentrations and evaluated 4 side effects: cough, throat burning, dizziness, and salivation. Increasing pH was associated with a higher mean rise in plasma nicotine concentration. However, there was no difference in the incidence of side effects seen with the three aerosols. We conclude that a more alkaline aerosol enhances absorption from the respiratory tract. The large particle size may be responsible for the apparent irritant effects of the aerosol and the relatively large dose required to achieve levels comparable to cigarette smoking.

INTRODUCTION

Delivery of nicotine as an aerosol may have potential in nicotine replacement therapy for smoking cessation. Optimal nicotine replacement may require reproducing the rapid peak nicotine levels seen in cigarette smoking, so that the smoker's nicotine dependency can be temporarily satisfied while the behavioral aspects of smoking can be treated (1). Nicotine gum and transdermal nicotine patches, the only commercially available forms of nicotine replacement, fail to achieve the rapid peak nicotine levels produced by smoking (2-4). Long-term success rates with nicotine gum have been modest, though superior to placebo gum when used in conjunction with behavior modification (5-7). Less is known about the potential for long-term success with transdermal nicotine patches (8,9). Due to the tremendous impact of cigarette smoking on our nation's health, there is an urgent need for better methods of smoking cessation.

In a previous study, we gave 5 mg of aerosolized nicotine with a pH of 11 to smokers and produced nicotine levels which were similar to those reached with cigarettes and superior to those

KEY WORDS: Nicotine aerosol, smoking cessation, particle size, nicotine addiction

produced by 2 mg nicotine gum (10). Cough was a limiting side effect in that study. Other investigators have shown that the free base form of nicotine, which predominates at an alkaline pH, is absorbed more efficiently across mucous membranes than the salt form at an acidic pH (11). Since cigar smoke is alkaline whereas cigarette smoke is acidic, the pH of cigar smoke may contribute to its greater irritant effect on the airway (12,13).

We postulated that increasing the pH of the nicotine aerosol might facilitate nicotine absorption but might also increase the side effects produced by the aerosol. The purpose of this study was to compare nicotine absorption and side effects from inhalation of nicotine aerosols of varying pH.

SUBJECTS AND METHODS

Subject Selection

We recruited 10 healthy smokers for the study. Nine of these were healthy hospital employees. The subjects ranged in age from 28 to 60 with a mean age of 40. No subject had significant past or present illness by history, and all were current smokers. The subjects smoked an average of 26 cigarettes per day (range, 10 - 40). All gave informed consent for the study.

Nicotine Solutions

The solutions for aerosolization were prepared by first mixing L-nicotine (Eastman Kodak, Rochester, N. Y.) with normal saline to a concentration of 130 mg/ml. This solution had a pH of 11. Additional solutions with pH's of 7.5 and 5.6 were made by titration with hydrochloric acid.

Aerosol Production

A dosimeter (Erich Jaeger GmbH & Co. KG, Würzburg, Federal Republic of Germany) equipped with a Sandoz jet nebulizer was used to produce the aerosol. A diagram of the dosimeter is shown in Figure 1. This dosimeter generates the aerosol just after the beginning of inspiration and accurately controls the quantity, timing, and duration of aerosolization. A pressure transducer located adjacent to the mouthpiece detects when the subject generates negative 2 mm of water pressure. At this point a compressor is activated. The driving pressure of the compressor was measured and found to be 15 psi. The duration of aerosolization can be preset to a desired time interval during inspiration. A flow rate was calculated for the nebulization container by aerosolizing a solution of normal saline for a preset time and weighing the container plus saline before and after aerosolization. By this method, our dosimeter was found to deliver 0.0062 ml/sec. Each aerosolization or "puff" was 0.6 seconds in duration. Using the solution described above, this combination would be predicted to give a dose of 0.484 mg of nicotine per puff. To confirm that this amount of nicotine was really being delivered, we did several trial runs in which we collected the aerosolized nicotine onto filters and extracted the nicotine, which was then quantified by gas chromatography. A calibrating syringe was used to mimic a subject's tidal breathing. One 500 ml "breath" was drawn every 30 seconds for 5 minutes to trigger 10 nebulizations as in the subject trials. This process was carried out four times and the results were averaged.

Aerosol Particle Size

We measured the particle size output of the Sandoz nebulizer, since the solution itself might influence the particle size. Particle size output of nicotine solution was measured by a 6-stage Sierra cascade impactor (Anderson Instruments, Atlanta, GA). Nicotine solution (130 mg/ml) was nebulized in 0.6 second pulses every 30 seconds for 5 minutes and delivered to the cascade impactor, which was attached directly to the mouthpiece of the dosimeter. This arrangement simulated as closely as possible the delivery of nicotine to a human subject. Nicotine was extracted from the filters and the amount collected at each stage of the impactor was measured by gas chromatography.

Inhalation Protocol

Subjects were asked to abstain from smoking for at least 1 hour prior to the inhalation. During each trial, the 4.84 mg of nicotine total dose divided into 10 puffs given 30 seconds apart over a 5

minute period (time 0-5 minutes) during normal tidal breathing beginning at functional residual capacity. Each subject performed one trial with each pH solution for a total of 3 trials. Blood samples were drawn just prior to the beginning of inhalation (time zero) and at 2.5 minute intervals for 12.5 minutes. Samples were put on ice and immediately centrifuged to separate the plasma for analysis. Nicotine extraction was performed according to the method previously described using ethylnornicotine as an internal standard, with subsequent gas chromatographic analysis (14).

Side effects due to the inhalation were evaluated subjectively. Patients were assessed for four side effects: cough, throat burning, dizziness, and salivation. Each symptom was given a score of O (none), 1 (mild), 2 (moderate), or 3 (severe), and these scores were added for a total side effect score. Subjects were informed that if any of the side effects caused excessive discomfort, they could terminate the trial.

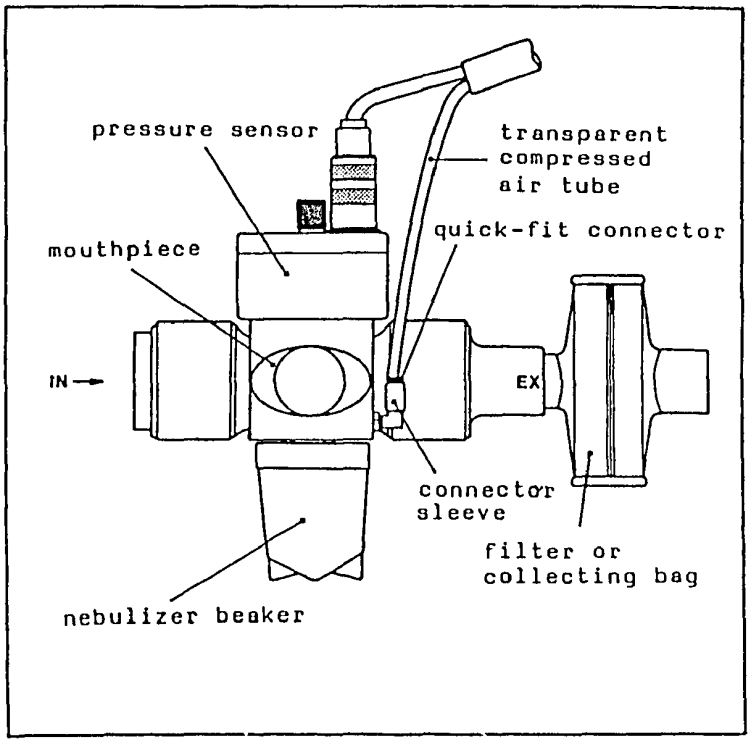


FIGURE 1. Diagram of the Jaeger dosimeter. (Reproduced with permission from Reference 25)

RESULTS

Data from the 4 dose-extraction trials gave a mean extracted dose of 4.57 mg nicotine (range, 4.39 to 4.74 mg). This amount compares favorably with the predicted aerosolized dose of 4.84 mg nicotine.

The measured particle size of the aerosolized nicotine was 8.5 μm mass median aerodynamic diameter (MMAD) with a geometric standard deviation of 2.

The mean plasma nicotine levels rose 8 ng/ml, 12 ng/ml, and 18 ng/ml from baseline to peak levels with aerosols of pH 5.6, 7.5, and 11, respectively (Figure 1). Our subjects had elevated baseline nicotine levels due to recent smoking, and there was no significant difference in the mean baseline for the 3 pH trials. The peak nicotine level for each pH occurred at 7.5 minutes.

Plasma nicotine levels versus time demonstrated that increasing aerosol pH correlated with higher nicotine levels (Figure 2).

The increase in nicotine level (baseline to peak) at each time interval for each pH solution was analyzed and the results are displayed in the table. An analysis of variance showed a significant

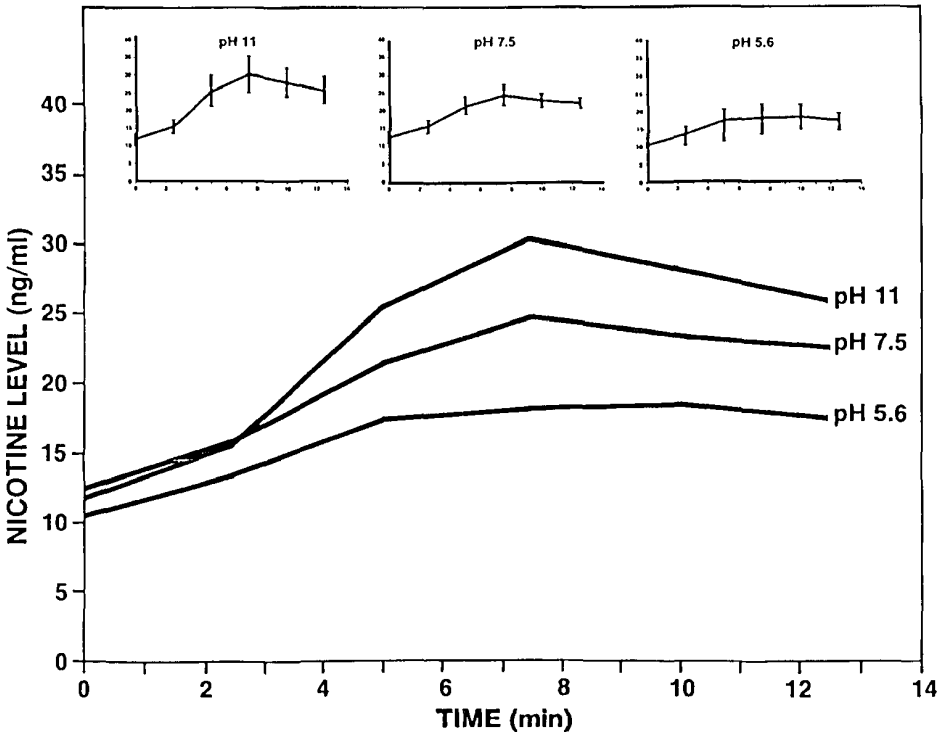


FIGURE 2: Plasma nicotine levels versus time after inhalation of nicotine aerosol of pH 5.6, 7.5, and 11. Inserts show S.E.M. for each pH.

difference in the nicotine levels produced by the three aerosols at 7.5 and 10 minutes ($p < 0.05$). Comparative t-tests between pH pairs at these time periods showed a significant increase in plasma nicotine levels for all comparisons except pH 5.6 versus pH 7.5 at 7.5 and 10 minutes.

TABLE
T-test Comparisons Between pH Pairs at 7.5 and 10 Minutes

	p value	
pH Comparisons	7.5 min	10 min
5.6 vs 11	.021*	.018*
5.6 vs 7.5	.051	.112
7.5 vs 11	.037*	.029*

*Significant difference at the $p < 0.05$ level.

Four side effects were observed during the inhalation: cough, throat burning, dizziness, and salivation. The means of the sums of the side effect scores were 3.2, 3.5, and 3.0 for pH 5.6, 7.5, and 11, respectively. The mean score for each individual side effect did not appear to differ among the three pH groups (Figure 3).

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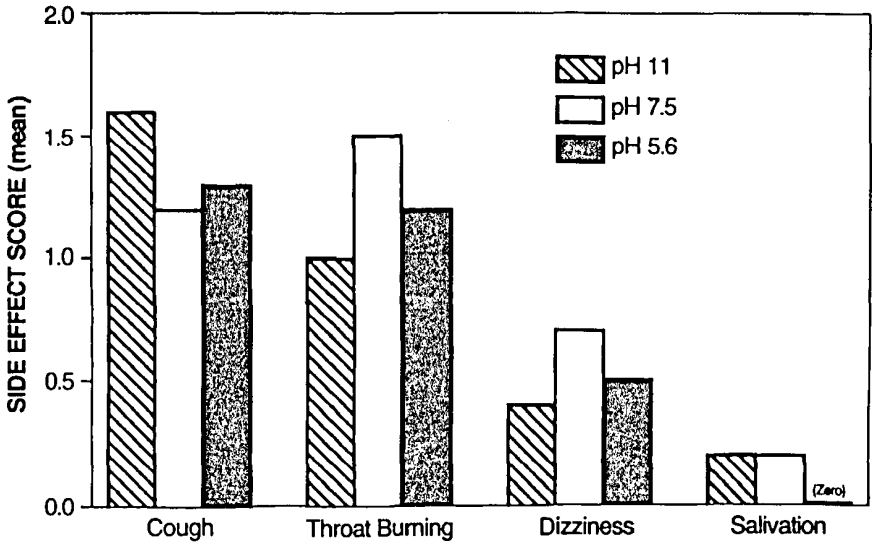


FIGURE 3: Mean score for each side effect at pH 5.6, 7.5, and 11.

DISCUSSION

Our data indicated that the pH of the nicotine aerosol significantly affects the absorption of nicotine. Increasing the aerosol pH produced significantly higher peak plasma nicotine levels. These results were similar to previously reported effects of pH on nicotine absorption across mucous membranes (11). An appreciable rise in nicotine level occurred rapidly with each pH, however. This finding is in agreement with earlier reports that aerosol absorption of nicotine is less pH-dependent than absorption across buccal mucosa (15).

The pH of the nicotine aerosol did not alter side effects. This finding was somewhat surprising, since cigar smoke is reported to be more irritating to the airways and is known to be more alkaline than cigarette smoke. Cigar smokers may inhale less than cigarette smokers due to the irritant effects of the cigar smoke (11,12).

We had previously hypothesized that particle size might be responsible for some of the side effects seen with aerosolized nicotine (16). In the current study, we measured the particle size that resulted when nicotine solution was aerosolized from the Sandoz nebulizer. We found a fairly large mass median diameter of 8.5 μm. Particles of this size are predicted to deposit preferentially in the upper airways (17). Using the theoretical model of Rudolf and coworkers and conditions simulating the nicotine exposure, predicted deposition is as follows: laryngeal 55%, tracheobronchial 9%, and acinar 12% (18). This degree of laryngeal deposition may have contributed to our subjects' symptoms of cough and throat irritation.

The relatively large particle size creates a potential paradox with respect to our attempt to understand the site of absorption of the nicotine aerosol. Cigarette smoke contains much smaller particles, which have been shown to deposit in distal lung regions. The smoke also contains nicotine in a vapor phase. Cigarette smoking produces peak nicotine levels as rapidly as when nicotine is given intravenously (15). This phenomenon has been presumed to be due to distal lung absorption (15). Studies in both dogs and humans have shown that nicotine solution instilled into peripheral lung units via a catheter produces nicotine levels as rapidly as the intravenous route, while absorption from solution placed into the trachea is much slower (19,20). Nasal nicotine solution has also been shown to produce rapid peak levels . Peak levels of nicotine from nicotine gum and transdermal patches have been shown to occur much more slowly than with either cigarette smoke or intravenous nicotine (2-4). These findings supported the idea that rapid peak levels required deposition in either the distal lung or the nasal passages. In our study, rapid absorption occurred with an aerosol whose particle size would not be expected to achieve much distal lung deposition.

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The relatively large total dose of nicotine that we gave may help to explain our findings. The dose used was four to five times that of a standard cigarette, yet it only increased the nicotine level by 8 to 18 ng/ml, which is at the lower range of levels produced by one cigarette. We speculated that despite the large MMAD of the aerosol, at high doses a sufficient number of smaller particles must have reached distal lung regions. While we cannot completely rule out the possibility that nicotine was rapidly absorbed from sites in the oropharynx and large airways, the previous studies cited do not support this idea (11,19,20).

Lux and Frecker reported that they prepared a small-particle nicotine aerosol with a MMAD of 0.5μm (22). The pH of the aerosol was 5.5, and the calculated inhaled dose was 1 mg. They measured nicotine levels every five minutes for one hour and reported a mean peak nicotine level of 46 nmol/liter, or 7.6 ng/ml . However, the baseline nicotine level and the timing of the peak were not reported.

It is not known whether a nicotine aerosol could be used as a form of nicotine replacement during smoking cessation. Our findings point out practical considerations of efficiency and side effects which in theory might be overcome with a small-particle aerosol. Whether a nicotine aerosol would prove effective in the cessation process is even less clear. Two forms of nicotine replacement are available: nicotine gum and transdermal nicotine patches. Nicotine absorption from both forms is slow, so that prevention of withdrawal-related cravings relies on maintaining a constant blood level of nicotine to ease symptoms throughout the day. This level is very low with the currently available 2 mg gum, and the patient must chew the gum all day long to maintain even these low levels, so compliance has been a problem. Peak nicotine levels reported with nicotine patches have generally been higher than from 2 mg nicotine gum (3,4), and the patch is easier to use. Still, the relapse rate with nicotine patches has been very high (8,9). Thus, there have been some apparent advances in nicotine substitution therapy without proven improvement in long-term quit rates. The high relapse rate has focused attention on the need for improved behavioral therapy and relapse prevention.

Russell and Feyerabend proposed that it may be the puff-by-puff nicotine bolus effect of cigarette smoking that leads to such fierce dependence, not just to nicotine itself but to that particular form of nicotine, so that other forms of nicotine do not satisfy (15). Nicotine aerosol would provide a pattern of nicotine substitution that would be more like the use of cigarettes. In theory, it might be more successful in preventing withdrawal symptoms, allowing more patients to achieve initial abstinence from smoking. However these same features, such as the rapid onset of action and the potential for high blood levels, are factors that might increase the potential for physical or behavioral dependence on the aerosol nicotine itself (23). It has been suggested that patients might vary in their degree of dependence on peak levels, trough levels, or combinations (15). Successful nicotine substitution might ultimately utilize multiple modalities that could be tailored to each patient. Benowitz proposed that more studies be done to evaluate the potential of rapid-delivery systems, such as nicotine aerosol, particularly in combination with slow-delivery systems like gum or transdermal patches (24).

In summary, we have shown that inhalation of an aerosolized nicotine solution produced rapid peak plasma levels that increased significantly as the aerosol pH was increased. Side effects were not affected by differences in pH and were thought to be due to the large particle size of the aerosol . Further study would be needed to determine whether this form of nicotine could be used successfully as nicotine substitution during smoking cessation.

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APPENDIX D

ORIGINAL INVESTIGATION

Nicotine Delivery to Rats via Lung Alveolar Region-Targeted Aerosol Technology Produces Blood Pharmacokinetics Resembling Human Smoking

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ABSTRACT

Introduction: Nicotine is a heavily used addictive drug acquired through smoking tobacco. Nicotine in cigarette smoke is deposited and absorbed in the lungs, which results in a rapidly peaked slowly declining arterial concentration. This pattern plays an important role in initiation of nicotine addiction.

Methods: A method and device were developed for delivering nicotine to rodents with lung alveolar region-targeted aerosol technology. The dose of delivery can be controlled by the nicotine aerosol concentration and duration of exposure.

Results: Our data showed that, in the breathing zone of the nose-only exposure chamber, the aerosol droplet size distribution was within the respirable diameter range. Rats were exposed to nicotine aerosol for 2 min. The arterial blood nicotine concentration reached 43.2 ± 15.7 ng/ml (mean ± *SD*) within 1–4 min and declined over the next 20 min, closely resembling the magnitude and early pharmacokinetics of a human smoking a cigarette. The acute inhalation toxicity of nicotine: LC_{50} = 2.3 mg/L was determined; it was affected by pH, suggesting that acidification decreases nicotine absorption and/or bioavailability.

Conclusions: A noninvasive method and toolkit were developed for delivering nicotine to rodents that enable rapid delivery of a controllable amount of nicotine into the systemic circulation and brain-inducing dose-dependent pharmacological effects, even a lethal dose. Aerosol inhalation can produce nicotine kinetics in both arterial and venous blood resembling human smoking. This method can be applied to studies of the effects of chronic intermittent nicotine exposure, nicotine addiction, toxicology, tobacco-related diseases, teratogenicity, and for discovery of pharmacological therapeutics.

INTRODUCTION

Tobacco smoking is the leading *preventable* cause of disease, disability, and death. Nicotine, a major component of tobacco, is highly addictive, underlying the fact that smokers quickly become addicted—about 1,200 per day in the United States (NIH/NIDA, 2008)—and have great difficulty quitting. To understand the numerous effects of nicotine and to develop more effective and safer medications for smoking cessation as well as for treatment of tobacco-related diseases, animal models relevant to human nicotine exposure are required.

In smokers (and often in those exposed secondhand), exposure to nicotine is chronic and intermittent. Cigarette smoke is an aerosol containing tiny particles within the respirable diameter range (Gowadia, Oldham, & Dunn-Rankin, 2009; Hinds, 1978). Respirable diameter is defined as the aerodynamic diameter of particles capable of reaching the gas exchange region in the lungs (the alveoli) for the organism under study (OECD, 2009). Cigarette smoke particles deposit in the alveoli, where nicotine crosses the pulmonary membrane into the circulation.

Inhalation of cigarette smoke leads to a rapid increase in arterial blood nicotine concentrations. When a human smokes one cigarette (takes ~5 min), their arterial blood nicotine concentration reaches its maximum (C_{max}) of 20–60 ng/ml in 3–5 min (T_{max}), which then declines over the next 20 min due to rapid distribution to all body tissues; the venous blood nicotine reaches C_{max} of 15–30 ng/ml in T_{max} of 5–8 min (Benowitz, Porchet, Sheiner, & Jacob, 1988; Henningfield, Stapleton, Benowitz, Grayson, & London, 1993; Hukkanen, Jacob, & Benowitz, 2005; Rose, Behm, Westman, & Coleman, 1999).

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Nicotine reaches the brain within ~8–10 s of inhalation (Matta et al., 2007) and it accumulates in the brain to its maximum value within 3–5 min (Rose, Mukhin, et al., 2010). Episodic exposure to nicotine in this pharmacokinetic pattern strongly stimulates brain nicotine receptors, inducing numerous psychological and behavioral effects and, eventually, nicotine dependence.

For drug abuse studies with animal models to be relevant to humans, the routes of drug administration as well as the blood pharmacokinetics and target tissue concentrations should be comparable between humans and animals (Brent, 2004; Matta et al., 2007). Commonly used nicotine administration methods for in vivo animal models include the following: (a) Oral application, for example, nicotine dissolved in drinking water. In this case, 70% of nicotine is metabolized in the liver, with only ~30% entering the systemic circulation (Matta et al., 2007). Moreover, oral nicotine absorption is slow compared to that during smoking. (b) Intraperitoneal (i.p.), subcutaneous (s.c.), or intravenous (i.v.) injection of nicotine. These methods are invasive and inconvenient for chronic intermittent exposure. In addition, i.p. nicotine delivery is affected by the first-pass liver metabolism. (c) Subcutaneous osmotic pump delivery (Epping-Jordan, Watkins, Koob, & Markou, 1998; Theeuwes & Yum, 1976). Here, delivery is slow (hours) and continuous. A slowly rising concentration of nicotine results in desensitization without activation of some types of nicotinic receptors (Dani & De Biasi, 2001). In contrast, episodic smoking induces periods of activation followed by a cycle of desensitization/resensitization (Matta et al., 2007). Unfortunately, some nicotine-stimulated neurotransmitter responses, such as increases in dopamine release in the nucleus accumbens (Balfour, 2004; Fu, Matta, Gao, Brower, & Sharp, 2000) or elevated norepinephrine secretion in the paraventricular nucleus (Fu, Matta, Brower, & Sharp, 2001; Sharp & Matta, 1993), depend upon sufficient and rapidly rising brain nicotine concentrations. Moreover, neurobehavioral plasticity and development of addiction are profoundly affected by whether the exposure is continuous or episodic (Rothwell, Gewirtz, & Thomas, 2010; Skjei & Markou, 2003). (d) Intravenous self-administration. This technique is invasive. Surgically implanting the catheter and maintaining i.v. patency for a long period of time are technically challenging (Corrigall & Coen, 1989; DeNoble & Mele, 2006). (e) Cigarette smoking machines (Beven, 1976; Moir et al., 2008), which are most relevant to human smoking. However, the use of cigarette smoke confounds the specific effects of nicotine with the effects of more than 4,000 other compounds (Borgerding & Klus, 2005); also the amount of nicotine delivered is hard to control. (f) Nicotine vapor inhalation (George, Grieder, Cole, & Koob, 2010; Waldum et al., 1996). Nicotine vapor is the gaseous state of nicotine. The concentration of a substance in a vapor form in air depends on its vapor pressure. Nicotine (freebase) is an oily, nonvolatile liquid (its vapor pressure is >600-fold *lower* than that of water; Meng, Lichtman, Bridgen, & Martin, 1997). Thus, the nicotine concentration in vapor form for inhalation is low. Delivery of nicotine through inhalation of nicotine vapor is slow. Moreover, the amount of nicotine that enters circulation is limited because nicotine vapor mostly deposits and is absorbed in nasal and buccal mucosa, while very little deposits in the lungs (George et al., 2010; Lunell, Molander, Ekberg, & Wahren, 2000; Waldum et al., 1996). Specifically, Bergstrom, Nordberg, Lunell, Antoni, and Langstrom (1995) and Lunell, Bergstrom, Antoni, Langstrom, and Nordberg (1996) used positron emission tomography imaging with radioactive ^{11}C-nicotine for investigating the deposition of nicotine in human subjects. They showed that most nicotine is deposited in the oral cavity and upper airways, while only a minor fraction (5%) of the nicotine is deposited in the lungs when subjects used a nicotine vapor inhaler. In contrast, in subjects who smoked cigarettes, a large fraction of nicotine is deposited in the lungs and a minimal fraction is found in the oral cavity and upper airways. Therefore, animals have to be continuously exposed to the vapor for hours to produce meaningful blood nicotine concentrations comparable to that of human smokers (George et al., 2010). The vapor inhalation method cannot model the kinetic profile of a high and rapid rise followed by a decline in arterial nicotine concentrations seen in cigarette smoking (Henningfield et al., 1993; Lunell et al., 1996, 2000; Rose et al., 1999; Schneider, Olmstead, Franzon, & Lunell, 2001).

Major advances in aerosol technology have led to increasing interest in systemic delivery of drugs by inhalation. Small molecules can be delivered with rapid action, low metabolism, and high bioavailability. Unlike vapor, aerosol is a suspension of small particles in a gas. Brownian diffusion is the dominant mechanism for aerosol particle deposition in the alveolar region. Particle size is critical, as large particles deposit in the airways, mouth, and throat, while particles that are too small can be exhaled, thereby reducing alveolar deposition (OECD, 2009; Patton & Byron, 2007). The purpose of this study was to develop a noninvasive and effective method to deliver nicotine targeting the alveolar region of rodents with advanced aerosol technology. This methodology ensures delivery of adequate and controllable amounts of nicotine into the systemic circulation and brain that mimic the kinetic profile and blood concentration of human cigarette smoking.

METHODS

Animals

All animal use procedures were in accordance with The National Institutes of Health (United States) Guide for the Care and Use of Laboratory Animals and were approved by the UCLA and AfaSci Inc. Institutional Animal Care and Use Committee. Efforts were made to minimize the number of animals used and their pain and suffering. Male Sprague-Dawley rats of 8–11-week-old (body weight 250–400 g) were used in this study. They were housed in the vivarium under a 12-hr light/dark cycle and had *ad libitum* access to food and water.

Nicotine Aerosol Generation and Exposure System

An experimental system was made that included a 3-jet Collison nebulizer (BGI Inc.), an air pressure gauge (Ashcroft® filled gauge, 0–100 psi, Cole-Parmer), an air flowmeter with a valve (150-mm Direct Reading, 23 LPM, Cole-Parmer) that regulated the airflow rate and the pressure entering the nebulizer (Figure 1), a homemade nose-only exposure chamber, and rat holders (Model #: CHT-250, CH Technologies Inc.). Nicotine aerosols with defined droplet size can be consistently generated using a Collison nebulizer. The outlet of the exposure chamber was opened to a fume hood through a plastic tubing. About 30 ml nicotine solution was put in the nebulizer jar.

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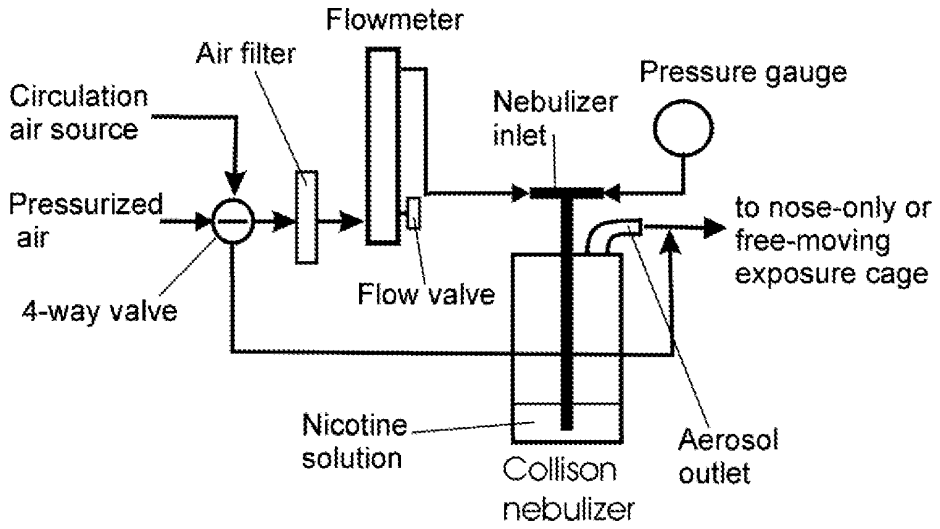


Figure 1. Diagram of nicotine aerosol generation system. The connections ensure constant pressurized air with constant flow rate applied to the nebulizer and minimize the distance from the nebulizer outlet to the respiratory zone of animals (the components of the diagram are not in proportion).

One or two rats can be exposed to nicotine aerosol simultaneously by inserting rat holders into a nose-only chamber. An experimental system where the output of the nebulizer was connected to a sealed cage was made for freely moving rodents. The outlet of the sealed cage was opened to a fume hood. For experimental accuracy, only one rodent was put into the sealed cage. The pressure of the air that enters into the nebulizer for generation of aerosol determines the volume, the droplet size distribution, and the concentration of the output aerosol. The air pressure and flow rate were well controlled and continuously monitored during the nicotine aerosol exposure experiments.

Note: the air flow indicated on a flowmeter (Q_i) under pressure of Pr can be converted to "true" flow rate Q_{stp} under standard conditions, for example, one atmosphere, with the equation:

$$Q_{stp} = Q_i((P_{stp} + \mathrm{Pr})/P_{stp})^{1/2} \quad (1)$$

where P_{stp} is one atmosphere and Pr is pressure in system (Hinds, 1999).

Determination of Nicotine Aerosol Droplet Size Distribution

The experiments were done in a fume hood at room temperature of 22 ± 1 °C. Nicotine (freebase) was dissolved in water or NaCl solution for an osmolality ~300 mOsm/kg. pH was adjusted with HCl to pH 8.0 except those indicated in the Results section.

An Aerodynamic Particle Sizer (APS 3321, TSI Inc.) was used to measure the droplet size distribution of nicotine aerosol generated from nicotine solution at different concentrations in the solution jar of the nebulizer. Since the aerosol was from nebulization of a low vapor pressure liquid (nicotine freebase) dissolved in a relatively volatile solvent (water), the water would evaporate rapidly after droplet formation in general laboratory relative humidity (RH) conditions (Hinds, 1999). To avoid bias in measuring the droplet size, we made a container (volume >11 L [~3 gallons]) with a short inlet tubing (5.2 cm) from the breathing zone of the nose-only chamber. Water was put into the container and sealed it for >2 hr. The RH inside the container was closed to 100% (measured with a Q-Trak Indoor Air Quality Monitor Model 8550, TSI Inc.) (Figure 2). The inlet tubing of the APS sampled the aerosol in the container a short distance away from the breathing zone. In these conditions, evaporation of aerosol droplets entering into the APS was minimized. The container also functioned to dilute the aerosol to avoid saturation of the APS. To further reduce the aerosol droplet concentration to avoid saturation for droplet size distribution measurement, we blocked two of the three holes that supply the liquid to the nozzles. The amount of aerosolized nicotine solution was then reduced to one third of the 3-jets nozzle without changing the airflow. Therefore, the aerosol concentration at the output of the nebulizer would be reduced to one third.

Determination of Nicotine Aerosol Mass Concentration in Air

Mass concentrations of the nicotine aerosol were measured with a one-stage cascade impactor (SKC Inc.). The length of the impactor inlet tubing was minimized and directly connected to the breathing zone of the nose-only chamber. The nebulizer worked as 3-jet nebulizer without modification (the above 3-to-1 jet reduction version of the nebulizer was only for droplet size distribution measurement). Before the assay, the filters (PTFE Membrane Disc Filters, Pall Co.) for the impactor were balanced in a temperature (22 °C) and humidity (49%) controlled environment where the electronic balance (Mettler-Toledo MX5 Microbalance, Mettler-Toledo Inc.) for weighing the filters was located. The filter weight difference between pre- and post-nicotine aerosol collection is the mass collected in a preset duration, for example, 1 min. To compensate the weight loss due to vaporization of the solvent (water) in the filter, we monitored the weight change during a period equivalent to the time needed from the end of aerosol sampling

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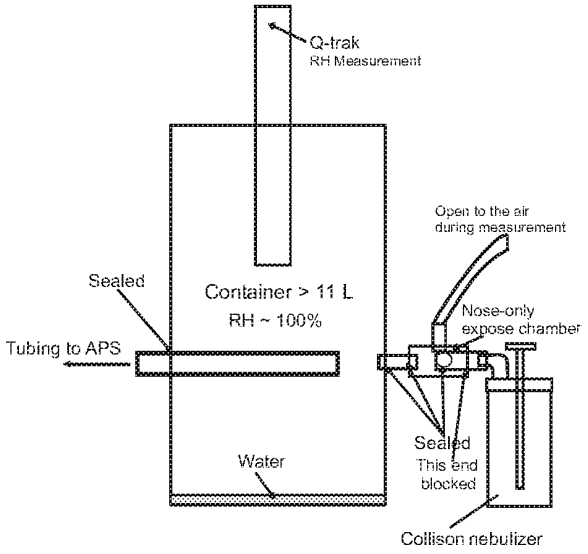


Figure 2. Diagram for measuring droplet size distribution of nicotine aerosol in the nose-only exposure system (the components of the diagram are not in proportion). The measurement was made in a container where the relative humidity was closed to 100% to minimize droplet evaporation. APS = Aerodynamic Particle Sizer.

to the point the filter was weighed on the balance and added this equivalent weight lost to the measured value.

Arterial and Venous Blood Sample Collection and Plasma Nicotine Level Measurement

For arterial blood sample collection, femoral artery pre-catheterized rats (8–9-week-old) were ordered from Harlan Laboratories. For venous blood collection, local anesthetic cream was applied to the rat tail 30 min prior to insertion of the catheter. The rat was put into the rat holder and the tail was warmed with warm water or an infrared light. A temporary catheter (24G) was inserted into the lateral tail vein. Warm saline (2.5 ml) was infused into the arterial or venous catheter for blood volume compensation before blood collection. Then 0.1–0.2 ml of heparin (100 U/ml) was injected.

The first sample as pre-nicotine control was collected. Then nicotine aerosol was generated from the nebulizer and at the same time, a timer was started. The rat was exposed to the nicotine aerosol for 2 min. Blood samples (equivalent to 0.2 ml plasma) were collected at a series of timepoints (see Results section) with 0.6-ml capillary blood collection tubes containing ethylenediaminetetraacetic acid-K_2 (RAM Scientific Inc.). Dropping from the venous catheter was sometimes slow. Bleeding can be greatly facilitated by massaging the tail over the vein.

Samples were centrifuged within 15 min of collection at 1,000 g (gravity) for 12 min at room temperature. Supernatant plasma was transferred to labeled eppendorf tubes and store below −20 °C. The plasma samples were sent to NMS Labs for measurements of nicotine and its metabolite cotinine. The analysis was performed on a Waters TQD MS with ACQUITY UPLC system equipped with an ACQUITY HSS T3 2.1 × 50 mm, 1.8 μm analytical column, with in-line filter and positive-ion electrospray mass spectrometry (LC-MS/MS). Each analytical run was independently calibrated at concentrations of 2.5, 5.0, 15, 50, 150, and 400 ng/ml. Two levels of control were run in each analytical batch. This UPLC method had a lower limit of quantification of 2.5 ng/ml and between run % CV's (coefficient of variation) of 7.42% and 6.25% at 10 and 300 ng/ml, respectively for nicotine and between run % CV's of 5.05% and 3.62% at 20 and 600 ng/ml, respectively for cotinine.

Statistics; the Up and Down Procedure to Determine Inhalation LC_{50}

For evaluating acute inhalation toxicity, median lethal concentration (LC_{50}), not median lethal dose (LD_{50}), is recommended by the U.S. Environmental Protection Agency (EPA) Guidelines for Acute Inhalation Toxicity (EPA, 1998). LC_{50} is the concentration of a substance in air that causes death during exposure or within a fixed time after exposure in 50% of animals exposed for a specified duration. LC_{50} is expressed as weight of test substance per unit volume of air, for example, mg/L.

Nicotine LC_{50} in rats was examined using the up and down procedure (UDP) recommended by EPA Health Effects Test Guidelines (EPA, 2002). The purpose of the UDP is to minimize the number of animals for toxicity testing. With this method, 6–9 animals could be used to obtain LC_{50} and its confidence interval (*CI*) with an accuracy comparable to using 30–50 animals with a conventional LC_{50} method (also refer to Bruce [1985]).

As conventional LC_{50} experiments, a range of concentrations was chosen for testing with UDP. Concentration progression factor refers to the multiple by which a concentration is increased or decreased, chosen according to the steepness of the concentration–response curve of the testing substance. A concentration progression factor of antilog 0.5 is commonly used. Animals were exposed to the aerosol in a nose-only system, one at a time. The first animal was exposed to a concentration a step below the level of the best estimate of LC_{50}. If the animal survived, the concentration for the next animal was increased by one step; if it died, the concentration for the next animal was decreased by one step. Dosing was continued until the statistical criteria were satisfied (EPA, 2002). A computer program (AOT425StatPgm) to facilitate animal-by-animal calculations that establish testing sequences has been developed by the USEPA and is available from the EPA Web site. The program gives the estimates of LC_{50} and its *CI* from the animal outcomes at test termination. After the experiments, the surviving rats were observed for additional 24 hr to observe any delayed deaths.

Data are presented as mean ± *SD* except those specified as *CI* or geometric standard deviation (GSD).

Chemicals

Nicotine used in this study was (s)-(-)-nicotine freebase (liquid, 99%) ordered from Alfa Aesar Co.

RESULTS

Nicotine Aerosol Droplet Size Distributions and Mass Concentration in the Breathing Zone of Exposure Chambers

The manufacturer of the Collison nebulizer states that the mass median aerodynamic diameter (MMAD) of aerosol droplets generated in the nebulizer is ~2.5 μm and GSD is 1.8

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(http://www.bgiusa.com/agc/output_distribution.htm). These measurements were made using a nonvolatile liquid. However, generation of aerosol from a liquid depends on the later's physical properties such as viscosity, vapor pressure, and surface tension. After the aerosol is generated, it is a dynamic process whose droplet size distribution and concentration in air vary with time, affected by factors such as coagulation, condensation, and evaporation (Hinds, 1999). Evaporation is a particularly critical process if the solvent, for example, water, is volatile. Therefore, for delivering drugs to the body through the lungs with aerosol technology, one has to establish specific procedures for different drugs based on physical properties of the drugs and their solvents. The characteristics of the aerosol such as droplet size distribution and drug concentration need to be measured at the breathing zone to obtain the information about the aerosol the animal actually inhales. In the Acute Inhalation Toxicity Testing Guidance Document (OECD, 2009) (also refer to EPA [1998]), a respirable droplet size of MMAD between 1–4 μm is recommended.

The aerosol droplet size distribution and mass concentrations in the breathing zones of our nose-only exposure systems were determined with solutions of nicotine at concentrations as they were actually used in experiments (Figure 3, Table 1). The airflow rate and MMAD values obtained in our experiments at 20 and 40 psi are consistent with those of the output data document from BGI Inc. (http://www.bgiusa.com/agc/collison.htm). Table 1 shows that (a) increasing air pressure from 20 to 40 psi led to higher aerosol mass concentration and smaller MMAD, while further increases in pressure did not increase the mass concentration and even decreased it due to the increase in air flow (data not shown). (b) Using a higher nicotine concentration in solution led to an increase in MMAD and in mass concentration, suggesting that physical properties of the solution, for example, solutions with higher nicotine concentration are higher in viscosity and lower in vapor pressure, affect the droplet size distribution and mass concentration of the aerosol.

These results suggest that the nicotine aerosol droplet size in the breathing zone in our nose-only exposure systems was within the range of respirable droplet size recommended by USEPA (EPA, 1998; OECD, 2009). High nicotine mass concentrations for inhalation for animals (3–4 orders of magnitude higher compared to vapor inhalation methods; George et al., 2010) can be achieved in this system.

Nicotine Acute Inhalation Toxicity

Nicotine in water can be in three forms: freebase (Nic), monoprotonated ($NicH^+$), and diprotonated ($NicH_2^{2+}$). Nic and $NicH^+$ are predominant, with pK_a = 8.06 at 20 °C (Pankow, Tavakoli, Luo, & Isabelle, 2003). Therefore, ~50% of nicotine is as Nic at pH 8.0. For inhalation route, the pH of the particles of tobacco smoke or testing aerosol affects nicotine absorption in the lung and its bioavailability (Burch et al., 1993; Pankow et al., 2003).

Rats were exposed to nicotine aerosol for a fixed time (20 min) and with a fixed air pressure (40 psi) to the nebulizer. To determine the inhalation LC_{50} of nicotine for rats using the UDP, we varied the nicotine concentrations in the nebulizer solution container. An ordered concentration progression in a range of 5%–56% nicotine was defined. Since the nicotine dose–response curve is quite steep, a concentration progression factor of antilog 0.25 = 1.78 was chosen. pH was 8.0 in the first experiment.

Rats were exposed to nicotine aerosol in a nose-only system, one at a time. Starting with a nicotine concentration of 10% in the nebulizer container, the first rat survived. A concentration of 18% (increase of one progression factor) was used for the next rat. According to the UDP, if the animal survives, the concentration for the next animal is increased by one step;

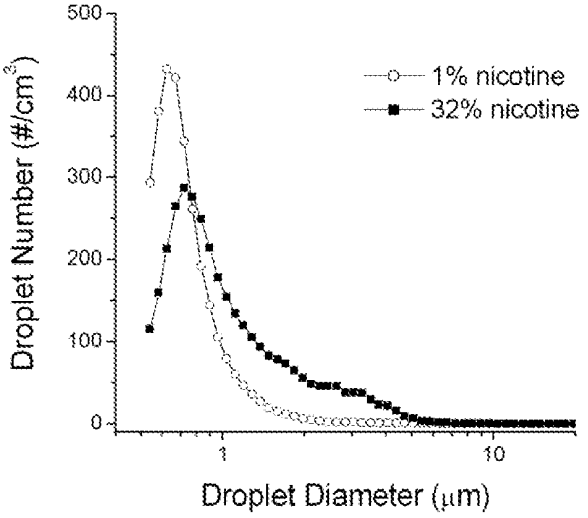


Figure 3. Droplet size distribution of the nicotine aerosol in the breathing zone of a nose-only exposure chamber. The nicotine concentration in the nebulizer container was 1% or 32%. Air pressure in the inlet of the nebulizer was 40 psi. Air flow rate was 9.55 L/min (standard conditions, adjusted with Eq. 1). Using the 1-jet nebulizer modified from a 3-jet unit (refer to Methods section). The aerosol sampling time was 10 s with the APS.

Table 1. Nicotine Aerosol Characteristics in Different Experimental Conditions

Chamber	Nicotine concentration in nebulizer	Air pressure (psi)	MMAD (μm)	GSD	Aerosol mass concentration (mg/L)	Nicotine concentration in air (mg/L)
Nose-only	1%	20	1.95	2.48	2.96	0.0296
	1%	40	1.69	2.59	4.22	0.0422
	32%	40	3.55	1.83	7.17	2.3

Note. GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter.
Nicotine concentration in air = nicotine concentration in solution in the nebulizer × aerosol mass concentration.
The aerosol sampling time was 10 s for the droplet size distribution with the Aerodynamic Particle Sizer and 1 min for the mass concentrations measurement with the impactor.

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Table 2. The Effects of pH of Nicotine Solution on LC_{50}

pH	Nicotine concentration in nebulizer (%)	95% *CI*	LC_{50} in air (20 min) (mg/L)[a]	95% *CI* of LC_{50} (mg/L)[a]	*n*
6.8	>56[b]		> 4.1		6
7.4	32	20.4–69.2	2.3	1.46–4.96	7
8.0	32	17.3–56.7	2.3	1.24–4.07	7

Note. *CI* represents confidence interval. Air pressure for generating nicotine aerosol was 40 psi in LC_{50} experiments.
[a]LC_{50} in air and its *CI* are calculated as nicotine concentration in solution × aerosol mass concentration in air (Table 1).
[b]The value is at least 56%. Only one rat died at 56% nicotine solution during the up and down procedure. No other rats died at 32%, 56%, or 68% in multiple trials.

if it dies, the concentration for the next animal is decreased by one step. The test result (either death or survival) for each rat was entered one by one into the spreadsheet of the program AOT425StatPgm from the USEPA.

When rats were exposed to nicotine aerosol in this high concentration range, they showed a Straub tail within 20–60 s. Within 1–2.5 min, the rats became apneic, interspersed with gasps. This lasted 2–5 min, and then respiration recovered, but was weak in some rats. Some rats had clonic and/or tonic convulsions and died at 6–20 min. Some of them died within 1–3 min after the end of nicotine aerosol exposure period of 20 min. This experiment proceeded until the result for the seventh rat, which met the "stopping criteria" of the program, with an estimated LC_{50} = 32% nicotine concentration in the nebulizer container with a 95% *CI* of 17.3%–56.7%. To convert percentage concentration in the nebulizer into nicotine concentration in air, we calculated: LC_{50} (20 min) = 0.32 × 7.17 = 2.3 mg/L (nicotine per liter of the breathing air containing the aerosol); *CI* was 1.24–4.07 mg/L, based on the mass concentration of aerosol at the breathing zone 7.17 mg/L at 40 psi (Table 1, the density of nicotine liquid is 1.01 at 20 °C).

Further, we tested if pH affected inhalation LC_{50} using nicotine solutions of pH 6.8 and 7.4, as the effective pH of smoke particles from commercial cigarettes is in a range of 6–7.8 (Pankow et al., 2003).

LC_{50} values were not significantly different between experimental groups of nicotine solutions at pH 7.4 and at pH 8 (Table 2). Note that the *CI* values of LC_{50} at pH 8 were slightly lower than those at pH 7.4. However, the LC_{50} of nicotine solution at pH 6.8 was >4 mg/L (>56% nicotine concentration in the nebulizer). The factor that prevented us going higher in nicotine concentration was that pure nicotine freebase is liquid and very alkaline (pH ~10). The amount of HCl required to adjust pH to 6.8 significantly diluted the solution; therefore, 68% was the maximum concentration we could achieve. Although the exact value of LC_{50} cannot be determined, our complete result (see legend of Table 2) in this experiment with pH 6.8 suggests that LC_{50} at pH 6.8 is much higher than those at pH 7.4 and pH 8.

These results suggest that the method of delivering nicotine through aerosol inhalation is very efficient. Exposure to 2.3 mg/L nicotine in air for 20 min causes death in 50% of rats. This method can deliver controllable amount of nicotine rapidly into the circulation and brain-inducing dose-dependent pharmacological effects, even enough to cause death. In addition, we showed that pH affects nicotine actions. Acidification, but not basification, of the nicotine solution in the nebulizer minimizes the effects of nicotine, probably due to a reduction in nicotine absorption and/or bioavailability in the lungs.

Nicotine Pharmacokinetics in Arterial and Venous Blood

Rats were exposed to nicotine aerosol generated from 1% nicotine solution in the nebulizer in a nose-only system for 2 min. The time course and magnitude of plasma nicotine and the nicotine metabolite cotinine in arterial or venous blood (separate rats) were measured from the start of nicotine aerosol delivery until 40 min later. The arterial blood nicotine concentration reached a maximum of 43.2 ± 15.7 ng/ml (n = 5) within 1–4 min and declined over the next 20 min to 16.0 ± 3.7 ng/ml (Figure 4A). Plasma nicotine levels in venous blood increased slowly to 21.0 ± 8.2 ng/ml at 3.5 min and then varied between 15 and 25 ng/ml in the following 36 min (Figure 4A). By comparing our results with those from human subjects smoking a cigarette (Fig. 1B in Lunell et al. [2000]), we demonstrate that the magnitude and early pharmacokinetic pattern of nicotine in arterial and venous blood in rats closely resembled that seen in human smoking (also see Hukkanen et al., 2005). The duration of the peak nicotine concentration was slightly shorter in rat with our experimental conditions compared to that of human smoking a cigarette likely because smokers took 5 min to smoke a cigarette in Lunell et al.'s experimental conditions. We noticed that, unlike in human where the arterial blood nicotine level varies widely depending on the smoking pattern (Henningfield et al., 1993; Lunell et al., 2000; Rose et al., 1999), the arterial blood nicotine kinetic patterns were quite consistent among rats in our experimental conditions (note that the error bars in Figure 1A and 1B are *SD*, not *SE*). Plasma cotinine levels in both arterial and venous blood started to be detectable after the peak arterial nicotine levels and grew slowly (Figure 4B) consistent with the metabolism of nicotine and the slow metabolism rate of cotinine in naïve rats (Hukkanen et al., 2005).

These results suggest that the nicotine aerosol/inhalation method can deliver nicotine to rats with a pharmacokinetic pattern in both arterial and venous blood quantitatively resembling that of a human smoking a cigarette. The magnitude and rapid rise in arterial nicotine concentration are consistent with the hypothesis that nicotine aerosol reaches and deposits in the alveolar region where it is quickly absorbed into the pulmonary circulation during aerosol inhalation.

DISCUSSION

Through inhalation of tobacco smoke, nicotine is deposited and absorbed in the lungs leading to a rapid increase in arterial blood nicotine concentration, entering the systemic circulation and the brain quickly (Matta et al., 2007). Nicotine in

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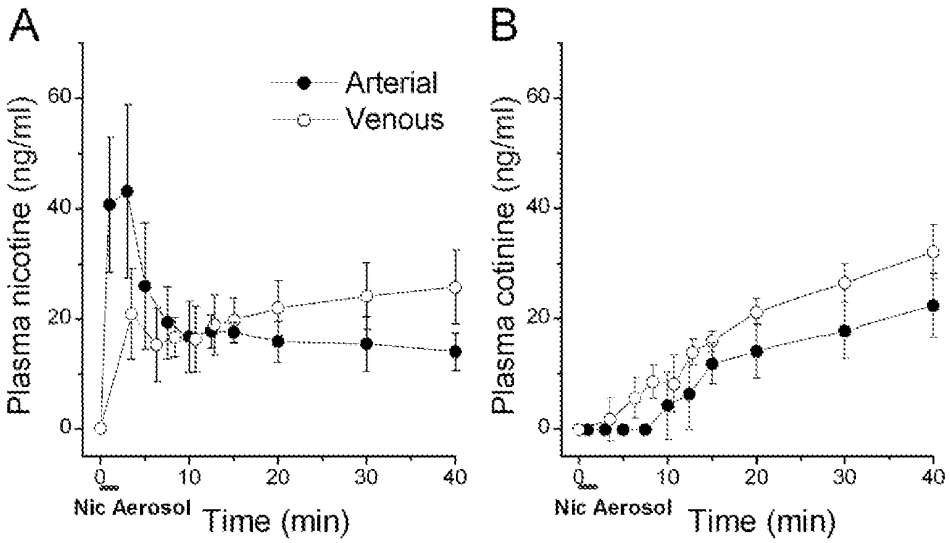


Figure 4. Nicotine aerosol inhalation in rats produces blood pharmacokinetics resembling human smoking. (A) Plasma nicotine levels (mean ± *SD*). (B) Plasma cotinine (a major nicotine metabolite) levels. Rats were exposed to nicotine aerosol in a nose-only exposure chamber for 2 min (indicated as a short bar below the time axis in (A) and (B)). Nic = nicotine. Nicotine solution in the nebulizer contained 1% nicotine in 0.7% NaCl (pH 8, osmolality ~300 mOsm/kg). Air pressure for generating nicotine aerosol was 20 psi in these pharmacokinetics experiments. We collected first sample as pre-nicotine control, then collected arterial blood samples at timepoints (take starting of nicotine aerosol generation as 0 min): 1, 3, 5, 7.5, 10, 12.5, 15, 20, 30, 40 min (n = 5). We collected venous blood (separate rats, n = 5) at timepoints: 3.5, 6.3, 8.4, 10.7, 12.8, 15, 20, 30, 40 min (since venous blood dropped slowly, the timepoints are averages of the mid points of collection durations from every rat).

this rapid arterial peak/decline concentration pattern stimulates brain nicotinic acetylcholine receptors, activating the dopaminergic reward system that plays an important role in initiation of addiction (De Biasi & Dani, 2011; Henningfield & Keenan, 1993). In addition, nicotine induces diverse effects in the central nervous system (CNS), such as improving cognitive function (Herman & Sofuoglu, 2010; Levin, McClernon, & Rezvani, 2006; Sarter, Parikh, & Howe, 2009), affecting anxiety-like behavior (File, Cheeta, & Kenny, 2000), and analgesia (Marubio et al., 1999; Semenova, Contet, Roberts, & Markou, 2012). In this study, we developed a noninvasive method of nicotine aerosol inhalation. We, for the first time, actually measured nicotine pharmacokinetics in both arterial and venous blood in rodents during and after aerosol inhalation and are able to achieves a rapid nicotine peak/decline pharmacokinetic pattern in the arterial blood that quantitatively simulates that of a human smoking a cigarette. The peak declines due to extensive distribution to body tissues (steady state volume of distribution = 2.2–3.3 L/kg) (Hukkanen et al., 2005). On the other hand, nicotine concentrations in venous blood increased slower and after the initial 2-min aerosol exposure it kept increasing slowly consistent with nicotine release from tissues (Hukkanen et al., 2005). We do not exclude the possibility that residuals of certain percentage of relatively large aerosol droplets deposit in the nasal or buccal mucosa that are absorbed slower and last longer than 2 min. Nicotine can be administered with this aerosol/inhalation method in vivo under various experimental conditions including freely behaving, sleeping, restrained, anesthetized, or artificially ventilated rodents. This method can be readily used for chronic intermittent nicotine exposure. The devices and method represents a powerful tool for studies of nicotine addiction, nicotine toxicology, tobacco-related diseases affecting, for example, the CNS, the lungs, the cardiovascular system, and, if applied to pregnant rodents, nicotine teratogenicity. This method could have important implications in nicotine replacement therapy (NRT) for smoking cessation and ultimately, for discovery of new pharmacological therapeutics.

In tobacco smoke, nicotine is present in protonated or unprotonated free-base forms. The ratio of protonated and free-base forms is pH dependent. The amount of free-base form of nicotine delivered to the smoker, in addition to the total amount, is an important factor in continuing use of tobacco products, that is, addiction, following an initial exposure (Ashley, Pankow, Tavakoli, & Watson, 2009). pH is hypothesized to dramatically affect nicotine bioavailability because the protonated form is hydrophilic, while the unprotonated free-base form is lipophilic and thus readily diffuses across membranes (Armitage & Turner, 1970; Schievelbein, Eberhardt, Loschenkohl, Rahlfs, & Bedall, 1973). Increasing pH in aerosolized nicotine produces a higher peak plasma nicotine concentration in humans (Burch et al., 1993). As drug delivery rate correlates to addiction potential (Henningfield & Keenan, 1993), increased free-base levels leads to increases in delivery rate, affecting the addiction potential (Ashley et al., 2009). However, this issue is controversial due to the difficulty and uncertainty of pH measurements in cigarette smoke (Pankow, 2001; Seeman, 2007). Some authors argue that because of the buffering capacity of the large surface area of the lungs and the relatively small amount of nicotine in cigarette smoke particles, the pH of nicotine aerosol in the range of effective pH of smoke of commercial cigarettes would not affect the absorption rate and bioavailability of nicotine in the lung (Seeman & Carchman, 2008). To test the hypothesis that pH of nicotine aerosol affects the absorption and bioavailability of nicotine, we examined the inhalation LC_{50} using nicotine aerosol generated from solutions with known pH.

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At pH 7.4 and at an alkaline pH 8.0, within the range of smoke effective pH of commercial cigarettes (Pankow et al., 2003), LC_{50}s were equivalent (Table 2), while at pH 6.8, LC_{50} dramatically increased. These results suggest that a mild increase of pH from the physiological pH has no effect on nicotine absorption and/or bioavailability. While acidification in our conditions of lethal amounts of nicotine application may exceed the buffering capacity in the fluid lining the lungs, leading to reduction of free-base nicotine and thus a decrease in the delivery rate and/or the bioavailability of nicotine.

The nicotine concentrations in the mainstream smoke particulate matter of reference cigarettes are 7%–8% (Chambers, 2003). Our data show that exposure to nicotine in concentration of 32% in aerosol droplets (4–5 times higher than that in cigarette smoke particles) continuously for 20 min kills 50% of laboratory rats. LD_{50} of i.p. injection of nicotine is 23.5 mg/kg body weight for rats (Hicks & Sinclair, 1947). LD_{50} for orally delivered nicotine is 70 mg/kg for Sprague-Dawley rats (van den Heuvel et al., 1990). With a simple calculation, Inhaled dose = nicotine concentration in air × minute ventilation × exposure time (Paulus, 2003), we can roughly estimate LD_{50} from LC_{50}. According to Strohl et al. (1997), minute ventilation/100 g body weight of Sprague-Dawley rats is 28.17 ± 1.37 ml. We get LD_{50} = 13 mg/kg body weight for inhalation for rats. This value is lower than those for oral or i.p. administration, and is consistent with the first-pass metabolism of nicotine in the liver before it enters the systemic circulation when nicotine is administered orally or i.p. (Matta et al., 2007). We are aware of a limitation in this estimation of LD_{50}. Respiratory parameters, for example, minute ventilation, vary during nicotine intoxication. This estimate is only for comparison purposes. Nicotine inhalation toxicity is formally reported as LC_{50} and its *CI* as well as exposure time, as recommended by USEPA and OECD (EPA, 1998; OECD, 2009), in this study. Our LC_{50} experiment results also provide reference data for establishing inhalation dosage regimen for nicotine research.

Nicotine inhalers that generate nicotine vapor for inhalation for human use are commercially available (such as Nicotrol®) and are used as NRT for smoking cessation (Lunell et al., 2000; Schneider et al., 2001). Nicotine vapor is primarily deposited in the mouth, nose, and throat leading to a slow increase in arterial blood nicotine concentration (Bergstrom et al., 1995; Lunell et al., 1996, 2000; Schneider et al., 2001). The pharmacokinetics is not comparable to that of smoking a cigarette. There are reports of nicotine administration to humans through aerosol inhalation. Their clinical significance has yet to be demonstrated (Burch, Erbland, Gann, & Hiller, 1989; Rose, Turner, Murugesan, Behm, & Langesen, 2010; Simis et al., 2008). Chronic nicotine administration to rats by aerosol inhalation was suggested in an abstract (Littleton & Umney, 1977), but this study has not resulted in further publication. The aerosol droplet size distribution and nicotine pharmacokinetics in rodents was not determined. Without this information, nicotine aerosol inhalation methodology was not established (Chowdhury, Rayford, & Chang, 1992). We developed methods for nicotine delivery to rodent models through an aerosol inhalation route for research of nicotine addiction, tobacco-related diseases, etc., importantly research projects that cannot be done in humans. The potential of nicotine aerosol for therapeutic uses, for example, the efficacy and safety of NRT for smoking cessation, will need to be tested thoroughly in animal models.

During experiments with nicotine aerosol delivery, the nicotine solution concentration in the nebulizer container gradually increases due to evaporative losses of water (Niven & Hickey, 2007). In this study, there would not be a problem for single use of 2 min (nicotine pharmacokinetic experiments) or 20 min (LC_{50} experiments). However, for experiments on chronic intermittent exposure of nicotine aerosol, for example, 2 min each multiple times a day, it would be important to replace the nicotine solution frequently, for example, at least once a day.

Recently, electronic cigarettes (E-cigarettes) were introduced into the U.S. market as an alternative to (ordinary) cigarettes (Cobb, Byron, Abrams, & Shields, 2010; Etter & Bullen, 2011). People also use E-cigarettes to treat nicotine withdrawal symptoms and to aid smoking cessation (Bullen et al., 2010; Siegel, Tanwar, & Wood, 2011). Public health experts and organizations including the WHO, the CDC, and the American Cancer Society have expressed concerns about the safety of these products (http://www.fda.gov/forconsumers/consumerupdates/ucm173401.htm). In fact, little research has been done on the health risk of E-cigarettes, and in general, on the health risk of inhalation of nicotine. As commercially available nicotine inhalation products like E-cigarettes become more popular, it becomes necessary to further study the health risk of inhalation of pure nicotine with animal models. The method developed in this study provides an effective and highly relevant tool for this line of research.

CONCLUSIONS

(a) A noninvasive method delivering nicotine to rodents through aerosol inhalation is developed. This method, through the same route as smoking tobacco, induces dose-dependent pharmacological effects. (b) In the breathing zone of this aerosol exposure system, the droplet size distribution of the nicotine aerosol was determined to be in the range of respirable size suggesting reaching the alveolar region, enabling rapid delivery of nicotine into the pulmonary circulation and then through the left heart and the arteries to all body systems including the brain. (c) The aerosol inhalation methodology can produce early pharmacokinetics in both the arterial and venous blood closely resembling those of a human smoking a cigarette. (d) This method is able to deliver substantial quantities of nicotine, high enough to rapidly reach fatal blood concentrations. The nicotine dose can be easily controlled by varying the nicotine concentration in solution in the nebulizer container or by varying the duration of aerosol exposure. We report, for the first time, that the acute inhalation toxicity of nicotine, LC_{50} is 2.3 mg/L in air with a *CI* of 1.24–4.07 mg/L (20 min) for rats. (e) pH of nicotine aerosol in the range of 7.4–8.0 had similar effects, while lower pH reduced these effects, suggesting acidification decreases nicotine absorption and/or bioavailability.

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DECLARATION OF INTERESTS

There are no conflicts of interests for XMS, BX, JL, YZ, and JLF. XSX is the founder and owns stocks of AfaSci Inc.

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APPENDIX E

The art of medicine

Electronic cigarettes and history

Electronic cigarettes are currently the subject of much public, media, and regulatory attention. Discussion centres on whether e-cigarettes encourage or discourage smoking. Should they be banned? Should they be regulated as consumer products, tobacco products, as medicines, or a combination of approaches? It seems likely that some countries will opt for the EU approach of regulation as a tobacco product, whereas others will go for medicines regulation which allows claims about smoking cessation to be made. The recent entry of the tobacco industry in the e-cigarette market has caused concern among some public health interests, not least because it enables the industry to present products for medicines regulation and to circumvent the restrictions in the Framework Convention on Tobacco Control on industry engagement with policy makers. Other medical experts have called on WHO to resist the urge to control and suppress e-cigarettes.

This seems to be an issue that has blown up very recently. But responses to e-cigarettes can only be understood in the light of longstanding tensions and debates about smoking and public health. The battle lines currently drawn are imbued with history. Two key historical areas that frame the debate are attempts since the 1950s at product modification to achieve "safer smoking", and the changing status of nicotine in relation to tobacco since the 1970s.

New technology has always been a driver of change in smoking habits—just think of the arrival of the Bonsack machine in the 19th century and the ensuing mass production of cigarettes. But the technical change with direct relevance was the move from the 1950s both in the UK and in the USA to change the cigarette itself so that smoking it would be "safer". This product modification was a major driver of smoking policy for two decades. Once the link between smoking and lung cancer had been discovered in the early 1950s, industry, government, and public health interests worked together and aimed to reduce the harm from cigarettes. In the UK, the tobacco industry had a close relationship with government because of the wartime control of tobacco as an essential product for the population. It gave money to the Medical Research Council in the 1950s for a programme of research and set up its own research laboratories at Harrogate in Yorkshire where research was done on the components of the cigarette with the aim of removing what was harmful. Imperial Tobacco, the main UK manufacturer in the 1960s, wanted the publication of tar and nicotine tables and labelling. The government was opposed because the safety implied by labelling could not be supported scientifically. The tactic of differential taxation, also discussed in the 1960s, failed for the same reason. There would need to be a clear scientific distinction between what was and was not harmful if different rates of taxation were to be imposed on different products.

From the 1960s onward, attention focused on the development of the "safer cigarette". Wills, part of the Imperial Group, was a large producer of filter cigarettes by the mid-1960s, and even tried to produce a filter cigar, codenamed "Pongo"; its low tar product named "Wallflower" never came off the shelf. These were also strategies followed in the USA. There, in the 1960s and 1970s, the National Cancer Institute programme on smoking and health pursued the overall aim of harm reduction. In the UK in 1971, the Royal College of Physicians' second report on smoking supported "less dangerous forms of smoking". It called for smokers to change to pipes and cigars or for more research on reduced tar and nicotine cigarettes. By the end of the 1970s, the low tar/low nicotine tactic was out of favour. Smoking researchers criticised the model of smoking behaviour that underpinned it. Low tar and nicotine cigarettes might actually lead smokers to take in more tar rather than less through "compensatory smoking".

These types of arguments are echoed in current debates about the status of e-cigarettes and the need to research their effects. Then, too, attention shifted to replacement products rather than making smoking safer. But new smoking products proved to be a blind alley. Gallahers and Rothmans worked on a product called Cytrel 361, while British American Tobacco developed a product called BATFLAKE. Imperial joined forces with ICI, the pharmaceutical company, to produce New Smoking Material (NSM) as an economically viable alternative to tobacco. The process led to regulatory developments with parallels with the present day. David Owen, Minister of Health and a keen anti-smoker, aimed to bring the substitutes under medicines regulation in the 1970s, with the implication that tobacco too would ultimately go down the same route. Owen's departure from the ministry took the political heat out of the issue. When NSM left the warehouse in July, 1977, sales were poor. It was taxed in the same way as tobacco, and so there was no financial incentive for purchase. NSM fell foul of consumer resistance, something which has not been the case with e-cigarettes, which have met with the support of some consumers.

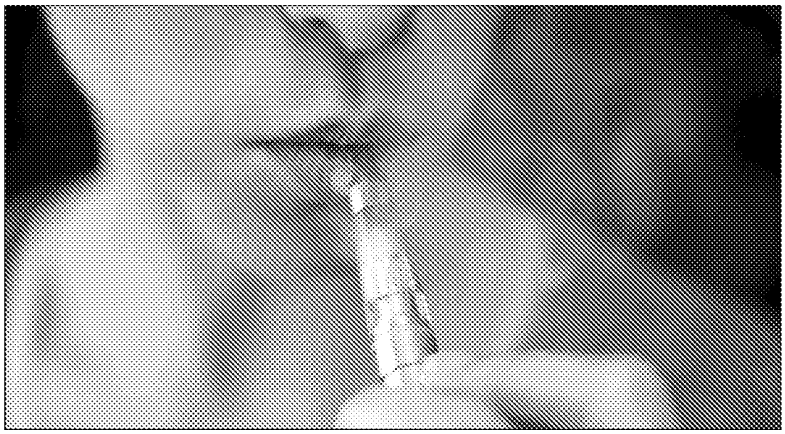
A key outcome of these decades of failed attempts at harm reduction was a growing and emphatic hostility from public health interests to taking them further. The previous desire for cooperation with industry was replaced by an implacable hostility. This explains the vehemence of opposition from some public health interests to e-cigarettes in the present. Back in the 1970s, the UK's central health education agency, the Health Education Council, called smoking safer cigarettes

the equivalent of jumping from the 36th instead of the 39th floor of a tall building. The alliance around product modification came to an end. The public health agenda shifted to abstention with strong opposition to any liaison with industry. It was this stance that has underpinned public health responses since then. In the 1980s, such opposition effectively killed off industry moves to produce and market Skoal Bandits in the UK, a type of oral tobacco. Use of snus, the popular Swedish equivalent, was banned for wider use by the EU because of public health opposition. The default response for public health became opposition to industry and to reduction of harm, a stance displayed across a range of public health issues, from alcohol through to food and diet.

This default position also explained the lack of interest in another development relevant to the e-cigarette. The recategorisation of nicotine and its separation from tobacco as a harm reduction product was the next phase of e-cigarette history. Back in 1971, two Swedish researchers from the department of clinical physiology at the University of Lund appeared at the world conference on smoking in London. They presented their results on "nicotine containing chewing gum as a substitute for smoking". The chewing gum had been developed because of a request from the Swedish navy, where a strict no smoking policy caused problems for crews during long periods at sea. The Swedish pharmacologist Ove Fernö, director of the Leo pharmaceutical company in Helsingborg, formed an alliance with Michael Russell, head of the smoking research section of the Addiction Research Unit at the Institute of Psychiatry in London. They later launched a product called Nicorette. Nicotine began a process of boundary change.

Russell was a psychiatrist working in an addiction setting, who was critical of the public health emphasis on abstention. In a 1991 piece in *The Lancet*, he argued the case for nicotine maintenance and asked "Why have governments persisted in allowing the manufacture, extensive advertising, and promotion of such a lethally contaminated drug delivery system as the cigarette, while putting so little pressure on the tobacco industry to develop more purified forms of nicotine delivery?" Russell's call for a purified form of nicotine delivery and the involvement of the tobacco industry was not to be answered until the arrival of the e-cigarette more than 20 years later. Why this hiatus? His work on nicotine and addiction had begun in the early 1970s, but it carried little weight with public health. His base in psychiatry, the association with the pharmaceutical industry, the emphasis on harm reduction, were all at odds with the dominant public health ethos of abstention and opposition to industry connections.

The convoluted struggles over nicotine and its regulation that followed in the 1980s were far from the public health mainstream. Then further psychopharmacological work on nicotine and on addiction developed in the USA and UK: research on nicotine recognised addiction as a double



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edged sword, either a reason to maintain nicotine levels in cigarettes or to lower them in order to wean people off the habit. There was also a revival of interest in the public health field in harm reduction. The adoption of the concept of addiction for tobacco as well as for drugs meant that ideas from the drug field spilled over into the tobacco arena. At the same time, drugs were becoming more of a public health rather than a mental health issue; a key issue there was HIV/AIDS, which stimulated a revival of harm reduction strategies including medication with methadone. There were growing parallels between the two sets of substances. Researchers such as Ann McNeill in the tobacco field began to talk about harm reduction, a topic which had been anathema for smoking experts for 20 years. The recognition of a group of smokers who would or could not give up helped to raise the profile of the concept of addiction. Concern about inequality and health also led to support for nicotine from some public health interests. The arrival of e-cigarettes has provided a further stimulus for this emergent discussion.

Research is now underway to examine the health effects of e-cigarettes, and their relation to reductions or increases in smoking, whether they act as gateways to increased consumption, or to abstinence. The position of the pharmacist as a health professional exemplifies this dilemma. In the UK, pharmacists often held tobacco licences until the 1940s. Will their current sale of e-cigarettes build on that legacy, or on the more recent over-the-counter sale of other nicotine-replacement products? There should be a looking back as well as forward in the current debate. E-cigarettes raise some longstanding issues for public health, not least the nature of the relationship with industry interests and whether reduction of harm is a valid strategy.

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APPENDIX F

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Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Clinical Laboratory Model for Evaluating the Acute Effects of Electronic "Cigarettes": Nicotine Delivery Profile and Cardiovascular and Subjective Effects

Andrea R. Vansickel, Caroline O. Cobb, Michael F. Weaver, and Thomas E. Eissenberg

Abstract

Background: Electronic "cigarettes" are marketed to tobacco users as potential reduced exposure products (PREP), albeit with little information regarding electronic cigarette user toxicant exposure and effects. This information may be obtained by adapting clinical laboratory methods used to evaluate other PREPs for smokers.

Methods: Thirty-two smokers participated in four independent Latin-square ordered conditions that differed by product: own brand cigarette, "NPRO" electronic cigarettes (NPRO EC; 18 mg cartridge), "Hydro" electronic cigarettes (Hydro EC; 16 mg cartridge), or sham (unlit cigarette). Participants took 10 puffs at two separate times during each session. Plasma nicotine and carbon monoxide (CO) concentration, heart rate, and subjective effects were assessed.

Results: Own brand significantly increased plasma nicotine and CO concentration and heart rate within the first five minutes of administration whereas NPRO EC, Hydro EC, and sham smoking did not. Own brand, NPRO EC, and Hydro EC (but not sham) significantly decreased tobacco abstinence symptom ratings and increased product acceptability ratings. The magnitude of symptom suppression and increased acceptability was greater for own brand than for NPRO EC and Hydro EC.

Conclusions: Under these acute testing conditions, neither of the electronic cigarettes exposed users to measurable levels of nicotine or CO, although both suppressed nicotine/tobacco abstinence symptom ratings.

Impact: This study illustrates how clinical laboratory methods can be used to understand the acute effects of these and other PREPs for tobacco users. The results and methods reported here will likely be relevant to the evaluation and empirically based regulation of electronic cigarettes and similar products. *Cancer Epidemiol Biomarkers Prev; 19(8); 1945–53. ©2010 AACR.*

Introduction

A variety of potential reduced exposure products (PREP) are/were marketed to cigarette smokers with explicit or implied claims that their use is associated with less exposure to lethal smoke constituents (1-3). These PREPs for smokers include products that involve burning specially cured tobacco that contains lower levels of some toxicants, that primarily heat rather than burn tobacco, or smokeless tobacco (4-6). As has been argued many times (1, 7, 8), objective empirical evaluation of these products is critical as a means of determining the extent to which PREP use is associated with reduced toxicant exposure, e.g., to nicotine or carbon monoxide (CO), and suppression of tobacco/nicotine abstinence symptoms. Clinical laboratory work has been very revealing, and sometimes shows reduced toxicant exposure and often shows a failure to suppress aversive abstinence symptoms fully (9, 10). In theory, toxicant exposure reduction may be associated with long-term decreased health risk, but this theoretical decreased risk is very unlikely with a product that is not used because it fails to suppress abstinence symptoms and/or is otherwise unacceptable.

So-called electronic "cigarettes" are one of the newest types of PREPs available, and anecdotal evidence suggests that, at least for some smokers, electronic cigarettes can completely replace tobacco cigarettes (11, 12). Many electronic cigarette brands are available in retail outlets and over the internet. Electronic cigarettes consist of a rechargeable battery, heater, and a cartridge that contains a liquid made of propylene glycol, nicotine, and other chemicals (13). When the battery-powered heater is activated, it heats the solution to produce a vapor that can then be inhaled by the user (14, 15). Electronic cigarettes are

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Note: The results of this study were presented in poster form at the annual Society for Research on Nicotine and Tobacco meeting held in Baltimore, MD February 24-27, 2010.

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marketed as PREPs for smokers, with manufacturer claims such as "alternative to smoking that will satisfy your nicotine urges and cravings" (16), "helps smokers quit, cut down or smoke healthier" (17), and "gives smokers all the pleasure and satisfaction of traditional smoking without all the health, social and economic problems" (18). To date, however, there are few objective data to substantiate these claims. Indeed, there is little objective information describing electronic cigarette toxicant content and yield or user toxicant exposure and effect.

The little available data suggest that electronic cigarette cartridges and vapors may contain trace amounts of impurities and tobacco-specific nitrosamines (13, 19). Electronic cigarette cartridge nicotine content may be less than the product labeling indicates, and the vapor produced from the cartridge may yield very little nicotine (13, 19). The scant data from human laboratory studies suggest that electronic cigarette use is likely to involve little nicotine exposure and tobacco abstinence symptom suppression that is far less than that produced by a tobacco cigarette (20, 21). Existing clinical models that have been used to evaluate combustible and noncombustible PREPs (10, 22, 23) might be adapted to quickly and efficiently provide necessary information regarding electronic cigarette toxicant exposure and effect.

The purpose of this study was to describe clinical laboratory methods that could be used to characterize electronic cigarette users' nicotine and CO exposure, cardiovascular response, and ratings of tobacco/nicotine abstinence symptom suppression and product acceptability. Accordingly, this within-subject study used these outcomes to compare, in 32 tobacco cigarette smokers, the effect of two marketed electronic cigarette brands with own brand cigarettes and sham smoking (i.e., puffing on an unlit cigarette). Based on preliminary data presented elsewhere (20, 21) we hypothesized that, compared with own brand, electronic cigarettes would deliver less nicotine and no CO and would be less effective at reducing symptoms of tobacco abstinence while producing lower acceptability ratings.

Materials and Methods

Participants

This study was approved by the Institutional Review Board of Virginia Commonwealth University and was conducted in accordance with the Declaration of Helsinki. Sixty-six men and women recruited from the Richmond, Virginia area provided written, informed consent. Prior to participation in any experimental sessions, 18 individuals were disqualified based on health concerns (e.g., high blood pressure) or failure to meet other inclusion/exclusion criteria (see below). In addition, 2 participants withdrew from the study and another 14 were withdrawn due to failure to comply with study procedures ($n = 9$), poor venous access ($n = 3$), or because study enrollment was completed ($n = 2$). The remaining 32 participants (13 women; 18 white) completed the study proper and were included in the analyses. Participants smoked at least 15 cigarettes per day (mean, 22 cigarettes per day; SD, 8.8), were between the ages of 18 to 55 years (mean, 33.6; SD, 12), provided an afternoon screening CO of at least 15 ppm (mean, 23.5; SD, 8.8), and had a urine cotinine result of at least 4 on a 7-point scale (0-6; NicAlert, Nymox Corp.; mean, 5.9; SD, 0.2). Exclusion criteria included self-reported history of any chronic mental or physical health condition, pregnancy or breastfeeding, active menopause, self-reported use of electronic cigarettes, current smoking cessation attempt, current drug use (other than marijuana), and >20 days self-reported marijuana or alcohol use in the past 30 days.

Study design and procedures

This study was conducted on an outpatient basis at the Clinical Behavioral Pharmacology Laboratory at Virginia Commonwealth University. Participants completed four laboratory sessions; each approximately 150 minutes in duration. One of four Latin-square ordered conditions was presented each session (separated by at least 48 hours) that differed by product administered: own brand (i.e., a lit cigarette of the participant's preferred brand), sham (i.e., an unlit cigarette of the participant's preferred brand), "NPRO" electronic cigarettes (NPRO EC; 18-mg cartridge; NJOY), and "Hydro" electronic cigarettes (Hydro EC; 16-mg cartridge; Crown Seven).

Participants were asked to refrain from cigarette smoking for at least 12 hours prior to their scheduled session. Smoking abstinence was verified upon arrival at the laboratory by an expired air CO level ≤10 ppm. At the start of a session, a heparinized catheter was inserted into a forearm vein, physiologic monitoring equipment was attached, and continuous physiologic recording commenced. Thirty minutes after session onset, participants responded to the subjective effect questionnaires, blood (7 mL) was sampled, and product was administered. Product administration consisted of 10 puffs with a 30-second interpuff interval (IPI; puff number and IPI were monitored by study staff): package instructions state that electronic cigarettes should be used similarly to a tobacco cigarette, and 10 puffs with a 30-second IPI approximates *ad libitum* cigarette smoking (24). Five, 15, 30, and 45 minutes after the first of 10 puffs of the initial product administration, participants responded to the subjective effect questionnaires and blood (7 mL) was sampled. Expired air CO was recorded at 15, 30, and 45 minutes. At 60 minutes, participants responded to the subjective effect questionnaires, blood (7 mL) was sampled, and product was administered a second time (again, 10 puffs, 30-second IPI). Five, 15, 30, and 45 minutes after the second product administration, participants responded to the subjective effects questionnaires and blood (7 mL) was sampled. Expired air CO was recorded at 15, 30, and 45 minutes. At session's end, the venous catheter was removed, participants were compensated for their time, and, if necessary, additional sessions were scheduled.

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Materials

NPRO EC was purchased from NJOY (25). The NPRO EC resembles a tobacco cigarette in length and diameter and consists of a disposable mouthpiece that houses a cartridge, a small heating element (vaporizer) that is activated when the user draws air through the device, and a rechargeable lithium battery. Cartridges come in a variety of flavors with varying nicotine content (0-18 mg). According to the NJOY website, cartridge ingredients include nicotine, propylene glycol, water, ethanol, glycerol, acetylpyrazine, guaiacol, mysomine, cotinine, and vanillin.

Hydro EC was purchased from Crown Seven (26). Hydro EC is similar in composition to NPRO EC and, according to the manufacturer's website, cartridges also come in a variety of flavors and contain nicotine (0-16 mg), propylene glycol, water, and tobacco flavoring.

For electronic cigarette conditions, a new 16-mg (Hydro EC) or 18-mg (NPRO EC) nicotine cartridge was used and batteries were fully charged before each session. The flavor of each electronic cigarette was matched to the participants' usual brand of cigarettes (regular or menthol). Consistent with product instructions, participants were instructed to puff from the electronic cigarette devices as they would a normal cigarette.

Participants' usual brand of cigarette was used in the own brand and sham conditions. According to the Federal Trade Commission (FTC, 2001), on average, usual brand yield was 1.06 mg nicotine (27), 14.7 mg tar, and 14.6 mg CO (based on available data for 26 participants).

Outcome measures

Physiologic measures. Heart rate was measured every 20 seconds (Model 506, Criticare Systems, fitted with a reusable pulse oximeter sensor). Blood samples were centrifuged and plasma was stored at −70°C. Plasma samples were sent to the Bioanalytical Analysis Core Laboratories of Virginia Commonwealth University's Department of Pharmaceutics and were analyzed for nicotine content using liquid chromatography/tandem mass spectrometry [limit of quantitation (LOQ) = 2.0 ng/mL; see ref. 24 for details]. Expired air CO was assessed using a BreathCO monitor (Vitalograph).

Subjective effect questionnaires. Participants responded to a computerized version of the Tiffany Drobes Questionnaire of Smoking Urges Brief (QSU Brief; ref. 28). The questionnaire consists of 10 items rated from 0 (strongly disagree) to 6 (strongly agree). Items from this scale are loaded onto two previously validated factors; factor 1 (intention to smoke) and factor 2 (anticipation of relief from withdrawal).

Participants responded to three computerized questionnaires containing visual analog scale (VAS) items. Each word or phrase was centered above a horizontal line that represented a scale from 0 to 100 points; the left anchor was "Not at all" and the right anchor was "Extremely". A mouse-controlled cursor produced a vertical mark on the line that could be adjusted by the participant. Scores on visual analog scale items were calculated as the distance between the vertical mark and the left anchor and were expressed as a percentage of line length.

Eleven VAS items were used to assess nicotine/tobacco abstinence symptom suppression (29). The direct effects of nicotine were assessed using 10 VAS items sensitive to nicotine effects (30, 31). Participants also responded to 14 visual analog scale items that assessed the direct effects of tobacco.

Data analyses

Heart rate values were averaged for 5-minute periods prior to each product administration or blood sampling. One heart rate measurement was missing for one participant in one session, and the missing value was replaced with an average of values before and after it. For plasma nicotine, values below the LOQ were replaced by the LOQ as in previous work (10, 32, 33).

We had previously reported the interim findings of this study, in a letter that examined nicotine exposure, heart rate, and craving results (21). The first 16 participants were included in that analysis. Prior to analyzing the data from all 32 participants described here, we first compared results of the first group of 16 participants with those of the second group of 16 participants using a repeated measures ANOVA with two within-subjects factors: condition (4 levels) and time [10 levels for nicotine, subjective, and heart rate (HR) data; 7 for CO data], and one between-subjects factor: study group (first 16 or second 16). No significant main effects or interactions involving the study group factor were observed on any measure. Given this failure to observe any differences across the two groups, all data were combined. Thus, the data from all 32 participants for plasma nicotine, CO, heart rate, and subjective measures were analyzed using repeated measures ANOVA with two factors: condition (4 levels) and time (10 levels for nicotine, HR data, and subjective data; 7 levels for CO). Huynh-Feldt corrections were used to account for violations of sphericity. Tukey's Honestly Significant Difference (HSD) test was used to examine differences between means ($P < 0.05$).

Results

Table 1 presents the main effects and interactions for all measures. The primary results of interest are those for which a significant condition by time interaction were observed, indicating that changes over time observed on that measure depended upon product used in that condition.

Physiologic measures

Plasma nicotine. A significant condition by time interaction was observed for plasma nicotine (Fig. 1A). Mean (SD) plasma nicotine increased from a preadministration level of 2.1 (0.32) ng/mL to a peak of 18.8 (11.8) ng/mL

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Table 1. Results of statistical analyses for all outcome measures

Measure	Condition F (*P*)	Time F (*P*)	Condition × time F (*P*)
Heart rate*	13.5 (>0.001)	62.0 (>0.001)	16.1 (>0.001)
Plasma nicotine*	112.2 (>0.001)	53.0 (>0.001)	45.2 (>0.001)
Carbon monoxide†	105.5 (>0.001)	107.0 (>0.001)	205.5 (>0.001)
Hughes and Hatsukami*			
Anxious	4.8 (0.01)	5.7 (>0.001)	1.8 (0.05)
Craving a cigarette	37.7 (>0.001)	25.7 (>0.001)	10.6 (>0.001)
Depression/feeling blue	0.5 (ns)	1.5 (ns)	1.1 (ns)
Difficulty concentrating	0.5 (ns)	3.4 (0.02)	0.8 (ns)
Drowsy	0.6 (ns)	3.9 (0.007)	1.6 (ns)
Hunger	2.6 (ns)	7.8 (>0.001)	1.8 (ns)
Impatient	4.3 (0.009)	3.7 (0.006)	2.5 (0.005)
Irritability/frustration/anger	5.8 (0.004)	2.3 (ns)	3.3 (0.001)
Restless	1.5 (ns)	2.5 (0.05)	1.9 (0.025)
Desire for sweets	1.7 (ns)	1.7 (ns)	1.7 (ns)
Urge to smoke	40.8 (>0.001)	28.2 (>0.001)	9.7 (>0.001)
QSU*			
Factor 1	40.6 (>0.001)	35.7 (>0.001)	16.9 (>0.001)
Factor 2	19.5 (>0.001)	16.6 (>0.001)	7.6 (>0.001)
Direct effects of nicotine*			
Confused	1.0 (ns)	1.4 (ns)	1.4 (ns)
Dizzy	1.5 (ns)	5.2 (0.002)	4.1 (0.002)
Headache	0.7 (ns)	0.9 (ns)	1.6 (ns)
Heart pounding	0.4 (ns)	2.9 (0.05)	1.9 (ns)
Lightheaded	1.2 (ns)	7.6 (>0.001)	5.8 (>0.001)
Nausea	0.1 (ns)	0.8 (ns)	1.1 (ns)
Nervous	1.0 (ns)	1.0 (ns)	1.2 (ns)
Salivation	0.5 (ns)	0.2 (ns)	1.0 (ns)
Sweaty	0.8 (ns)	0.9 (ns)	1.3 (ns)
Weak	0.1 (ns)	0.8 (ns)	1.1 (ns)
Direct effects of tobacco*			
Satisfying	76.2 (>0.001)	61.6 (>0.001)	17.2 (>0.001)
Pleasant	66.5 (>0.001)	68.5 (>0.001)	17.6 (>0.001)
Taste good	47.7 (>0.001)	66.8 (>0.001)	14.4 (>0.001)
Dizzy	19.2 (>0.001)	17.6 (>0.001)	7.2 (>0.001)
Calm	42.0 (>0.001)	31.1 (>0.001)	10.3 (>0.001)
Concentrate	17.9 (>0.001)	15.8 (>0.001)	5.5 (>0.001)
Awake	27.0 (>0.001)	22.0 (>0.001)	6.6 (>0.001)
Reduce hunger	24.2 (>0.001)	19.4 (>0.001)	5.6 (>0.001)
Sick	3.6 (0.02)	3.6 (0.01)	0.9 (ns)
Taste like own brand	115.5 (>0.001)	60.0 (>0.001)	26.9 (>0.001)
Feel like own brand	65.9 (>0.001)	67.0 (>0.001)	21.6 (>0.001)
Harsh as own brand	64.9 (>0.001)	49.2 (>0.001)	21.3 (>0.001)
Mild as own brand	62.4 (>0.001)	54.0 (>0.001)	20.5 (>0.001)
Smoke another cigarette RIGHT NOW	6.5 (>0.001)	38.3 (>0.001)	4.8 (>0.001)

Abbreviation: ns, nonsignificant.

*$df_{Condition}$, 3,93; df_{Time}, 9,279; $df_{Condxtime}$, 27,837.

†$df_{Condition}$, 3,93; df_{Time}, 6,186; $df_{Condxtime}$, 18,558.

five minutes after the first administration under the own-brand condition. No significant changes in plasma nicotine were observed for the Hydro EC, NPRO EC, or sham conditions.

Heart rate. A significant condition by time interaction was also observed for heart rate (Fig. 1B). Heart rate increased from an average (SD) of 65.7 (10.4) bpm at baseline to a peak of 80.3 (10.9) bpm five minutes after the

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first administration under the own-brand condition. No significant changes in heart rate were observed for the Hydro EC, NPRO EC, or sham conditions.

Expired air CO. A significant condition by time interaction was observed for expired air CO levels (Fig. 2). Mean (SD) CO increased from a preadministration level of 5.3 (2.1) ppm to a peak of 16.2 (4.5) ppm 15 minutes after the second administration under the own-brand condition. No significant changes in CO level were observed for the Hydro EC, NPRO EC, or sham conditions.

Subjective effect questionnaires

QSU brief. A significant condition by time interaction was observed for both factors of the QSU brief. Figure 3A shows data for factor 1 (intention to smoke; the QSU factor with the greater condition by time F value). Hydro EC and NPRO EC significantly decreased scores on both factors (relative to sham and/or baseline) at several time points. In contrast, own brand significantly decreased scores (relative to baseline and sham) on both factors at nearly every time point. In addition, the scores observed for own brand after product administration were significantly lower than Hydro EC and NPRO EC at almost every time point. A nearly identical pattern of results was observed for factor 2, although ratings were generally lower than those observed on factor 1.

Nicotine/tobacco abstinence symptom suppression. Significant condition by time interactions were observed on ratings of "anxious," "craving a cigarette/nicotine," "impatient," "irritability/frustration/anger," "restless,"

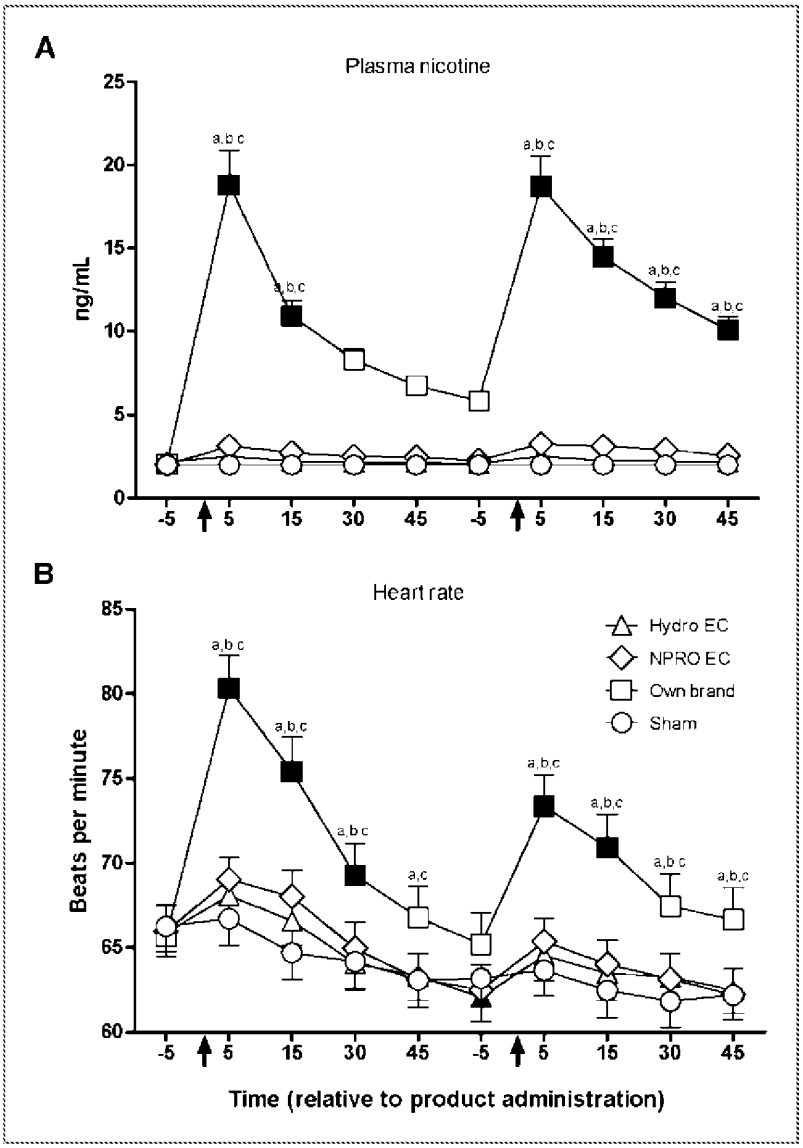


Figure 1. Mean data for nicotine blood plasma (A) and heart rate (B) as a function of condition and time. *X*-axes, time in minutes relative to product administration; arrows, first and second product administrations. *Y*-axes, A, nicotine blood plasma concentration (ng/mL); B, heart rate (beats per minute); filled symbols, significant difference from baseline. An "a," "b," or "c" indicates that own brand was significantly different from sham, Hydro EC, or NPRO EC at that time point. A "d" indicates that Hydro EC was significantly different from sham at that time point. An "e" indicates that NPRO EC was significantly different from sham at that time point (Tukey's HSD, $P < 0.05$). Unidirectional error bars, 1 SE.

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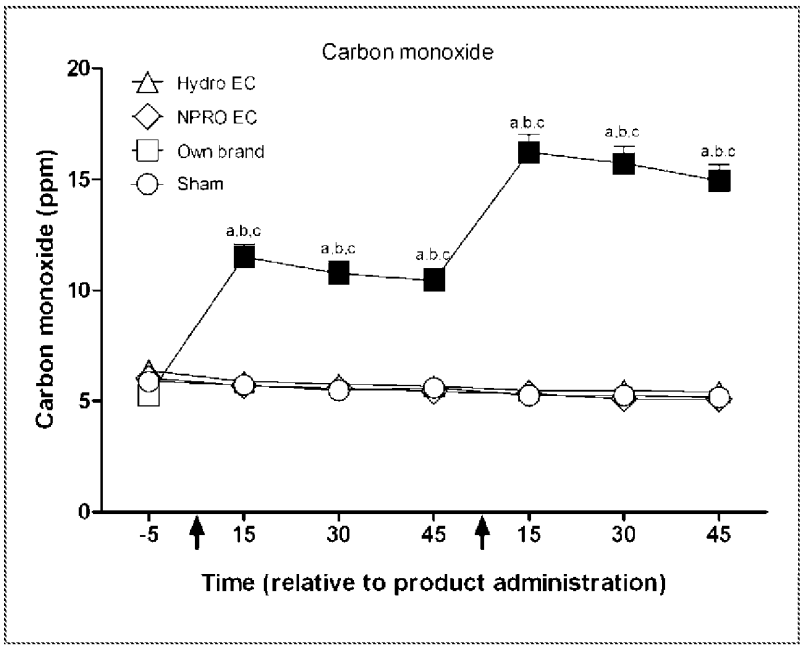


Figure 2. Mean data for carbon monoxide (CO) as a function of condition and time. *X*-axis, time in minutes relative to product administration; arrows, first and second product administrations. *Y*-axis, CO in parts per million (ppm); filled symbols, significant difference from baseline. An "a," "b," or "c" indicates that own brand was significantly different from sham, Hydro EC, or NPRO EC at that time point. A "d" indicates that Hydro EC was significantly different from sham at that time point. An "e" indicates that NPRO EC was significantly different from sham at that time point (Tukey's HSD, $P < 0.05$). Unidirectional error bars, 1 SE.

and "urge to smoke a cigarette." Own brand generally decreased ratings on all of these measures. NPRO EC and Hydro EC produced some abstinence symptom suppression on two measures: "craving a cigarette" and "urge to smoke." Figure 3B depicts data for ratings of "craving a cigarette" (the measure with the largest F-value). Ratings of "urge to smoke" decreased significantly 5 minutes following the first Hydro EC administration, and 5, 15, and 30 minutes following the first and second NPRO EC administrations relative to baseline. Ratings of "urge to smoke" decreased significantly at all time points following the first and second own-brand administrations relative to baseline, and own brand was significantly different from Hydro EC and NPRO EC at several time points. Similar effects of own brand, Hydro EC, and NPRO EC were observed on ratings of "craving a cigarette" (Fig. 3B).

Direct effects of nicotine. Significant condition by time interactions were observed on VAS items assessing "dizzy" and "lightheaded." Own brand significantly increased ratings of "lightheaded" and "dizzy" within the first five minutes following the first administration. NPRO EC, Hydro EC, and sham did not alter ratings significantly on these measures.

Direct effects of tobacco. Significant condition by time interactions were observed for ratings of "satisfying," "pleasant," "taste good," "dizzy," "calm," "concentrate," "awake," "reduce hunger," "taste like own brand," "feel like own brand," "harsh as own brand," "mild as own brand," and "smoke another cigarette right now." Ratings of "calm" and "satisfying" are shown in Fig. 3C and D. Ratings of "satisfying" and "pleasant" increased significantly at all time points under the Hydro EC, NPRO EC, and own-brand conditions (relative to baseline). Own brand increased ratings of "satisfying" and "pleasant" to a significantly greater degree than Hydro EC or NPRO EC. Ratings of "taste good," "calm," "concentrate," "awake," and "reduce hunger" increased significantly at all time points after own brand and at several time points after Hydro EC and NPRO EC (relative to baseline). Ratings of "taste like own brand," "feel like own brand," "harsh as own brand," and "dizzy" increased significantly at all time points under the own-brand condition (relative to baseline and sham). Ratings of "mild as own brand" increased significantly at all time points under the own-brand condition (relative to baseline and sham) and at nearly all time points under the Hydro EC condition (relative to baseline). Ratings of "smoke another cigarette right now" increased significantly relative to baseline at all time points under the Hydro EC and NPRO EC conditions, and 30 and 45 minutes postadministration 1 and 45 minutes postadministration 2 under the own-brand condition.

Discussion

The purpose of this acute study was to describe clinical laboratory methods that could be used to understand electronic cigarettes better by examining users' toxicant exposure, cardiovascular response, and subjective reports. The results of this study show the usefulness of the clinical model and suggest that, unlike puffing from a tobacco cigarette, two 10-puff bouts with the two electronic cigarettes described here expose users to no measurable nicotine or CO and do not increase heart rate. Despite the failure to deliver nicotine, acute use of

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the two products tested in this study produced some tobacco abstinence symptom suppression and increased subjective ratings of acceptability. Relative to the effects produced by an own-brand tobacco cigarette, these subjective effects of electronic cigarettes were modest.

With regard to nicotine exposure, the observation that 20 puffs from Hydro EC (16-mg cartridge) and NPRO EC (18-mg cartridges) did not increase plasma nicotine concentration significantly is entirely consistent with our preliminary report regarding these products (21). The plasma nicotine results are also consistent with the heart rate data reported here. That is, heart rate increases are observed when nicotine is administered via pharmaceutical products (34, 35) or tobacco products (32, 33, 36), and we observed increased heart rate when participants in this study smoked their own brand of cigarette (that also delivered nicotine). However, no heart rate increases were observed in either electronic cigarette condition (where no significant increases in plasma nicotine were observed). Finally, the mean peak changes from baseline in plasma nicotine concentration observed for NPRO EC (1.4 ng/mL) and Hydro EC (0.5 ng/mL) during the first product administration were similar in magnitude to the maximum nicotine concentration reported for a third electronic cigarette brand with a 16-mg cartridge (1.3 ng/mL; ref. 20). The consistency of results across participants, measures, and laboratories highlights the reliability of the clinical methods reported here (see also ref. 24), while also calling into question the ability of the three different electronic cigarettes that have been tested to date to approximate the nicotine delivery of a tobacco cigarette under acute conditions.

In spite of delivering no measurable nicotine, both electronic cigarettes tested in this study reduced ratings of "craving a cigarette" and "urge to smoke" and increased subjective ratings of product acceptability (e.g., "satisfying," "taste good," "pleasant"). These results are consistent with anecdotal reports from long-term electronic cigarette users and support the notion that electronic cigarettes may provide an alternative, perhaps a substitute, to cigarette smoking in some cases (11, 12). Interestingly, denicotinized cigarettes have also been shown to suppress tobacco abstinence symptoms for as

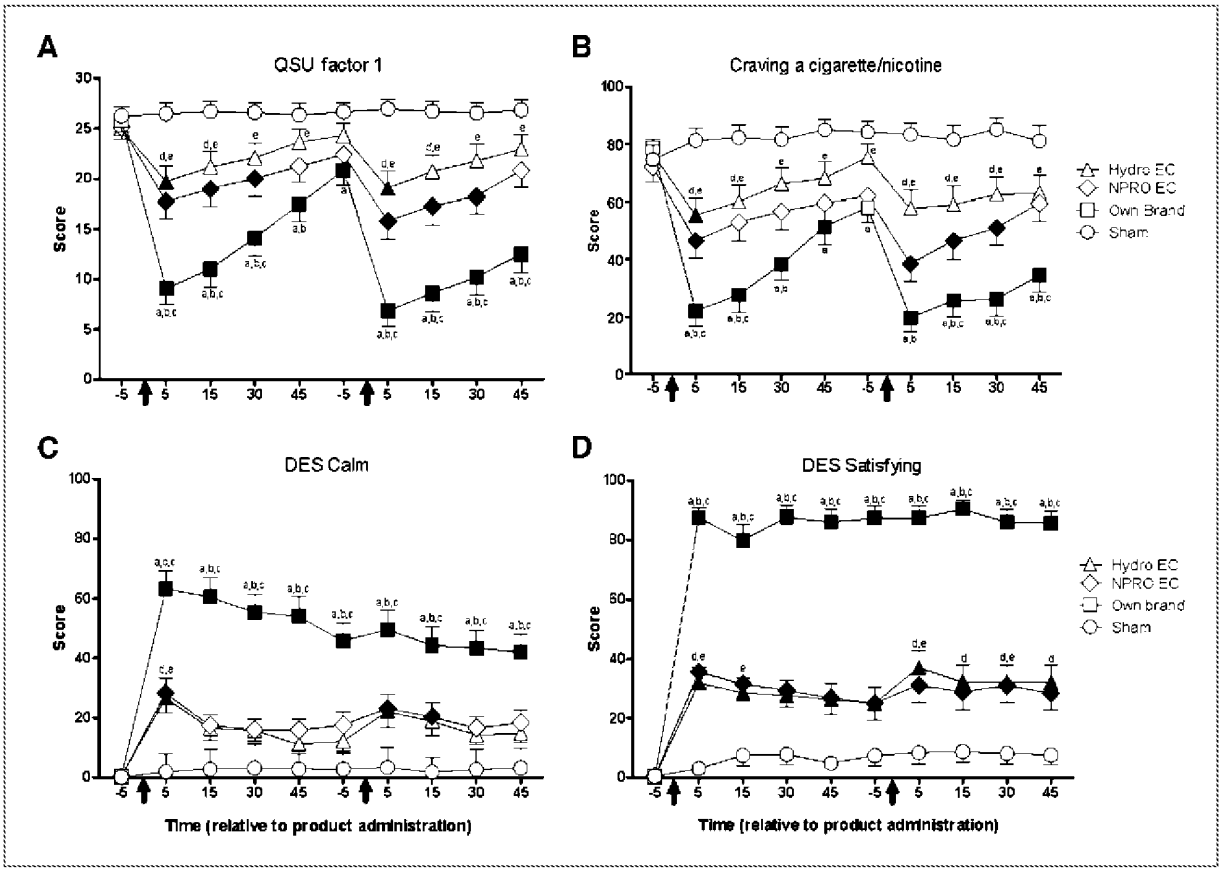


Figure 3. Mean data for QSU factor 1 ratings (A), ratings of "craving a cigarette" (B), ratings of "calm" (C), and ratings of "satisfying" (D) as a function of condition and time. *X*-axes, time in minutes relative to product administration; arrows, first and second product administrations. *Y*-axes, subjective ratings; filled symbols, significant difference from baseline. An "a," "b," or "c" indicates that own brand was significantly different from sham, Hydro EC, or NPRO EC at that time point. A "d" indicates that Hydro EC was significantly different from sham at that time point. An "e" indicates that NPRO EC was significantly different from sham at that time point (Tukey's HSD, $P < 0.05$). Unidirectional error bars, 1 SE. DES, direct effects of smoking.

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long as 96 hours (37). However, under the acute conditions reported here, the two electronic cigarettes did not suppress nicotine/tobacco abstinence symptoms fully, relative to own-brand smoking. Other PREPs that failed to suppress abstinence symptoms fully have been shown to supplement rather than substitute for cigarette smoking (9, 24, 37, 38). Further controlled evaluation is needed to determine the extent to which the effects reported here are sufficient for electronic cigarettes to substitute for tobacco cigarettes, and in what proportion of smokers and under what conditions this substitution effect might occur.

Importantly, neither of the electronic cigarettes tested in this study was associated with any measurable CO exposure. Long-term CO exposure has been linked to cardiovascular disease caused by tobacco cigarette smoking (39). In part for this reason, substituting noncombustible tobacco or nicotine products for cigarettes has been suggested as a potentially effective strategy for reducing the harm of tobacco smoking (40). Following this same logic, and taking into account the trace levels of tobacco-specific nitrosamines found in some electronic cigarette products (13), electronic cigarettes may also warrant careful empirical examination by those interested in harm reduction for smokers. Clinical laboratory methods have an important role to play in this empirical examination, and can reveal carcinogen exposure and abstinence symptoms suppression over several days' PREP use (22, 24, 33, 41). These methods will likely be extremely important to any future regulation of electronic cigarettes either as tobacco products or drug delivery devices in the United States (i.e., by the Food and Drug Administration) and elsewhere.

Methodologic considerations of the current study include the brief electronic cigarette exposure period, rigorous control over some aspects of smoking behavior, use of two brands of electronic cigarette with similar cartridge nicotine content, and inclusion of electronic cigarette–naïve participants who may be representative of cigarette smokers sampling an electronic cigarette for the first time, but not of a more experienced electronic cigarette user population. The results of some outcome measures might be influenced by longer-term use, different puffing profiles, other electronic cigarette models/cartridge strengths, and/or the user's previous experience with electronic cigarettes. In future studies, control conditions other than own brand and sham smoking might be of interest. Indeed, a recently published study compared the subjective and physiologic effects of another brand of electronic cigarette, the Ruyan electronic cigarette, to that of a pharmaceutical nicotine inhalator and found that the two products were associated with similar low levels of nicotine exposure, incomplete withdrawal suppression, and moderate acceptability (20). In addition, behavioral studies that assess the reinforcing/rewarding properties of electronic cigarettes could reveal the extent to which electronic cigarettes might be used or abused (42). Finally, the adverse event profile associated with long-term use of electronic cigarettes is uncertain, and must be explored empirically. Many of these methodologic issues and research questions can be addressed parametrically and conveniently in the clinical laboratory, highlighting the strength of these efficient and reliable evaluation methods (see also ref. 24).

In sum, this study revealed that two electronic cigarette brands do not expose electronic cigarette–naïve users to nicotine or carbon monoxide under the acute testing procedures described here, but do produce some tobacco abstinence symptom suppression and positive ratings of product acceptability. Although these results are necessarily a function of the products tested and procedures used, they suggest that electronic cigarette–naïve individuals may require substantial motivation if they are to learn whatever product/procedure combination maximizes these outcomes for them. Future clinical laboratory evaluation can build on these methods and results to establish the extent to which electronic cigarettes might be expected to substitute for tobacco cigarettes, and help to identify under what conditions this substitution might occur. Parallel studies addressing the abuse liability and long-term adverse event profile of electronic cigarettes are also required to ensure safety and appropriate labeling and marketing of these products.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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A Clinical Laboratory Model for Evaluating the Acute Effects of Electronic "Cigarettes": Nicotine Delivery Profile and Cardiovascular and Subjective Effects

Andrea R. Vansickel, Caroline O. Cobb, Michael F. Weaver, et al.

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APPENDIX G

Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial

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ABSTRACT

Objectives To measure the short-term effects of an electronic nicotine delivery device ("e cigarette", ENDD) on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects.

Design Single blind randomised repeated measures cross-over trial of the Ruyan V8 ENDD.

Setting University research centre in Auckland, New Zealand.

Participants 40 adult dependent smokers of 10 or more cigarettes per day.

Interventions Participants were randomised to use ENDDs containing 16 mg nicotine or 0 mg capsules, Nicorette nicotine inhalator or their usual cigarette on each of four study days 3 days apart, with overnight smoking abstinence before use of each product.

Main outcome measures The primary outcome was change in desire to smoke, measured as "area under the curve" on an 11-point visual analogue scale before and at intervals over 1 h of use. Secondary outcomes included withdrawal symptoms, acceptability and adverse events. In nine participants, serum nicotine levels were also measured.

Results Over 60 min, participants using 16 mg ENDD recorded 0.82 units less desire to smoke than the placebo ENDD ($p=0.006$). No difference in desire to smoke was found between 16 mg ENDD and inhalator. ENDDs were more pleasant to use than inhalator ($p=0.016$) and produced less irritation of mouth and throat ($p<0.001$). On average, the ENDD increased serum nicotine to a peak of 1.3 mg/ml in 19.6 min, the inhalator to 2.1 ng/ml in 32 min and cigarettes to 13.4 ng/ml in 14.3 min.

Conclusions The 16 mg Ruyan V8 ENDD alleviated desire to smoke after overnight abstinence, was well tolerated and had a pharmacokinetic profile more like the Nicorette inhalator than a tobacco cigarette. Evaluation of the ENDD for longer-term safety, potential for long-term use and efficacy as a cessation aid is needed.

Trial registration No.12607000587404, Australia and New Zealand Clinical Trials Register

Nicotine replacement therapies (NRTs) are safe and effective aids for smoking cessation[1]; however, they remain underutilised.[2] To widen their appeal to smokers, a variety of effective NRTs and cigarette smoking alternatives are needed. In 2004, a Beijing-based company, Ruyan Group (Holdings) Ltd, China, patented and launched an electronic nicotine delivery device (ENDD) or "e-cigarette",[3] a battery-powered device resembling a cigarette that contains a microelectrical circuit activated by drawing on the mouthpiece. With each puff, a small amount of nicotine-propylene glycol solution contained in replaceable cartridges is heated and vapourised, to create a visible mist without smoke or flame. Manufacturers now export a growing number and variety of these devices to industrialised countries. People report buying them to help quit smoking, to reduce cigarette consumption and costs, to relieve tobacco withdrawal symptoms due to workplace smoking restrictions, or as a replacement for cigarette smoking.[4]

Although ENDD use has not been comprehensively studied, to our knowledge, no deaths or hospitalisations from ENDD use have been reported. Analyses of emissions of the Ruyan V8 ENDD suggest a low risk of toxicity (M Laugesen, 2009, TC2009/034355, submitted). The risk of impurities in the cartridge liquid is, however, of concern to the US Food and Drug Administration,[5] and there is a lack of internationally certified manufacturing sites. Regulators also lack data on the ability of ENDDs to relieve the desire to smoke cigarettes and to suppress other tobacco withdrawal symptoms. Study designs that assess change in subjective withdrawal symptoms have been used to evaluate the utility of other novel nicotine delivery devices.[6–8] Using such an approach, this study compared the Ruyan V8 ENDD containing 16 mg nicotine cartridges to one containing 0 mg cartridges (identical in appearance and in chemistry but lacking nicotine), Nicorette nicotine inhalator and usual cigarettes. We measured change in desire to smoke, withdrawal symptoms, product preferences, serum nicotine levels and adverse events after 1 day's use.

METHODS

Participants

Participants were recruited from the local community in Auckland, New Zealand, between January 2008 and February 2008. They were assessed via an initial telephone call for eligibility (aged between 18 and 70 years, smoked 10 or more factory-made cigarettes per day for at least the past year, smoked their first cigarette of the day within 30 min of waking, and were not currently attempting to quit smoking or wishing to do so in the next 30 days). Eligible participants were invited to visit the study centre at The University of Auckland to give written informed consent, complete a questionnaire asking about demographic and smoking

characteristics and undergo screening (medical history, blood pressure, heart rate and urinalysis for glucose). We excluded people who reported recent myocardial infarction, angina pectoris or other serious medical conditions (diabetes mellitus, severe allergies, poorly controlled asthma or other airways disease, poorly controlled psychiatric disorders or current chemical dependence other than nicotine) and pregnancy (confirmed by positive urinary dipstick for βHCG), breast-feeding, blood pressure >180 mm Hg systolic and/or 100 mm Hg diastolic, weight <45 or >120 kg, or current use of any other smoking cessation medications. At this time, we invited all participants to indicate if they were also willing to give venous blood samples for analysis of nicotine.

Study medication

Ruyan V8 ENDDs supplied by the manufacturer, Ruyan Group (Holdings) Ltd, are pen-shaped devices that include a rechargeable lithium ion battery, an electronic circuit, a vaporiser, a replaceable cartridge and a mouthpiece. The cartridge labelled 16 mg contains 1.06 g of liquid comprising 8.8% water, 1.4% nicotine, 89.7% propylene glycol and 0.1% glycol (M Laugesen, 2009, TC2009/034355, submitted). Participants randomised to a day using the ENDD were asked to puff the device as they would their usual cigarette for 5 min. After the first hour, they left the study centre and used the device as required for a further 8 h before returning to complete the rating scales. We charged all batteries 2 weeks before the study and between each day of use to ensure they would operate as intended. Nicorette inhalators (manufactured at the time of the study by Pfizer Health AB, Helsingborg, Sweden) were purchased commercially. When participants used the inhalator, we gave them a blister pack of six inhalator cartridges, each containing 10 mg of nicotine for inhalation, with instructions to puff on the inhalator over 20 min in the first hour. Thereafter, they were instructed to use it freely, preferably hourly, up to a maximum of six cartridges over the day, as recommended by the manufacturer,[9] before returning to the study centre. When randomised to smoke their usual cigarettes, participants did so over the first 5 min in the first hour, then freely as they wished.

Sample size

Based on a previous study,[10] we estimated 48 participants would be needed to detect a one-point difference in desire to smoke on an 11-point (0–10) scale measured at 20 min, for the comparison between the 16 and 0 mg ENDD, assuming a within-participant SD of the response variable of 1.5 points and statistical power of 90% at a two-sided significance level of 5%.

Procedures

Participants were requested to abstain from smoking and alcohol from 20:00 on the night before each study day and from food and caffeine for at least 1 h before the session. On arrival at the study centre, carbon monoxide (CO) was measured in participants' expired breath using a Bedfont Smokelyser.[11] If CO was ≤15 parts per million (ppm), the assigned study treatment was allocated; however, if CO was >15 ppm or they reported smoking in the previous 12 h, participants were rescheduled wherever possible to a subsequent session. On the first study day, participants were randomised to use one of four different products: ENDDs containing nicotine (16 mg) or placebo (0 mg) capsules, Nicorette nicotine inhalator or their usual cigarette. Allocation was performed using a random sequence of four codes, each corresponding to one product, prepared in advance by the study statistician using the Latin-square method to control for time effects. Participants and investigators were blinded only to assignment to the ENDD condition (16 or 0 mg), and it was not possible to change the order of treatment allocation. Participants sat at desks in a room where they completed ratings of desire to smoke and other withdrawal symptoms 15 and 5 min before using their allocated product (these ratings were later averaged to provide baseline ratings). They rinsed their mouth with water (to equalise oral pH) and took their first dose at 08:30. When allocated to smoke their usual cigarettes, participants did so outside (required by law); however, when allocated to the ENDDs, participants used them indoors. Ratings were made at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min counting from the first puff on each product. Participants then left the study centre with instructions to continue their usual daily activities but not to smoke (unless in the usual cigarette group) and to use the study product regularly and freely throughout the day. They returned at 17:30 for CO measurement, to report product use including adverse events and the number of any cigarettes smoked, rate the degree of satisfaction and usefulness, and to return the remaining study product. Participants were allowed to smoke as they wished once these measures were collected and during the 3-day washout period between each study day. On the day allocated for using their own cigarette, participants did not take part in evening measurements.

A subset of participants gave venous blood samples for analysis of plasma nicotine concentrations. In this group, in addition to the procedures described above, on each study day, medical staff inserted an 18-gauge butterfly needle in a non-dominant forearm vein and withdrew 5-ml blood samples at baseline, then at 5, 10, 15, 30 and 60 min after initial dosing. Blood samples were held in vacuum tubes in a temperature-monitored cool box maintained between 0°C and 6°C and at the end of each study session were transported to a local laboratory for separation. The plasma fraction was frozen before being shipped to a national reference laboratory for nicotine concentration assay using the method developed by Mahoney and Al-Delaimy.[12]

Following study completion, participants were invited to attend a group cessation clinic run over 5 weeks. The majority attended at least one of these sessions.

Measures

We assessed withdrawal using three items from the Minnesota Nicotine Withdrawal Scale[13]: irritability, restlessness and difficulty concentrating. The other Minnesota Nicotine Withdrawal Scale items—increased appetite/weight gain, depression or insomnia—were not included because these would not be plausibly experienced in such a short period. We included an additional item, "desire to smoke" (a cigarette), a construct equivalent to the more commonly used terms "craving" or "urges",[14] which was measured by asking, "Right now, how much do you want a cigarette?" We asked participants to indicate their perception of all items by circling a visual analogue scale number between 0 and 10, where 0="not at all" and 10="extremely". Participants noted the occurrence of adverse events commonly experienced with NRT use using categories adapted from Hajek *et al*[15] and any other reactions not on this list. On the last study day, still blind to the ENDD condition, participants were asked to rate their satisfaction with the products compared to their usual cigarettes using scales (0="completely unsatisfying", 10="fully satisfying")[15]; on the same scale, they rated helpfulness (in keeping them from smoking), how pleasant the product was to use, how embarrassing it was to use in the company of others, the degree to

which they would use it to aid a quit attempt, and whether they would recommend it to a friend who wanted to stop smoking.

Statistical analysis

All analyses were undertaken on an intention-to-treat basis. We analysed the primary outcome, comparison of change in desire to smoke between the 16 and 0 mg ENDD, using area under the curve over 60 min as the dependent variable. The treatment effect was thus the average change in desire to smoke over the 60 min after first using each product. For this and the other ratings, the baseline score (the area under the curve at 5 min before product use), treatment effect and time period were fixed effects in the model. We also examined the change in desire to smoke between the ENDD and other products (inhalator and usual cigarette) using analysis of covariance with within-participant variation included as a random effect. We dealt with missing data using the last value carried forward method. Pharmacokinetic parameters (Cmax (peak plasma concentration) and tmax (time to reach Cmax)) were calculated based on plasma concentration-time data by model-independent methods using SAS version 9.2 (SAS Institute). Multiple comparisons between products were adjusted for using the Tukey-Kramer method and p values and 95% confidence intervals (CIs) were estimated for each comparison.

RESULTS

Participant characteristics

Figure 1 shows participant flow. Forty participants were randomised, 53% of whom were women. The mean age was 47.6 (SD 12.4) years and the mean level of nicotine dependence (Fagerström Test of Nicotine Dependence[16]) was 5.4. Participants smoked an average of 20.2 (SD 7.3) cigarettes smoked per day. Twenty-five participants had previously used nicotine patches, nineteen reported previously using nicotine gum, two had used the inhalator, but none had used an ENDD before. During the study days, most participants used the products regularly and abstained from smoking as instructed; however, when using the 16 mg ENDD, participants smoked on average 2.8 usual cigarettes over the day, compared with 4.5 cigarettes when using the 0 mg ENDD and 3.4 cigarettes when using the inhalator. Nine participants on average gave blood samples for pharmacokinetic analysis on each of 5 study days.

Desire to smoke and withdrawal symptoms

Figure 2 shows the change from baseline in desire to smoke over 60 min. Usual cigarette use resulted in significantly greater reductions in desire to smoke compared to ENDD (16 and 0 mg) and inhalator. Desire to smoke ratings reached their lowest level 5 min after the first puff with usual cigarettes, 10 min after the first puff with 0 mg ENDD, 15 min after first puff with 16 mg ENDD and on completing 20 min of puffing on the inhalator. Over the 60 min period, participants using the 16 mg ENDD experienced a greater decrease in desire to smoke (2.6 units) than participants using the 0 mg ENDD (1.8 units), a difference of 0.82 units (95% CI 0.25 to 1.38; p=0.006) (see table 1). In the comparisons between 16 and 0 mg ENDD at each time point, the difference in desire to smoke became significant from 25 min through to 60 min, when users recorded 1.3 units (95% CI 0.33 to 2.25, p=0.009) less desire to smoke with the 16 mg ENDD than the 0 mg ENDD.

Over 60 min, the use of the 16 mg ENDD reduced ratings for irritability, restlessness and difficulty concentrating more than the 0 mg ENDD; however, these differences were not statistically significant (table 1). Similarly, there was no difference in withdrawal symptoms between the 16 mg ENDD and inhalator, whereas usual cigarettes reduced withdrawal ratings more on all items than the other products.

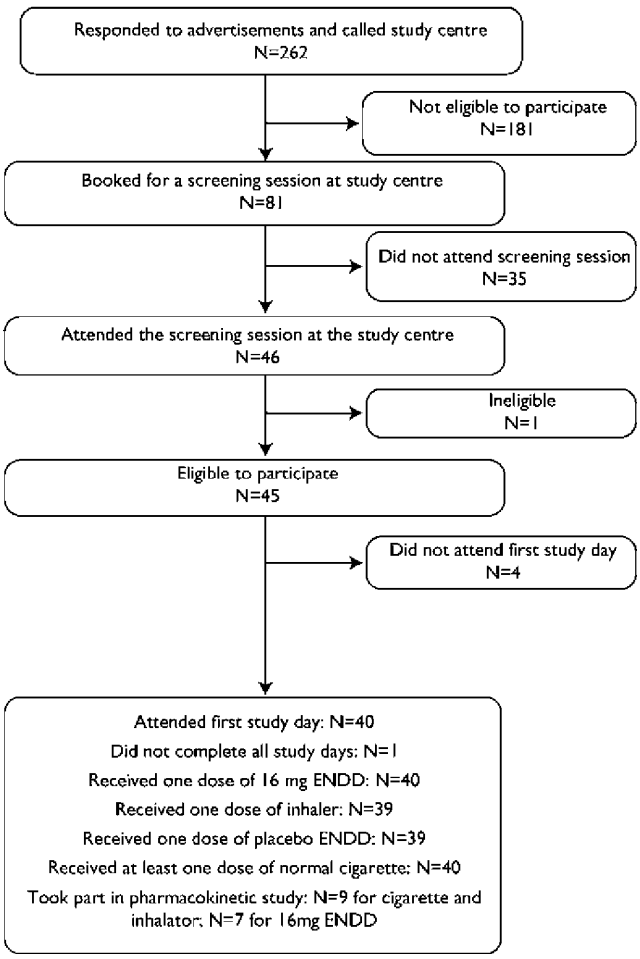


Figure 1 Participant flow.

Results of the secondary analyses comparing the 16 mg ENDD, inhalator, usual cigarette and 0 mg ENDD are shown in table 2. Although a greater reduction in desire to smoke was observed with the 16 mg compared to the 0 mg cigarette, this difference was no longer significant when adjusted for multiple comparisons.

Product preferences

The 16 mg ENDD rated higher for pleasantness of use than the inhalator, by 1.49 units (95% CI 0.23 to 2.74, p=0.016). Figure 3 shows that mean satisfaction ratings for 16 mg ENDD and inhalator were similar and were higher than those for placebo ENDD, and embarrassment associated with using the device in the company of others was low but not significantly different to the inhalator. The 16 mg ENDD was favoured over other products for enabling participants to keep from smoking, to be used as a potential quitting aid and for recommending to a friend who wanted to stop smoking. It was also the most preferred alternative to cigarettes: 58% of participants said they preferred the ENDD, 25% preferred the inhalator and 13% liked neither. The degree of ease of use was similar for ENDD and inhalator (48% and 45%, respectively).

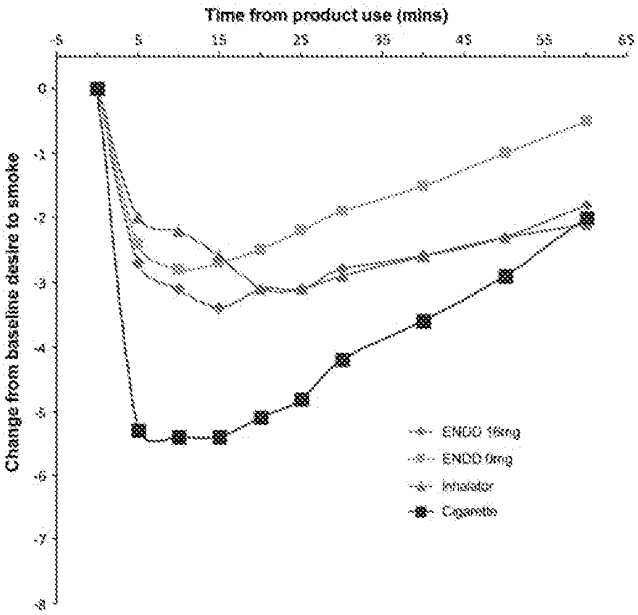


Figure 2 Change in desire to smoke from baseline over the first hour after each product use.

Pharmacokinetics

On average, the use of the 16 mg ENDD resulted in modest increases in blood nicotine levels (see table 3). The fastest time to peak nicotine concentration was obtained with usual cigarettes, followed by nicotine ENDDs and the inhalator. Usual cigarette use gave a significantly higher Cmax than the other products in the individual product and crossover analysis, with adjustment for multiple comparisons (p=0.01).

Adverse events

The most frequently reported adverse events were mouth and throat irritation (table 4), and were most common with the inhalator (88%) and least common with the 0 mg ENDD (22%). The differences between active and placebo ENDDs and inhalator were statistically significant (p<0.001). Nausea was most commonly reported after 16 mg ENDD use, but, as with the other between-product differences in adverse events occurrence, was not significant. No serious adverse events (ie, deaths or events requiring hospitalisation) occurred during the study.

DISCUSSION

The 16 mg Ruyan ENDD was significantly more effective than the 0 mg ENDD at reducing desire to smoke over 1 h of use. The 0 and 16 mg ENDD relieved desire to smoke within the first 10 min of use, but the 16 mg ENDD reduced desire to smoke most at 15 min (10 min after the last puff), more than either the 0 mg ENDD or the nicotine inhalator, which was still being puffed as per instructions given to participants. The reduction in desire to smoke in the first 10 min of ENDD use appears to be independent of nicotine absorption, and may be due to behaviours and oral and tactile sensations similar to cigarette smoking, and the anticipation of nicotine delivery.

Table 1 Primary comparisons of change in desire to smoke and other withdrawal symptoms from baseline between 0 and 16 mg nicotine ENDD

Withdrawal symptom*	Mean change (95% CI)	p Value
Desire to smoke	0.82 (0.25 to 1.38)	0.006
Irritability	0.26 (−0.48 to 0.99)	0.48
Restlessness	0.53 (−0.11 to 1.18)	0.10
Poor concentration	0.39 (−0.30 to 1.07)	0.26

*Visual analogue scale 0 to 10.

Table 2 Secondary analyses using multivariate* comparisons of change in desire to smoke from baseline between all products

Product comparison	Mean difference (95% CI)	Adjusted p value
0 versus 16 mg ENDD	0.80 (−0.27 to 1.86)	0.21
0 mg ENDD versus Nicorette inhalator	0.69 (−0.38 to 1.77)	0.33
0 mg ENDD versus usual cigarette	2.23 (1.17 to 3.30)	<0.0001
16 mg ENDD versus Nicorette inhalator	−0.10 (−1.16, 0.95)	0.99
16 mg ENDD versus usual cigarette	1.44 (0.39 to 2.48)	0.003
Nicorette inhalator versus usual cigarette	1.54 (0.48 to 2.59)	0.001

ENDD, electronic nicotine delivery device.
*Adjusted for treatment period, baseline craving, within-participant correlation as a random effect and multiple comparisons using Tukey-Kramer method.

In the pharmacokinetic analyses, the serum nicotine Cmax for usual cigarettes was comparable with other studies.[17] The 16 mg ENDD's performance was consistent with findings from intensive-mode smoking machine tests of this same make of ENDD, which delivered 10% of the nicotine per puff delivered by a regular Marlboro cigarette (M Laugesen, 2009, TC2009/034355, submitted). This suggests that it is more like a NRT product, concerning nicotine delivery, than a cigarette. The shorter tmax of the ENDD in comparison to the inhalator may reflect some absorption via the respiratory tract compared with buccal absorption for the Nicorette inhalator. The ENDDs in the study were not as consistent for puffing and nicotine delivery as the medicinal Nicorette inhalator. About one-third of participants showed no increase in blood nicotine when using the ENDD. Some participants reported that the device sometimes failed to produce mist when puffed. It is possible that technical problems could have affected the dose received. This is not altogether surprising given that these devices are not manufactured to the same standards required of pharmaceutical devices, such as the inhalator.

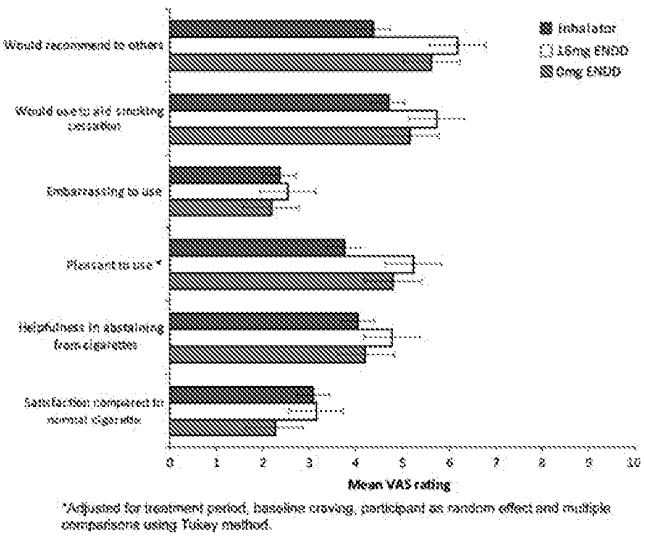


Figure 3 A higher rating is indicative of a greater likelihood of finding the product more satisfying, helpful, pleasant, embarrassing, likely to be used for aiding smoking cessation and to be recommended to others (error bars represent standard error).

Table 3 Pharmacokinetic properties of usual cigarette, 16 mg ENDD and Nicorette inhalator

Product	Mean tmax (min) (95% CI)	Mean Cmax (ng/mL) (95% CI)*
Usual cigarette (n=9)	14.3 (8.8 to 19.9)	13.4 (6.5 to 20.3)
16 mg ENDD (n=8)	19.6 (4.9 to 34.2)	1.3 (0.0 to 2.6)
Nicorette inhalator (n=10)	32.0 (18.7 to 45.3)	2.1 (1.0 to 3.1)

ENDD, electronic nicotine delivery device.
*Corrected for baseline nicotine levels.

We also noted that three participants (one using the inhalator, two using ENDDs) had high baseline serum nicotine values (12.8, 12.0 and 6.6 ng/ml), which declined over the hour, raising the possibility of recent smoking of a tobacco cigarette, despite CO readings suggesting otherwise. Excluding these data in a post hoc analysis on the primary outcome and withdrawal symptoms gave a small increment in the mean decrease in desire to smoke, from 0.82 to 0.91 units (95% CI 0.29 to 1.53), which was still significant (p=0.006) compared to placebo, with little change to the values and significance of changes in irritability, restlessness and poor concentration.

Overall, the Ruyan ENDD was similar to the Nicorette inhalator on a range of subjective ratings of user preferences, and users reported a similar frequency of most adverse events except for a far lower occurrence of mouth or throat irritation than for the inhalator.

The strengths of this study include the study population of dependent but "healthy" male and female smokers recruited from the community; the use of a crossover design to minimise variability, bias and confounding; and the use of items from validated instruments for measuring key outcomes. We used a range of statistical tests including mixed model analysis, which has the advantage of including all the data and accounting for within-subject correlation.

The study has a number of limitations. First, it was statistically powered to detect a difference between 16 mg ENDD and 0 mg ENDD, not to detect a difference between 16 mg ENDD and inhalator, and the desired sample size of 48 was not achieved despite best endeavours to recruit to this target. Second, low baseline ratings of desire to smoke may have limited the degree of observable change. Third, the study was limited to smokers not intending to quit, which may underestimate the reduction in desire to smoke expected in smokers intending to quit. Fourth, this was the first experience for participants and investigators with the ENDD and there was no period of familiarisation with the products before use nor did we test them to ensure normal functioning. Both factors could have affected the pharmacokinetic results and attenuated the ratings of desire to smoke. Fifth, the four-fold greater puffing time allowed for the inhalator is problematic for comparing products, as it is by no means clear yet whether an ENDD inhaling session should be for 5, 10 or 20 min a session. Finally, use of each study product for just 9 h did not allow sufficient time for assessment of delayed acute or chronic use effects, nor of the potential for long-term use.

Table 4 Adverse events reported by participants after 9 h of product use, by product

Adverse event	ENDD 0 mg n/N*	(%)	ENDD 16 mg n/N	(%)	Nicorette inhalator n/N	(%)
Mouth/throat irritation†	14/64	22	22/58	38	36/41	88
Aching jaws	4/35	11	3/37	8	2/37	5
Nausea	6/33	18	9/31	29	6/33	18
Flatulence/belching/ hiccups/heartburn	6/111	5	6/113	5	11/147	23
Vertigo/feeling high	9/69	9	14/66	21	12/66	18
Headache	7/32	22	6/34	18	6/33	18
Sweatiness/clammy skin	3/75	4	3/77	4	2/76	3
Palpitations	0/38	0	2/38	5	0/39	0

ENDD, electronic nicotine delivery device.
*n=number of events, N=numbers of participants in each group. In some cases, groups were pooled because of similarity of symptoms, hence the large numbers.
†ENDD 0 mg versus inhalator p<0.001; ENDD 16 mg versus inhalator p<0.001.

What this study adds

- The Ruyan 16 mg nicotine ENDD reduces desire to smoke.
- The ENDD has a pharmacokinetic profile more like the nicotine inhalator than a tobacco cigarette.
- Further research is needed on the pharmacokinetics, long-term use potential, safety, manufacturing quality and quitting efficacy associated with ENDD use.

CONCLUSIONS

The Ruyan V8 16 mg ENDD reduced desire to smoke more than the placebo ENDD and during 9 h of use was well tolerated, acceptable to most users, rated significantly more pleasant to use than the inhalator, and in the first hour exhibited a pharmacokinetic profile more like the inhalator than a tobacco cigarette, without excess adverse events. These findings suggest potential to help people stop smoking in the same way as a nicotine inhalator. Our findings should be regarded as preliminary and need to be confirmed for this and other brands of ENDD. The nicotine pharmacokinetics of ENDDs should be confirmed in other studies, and different ways of using these devices need to be explored. A large, well-conducted randomised trial is needed to evaluate the ENDD's efficacy as a quitting aid and to identify any delayed or long-term adverse effects.

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Competing interests CB, ST and RL have no competing interests to declare. HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. ML acted as contract manager with the sponsor, Ruyan Group (Holdings) Limited, via his company Health New Zealand Ltd. ML and Health New Zealand Ltd have no patent, stock or other financial interest in Ruyan Group (Holdings) Limited or any nicotine or tobacco company. MG has provided consultancy to the manufacturers of smoking cessation medications.

Ethics approval Ethical approval for the trial was obtained from the New Zealand Ministry of Health's Northern Y Ethics Committee (approval number NTY/07/10/109).

Contributors CB, HM, ST, MG, RL and ML designed and conducted the study, interpreted the data, and wrote the manuscript. CB, HM and ST are guarantors.

Provenance and peer review Not commissioned; externally peer reviewed.

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APPENDIX H

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REVIEW

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The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis

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Abstract
Objectives E-cigarettes are increasingly popular as smoking cessation aids. This review assessed the efficacy of e-cigarettes for smoking cessation as well as desire to smoke, withdrawal symptoms, and adverse events in adult smokers.
Methods A systematic review was conducted. Studies comparing e-cigarettes to other nicotine replacement therapies or placebo were included. Data were pooled using meta-analysis.
Results Of 569 articles, 5 were eligible. Study participants were more likely to stop smoking when using nicotine e-cigarettes (43/489, 9 %) versus placebo e-cigarettes (8/173, 5 %); however, this difference was not statistically significant (RR 2.02; 95 % CI 0.97, 4.22). The pooled effect estimates for the desire to smoke (RR −0.22; 95 % CI −0.80, 0.36), irritability (RR −0.03; 95% CI −0.38, 0.31), restlessness (RR −0.03; 95 % CI −0.42, 0.35), poor concentration (RR −0.01; 95 % CI −0.35, 0.32), depression (RR −0.01; 95 % CI −0.22, 0.20), hunger (RR −0.01; 95 % CI −0.32, 0.30), and average number of non-serious adverse events (RR −0.09; 95 % CI −0.28, 0.46) were not statistically significantly different. Only one study reported serious adverse events with no apparent association with e-cigarette use.
Conclusions Limited low-quality evidence of a non-statistically significant trend toward smoking cessation in adults using nicotine e-cigarettes exists compared with other therapies or placebo. Larger, high-quality studies are needed to inform policy decisions.

Keywords Meta-analysis · E-cigarettes · Smoking cessation · Withdrawal symptoms · Public health

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Introduction

An estimated 1.2 billion people use tobacco worldwide (World Health Organization 2014). Tobacco-related deaths are one of the main causes of preventable early mortality, claiming 5 million lives annually (World Health Organization 2014). Smoking cessation is associated with significant health benefits, including reducing the risk of developing lung cancer, heart disease, and stroke (Polosa and Benowitz 2011). Despite the benefits of cessation and the desire of most smokers to quit, approximately 80 % of those who attempt to quit on their own relapse within the first month of abstinence, and only 3-5 % remain abstinent for 6 months or longer (Hughes et al. 2004).

The most common aids for smoking cessation are nicotine replacement therapies (NRTs), such as skin patches and chewing gums. However, they do not provide the additional sensory rituals that smokers seek (Caponnetto

et al. 2013). It is suggested that electronic cigarettes (e-cigarettes) are a more analogous alternative (Caponnetto et al. 2012). E-cigarettes are battery-powered electronic drug delivery systems designed to provide users with a low concentration of nicotine, without the exposure to tobacco smoke and its harmful constituents. With each puff, a liquid containing nicotine is heated and vaporized to create a visible vapor without smoke or flame, while also allowing for handling and puffing actions (Yamin et al. 2010). Thus, e-cigarettes can address the psychological, cognitive, social, and behavioral elements of smoking, where most alternatives fail to do so (Caponnetto et al. 2012).

The e-cigarette is becoming an emerging phenomenon of increasing popularity with smokers. The use of e-cigarettes has increased from 3 % in 2010, to 7 and 11 % in 2012 and 2013, respectively. Furthermore, the number of people who reported having tried e-cigarettes has increased from 9 % in 2010 to 22 % in 2012 and 35 % in 2013 (ASH 2014). Given these statistics, many countries are in the process of creating regulations around e-cigarettes. Bans on e-cigarette sales have been proposed by some jurisdictions, and others have recommended that e-cigarettes should be regulated as tobacco products with lower nicotine content (Bam et al. 2014; MHRA 2014). Canadian regulations currently ban the sale, import, or advertising of e-cigarettes containing nicotine (Stanbrook 2013). However, online advertising from other countries where e-cigarettes are not prohibited is readily accessible. In summary, the use of e-cigarettes among smokers is increasing rapidly in Canada because of users' ability to smoke them in prohibited areas and the perception of their safety (Stanbrook 2013).

Results from a recent UK survey concluded that e-cigarettes might be effective in helping smokers quit or reduce their smoking and avoid relapse (Etter and Bullen 2011; Fidler et al. 2011). Furthermore, two prospective cohort studies suggest that e-cigarettes can aid smoking abstinence (Polosa et al. 2011, 2014). Health-care providers, regulatory agencies, and public health decision-makers are interested in whether e-cigarettes can reduce the harm associated with smoking and achieve smoking abstinence better than current methods. The clinical evidence regarding the effectiveness, safety, and harm associated with e-cigarettes for smoking cessation recently began to undergo a more thorough examination in a manner similar to other drugs and devices (Caponnetto et al. 2012).

There have been several narrative reviews (Franck et al. 2014; Harrell et al. 2014; Orr and Asal 2014; Pepper and Brewer 2013) summarizing the available studies on e-cigarettes, though at the time, the limited existing data prohibited estimating their overall safety and efficacy through meta-analysis. However, primary research on e-cigarettes is in high demand; thus many studies are underway, two of which have been published (Bullen et al. 2013; Caponnetto et al. 2013). Recently, a systematic review and meta-analysis was published by the Cochrane Collaboration group (McRobbie et al. 2014), which reported that participants using nicotine-containing e-cigarettes are approximately two-and-a-half times (RR 2.29; 95 % CI 1.05, 4.96) more likely to have abstained from smoking for at least 6 months compared to those using placebo-containing e-cigarettes. Their review included both comparative studies and cohort follow-up studies with 6 months or longer follow-up. Conversely, our review focuses only on comparative studies both long-term behavioral studies with 6 months or longer follow-up period and short-term pharmacotherapy studies, where nicotine-containing e-cigarettes are compared to placebo-containing e-cigarettes or any other NRTs. It also investigates additional patient-important outcomes not reported in previous reviews, including the desire to smoke and withdrawal symptoms. Hence, a thorough and well-conducted review investigating the efficacy and the short-term effects of e-cigarettes, compared to placebo or any other nicotine replacement therapies, would be timely and useful for public health decision-makers.

Methods

Literature search strategy

A comprehensive systematic literature search was developed by an information specialist (KC) and the primary reviewer (SK). Bibliographic databases were searched, using the OVID interface, up to May 26, 2014: MEDLINE (1946-present), EMBASE (1974-present), PsychINFO (1860-present) and the Cochrane Central Registry of Controlled Trials (CENTRAL; April 2014). Terminology was used to search controlled vocabularies (MeSH and EMTREE) and keywords on the concept of "electronic cigarette" or "e-nicotine" (Supplementary Table 1). No limits on year, language, or human subjects were applied. Gray literature was identified through searching the websites of health technology assessment (HTA) and related agencies, as well as reports of major smoking cessation conference proceedings. The Google search engine was used to search for additional Web-based materials and information. These searches were supplemented by reviewing the bibliographies of key papers. All search results were imported into a Reference Manager Version 12 database, for duplicate removal and reference management.

Inclusion criteria

Articles were included if they met the following criteria: randomized controlled trials (RCTs) or comparative observational studies; comparing interventions with nicotine-containing e-cigarettes (any brand, any dose) to other nicotine replacement therapies (e.g., nicotine patches, nicotine gums, nicotine inhalers etc.) or placebo-containing e-cigarettes; healthy adults (≥18 years old); current smokers (≥10 cigarettes per day) regardless of whether they were considering quitting; and reports of any of the following outcomes: smoking abstinence for at least 6 months from the start of e-cigarette use; desire to smoke for at least 1 h after e-cigarette use; number of cigarettes smoked per day; withdrawal symptoms (i.e., irritability, restlessness, poor concentration, anxiety, depression, and hunger); serious and non-serious adverse events.

Exclusion criteria

Trials with non-human subjects; subjects with comorbidities or other health complications; no comparison group; non-intervention trials (e.g., review, conference abstract, case report, comment, editorial, news, survey, recommendation, or expert opinion) were excluded.

Study selection

The reviewers (SK, TD) independently screened study titles and abstracts based on the pre-specified inclusion and exclusion criteria. The full text articles of potentially eligible studies were retrieved and assessed by both reviewers independently to confirm inclusion or exclusion. Disagreements were resolved through discussion and consensus. No third party was required, although available (LL).

Data abstraction

The reviewers (SK, TD) independently extracted data from included studies using predesigned and piloted forms, including details on the following: patient demographics, intervention, comparator, study outcomes, country, year and length of follow-up. Furthermore, information on the methodology of the study and the funding source(s) was also extracted for quality assessment. The authors were contacted when data were reported in graphical form, were unclear, or missing. A second reviewer verified the data abstraction.

Quality assessment

The reviewers (SK, TD) independently assessed the methodological quality of included RCTs using the Cochrane Collaboration's Risk of Bias Tool (Higgins and Green 2011). This tool assesses the methodological quality of RCTs, assigning low, unclear, or high risk of bias for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective reporting, or other sources of bias (e.g., possible funding by industry). The methodological quality of Controlled Before-After (CBA) studies was assessed using the same criteria as RCTs except that the "random sequence generation" and "allocation concealment" domains were both reported as "high risk of bias" by both reviewers based on the Cochrane guidelines (Higgins and Green 2011). Disagreements were resolved through discussion and consensus, and consultation with a third party (LL) when needed. Agreement was measured with the κ statistic and its 95 % confidence interval (CI).

Data analysis

A meta-analysis was conducted where studies were similar in terms of participants, intervention, and outcome measures to provide a meaningful summary of effect using the Cochrane Collaboration's Review Manager Analysis version 5.2 statistical software (RevMan 5.2). The pooled result of dichotomous outcomes was summarized using a relative risk (RR) and its 95 % CI, with the Mantel–Haenszel method. A random effect model was used to conduct the meta-analyses, since some heterogeneity exists between studies such as the length of follow-up and the study design. For all statistical tests, a significance level of 5 % was used. In the case of continuous outcomes, the pooled data were summarized using a mean difference and its 95 % CI. In studies where the standard deviation (SD) was missing and not reported, Buck's regression was used to meta-analyze the data (Buck 1960). Studies reporting mean values with no SDs or median with interquartile range (IQR) were not included in the meta-analysis and instead summarized narratively. The authors of one study (Dawkins et al. 2012) were contacted to obtain gender-stratified raw data to calculate the pooled estimates of the total mean change in Mood and Physical Symptoms Scale (MPSS) and their corresponding SDs in each study arm. A Poisson distribution was assumed to convert the number of adverse events into an average number of events experienced per subject in each study arm and their corresponding SDs.

Heterogeneity assessment

The heterogeneity between studies was assessed and quantified, using the I^2 statistics, representing the percentage of total variation across trials that are due to

differences rather than chance. In the case of moderate heterogeneity (I^2 = 30–60 %) or higher, a priori subgroup analyses were conducted, if feasible, in an attempt to explain the observed heterogeneity (Altman and Bland 2003).

Sensitivity analysis

When appropriate, a priori sensitivity analyses were conducted to assess the effect of methodological features, stratifying studies by low versus unclear or high risk of bias, as well as the effect of missing data (Akl et al. 2012).

Results

Literature search results

A total of 570 unique studies were identified. Of these, 91 full text articles were reviewed. Five studies were deemed eligible for inclusion. Eighty-six studies were excluded from the review. Seventy-one were not RCTs or comparative observational studies, one was an HTA report, three studies did not have comparators, one had inappropriate interventions, and ten did not report on outcome of interest. Study flow and reasons for exclusion are outlined in the PRISMA flowchart (Supplementary Fig. 1).

Study characteristics

Included studies

Table 1 summarizes the characteristics of the included studies. One study was a CBA, and the remaining four were RCTs. Studies were conducted in New Zealand (Bullen et al. 2010, 2013), the UK (Dawkins et al. 2012, 2013), and Italy (Caponnetto et al. 2013). In total, five studies were included in this review, including 840 participants where 581 received nicotine e-cigarettes and 259 received placebo e-cigarettes.

Participants in all studies were 18 years of age and older who smoked at least ten cigarettes per day. Participants in Bullen et al. (2013) were willing to quit, whereas those in Caponnetto et al. (2013) were not. The remaining three studies did not specify the participants' attitudes toward quitting. All five studies compared nicotine e-cigarettes to placebo e-cigarettes in adult smokers. Nicotine dosages varied according to study, since different brands of e-cigarettes were used. Finally, the studies differed in length of follow-up: 9 months after quit date (Caponnetto et al. 2013), 6 months after quit date (Bullen et al. 2013), and 1 day follow-up (Bullen et al. 2010; Dawkins et al. 2012, 2013).

Quality of included studies

The overall measures of agreement were excellent (κ = 0.81, 95 % CI 0.05–0.1), and all disagreements between the reviewers were resolved after discussion.

Random sequence generation and allocation concealment (selection bias)

Bullen et al. (2010, 2013), and Caponnetto et al. (2013) reported adequate sequence generation process and allocation concealment; hence, they were classified to be at "low risk of bias." These domains were not addressed in Dawkins et al. (2012), and thus it was classified to be at "unclear risk of bias." In Dawkins et al. (2013) it was classified to be at "high risk of bias" by default, based on the Cochrane guidelines (Higgins and Green 2011).

Blinding (performance bias and detection bias)

Only Bullen et al. (2013) reported blinding of participants and outcome assessors. The remaining four studies adequately blinded participants and personnel; however, they did not report on blinding of outcome assessors. Hence, they were classified to be at "low risk of bias" and "unclear risk of bias" for these domains, respectively.

Incomplete outcome data (attrition bias)

Missing outcomes were balanced between study arms, intention to treat (ITT) analyses was conducted, and more than 80 % of subjects completed the studies except in the study by Caponnetto et al. (2013). All five studies were classified to be at "low risk of bias."

Selective reporting (reporting bias)

Although the protocol of only one of the studies (Bullen et al. 2013) was published online, all outcomes listed in "Methods" of each of the five studies were reported. Hence, all were classified to be at "low risk of bias."

Other bias (source of funding)

One (Bullen et al. 2010) out of the five studies was funded by industry, and was classified to be at "high risk of bias." The remaining four (Bullen et al. 2013; Caponnetto et al. 2013; Dawkins et al. 2012, 2013) were not funded by industry, and thus were classified to be at "low risk of bias".

Table 1 Study characteristics of included studies

References	Country	Study design	Length of follow-up	Participants (*n*)	Intervention (n)	Comparator (*n*)	Clinical outcomes	Quality assessment, risk of bias
Long-term behavioral studies								
Bullen et al. (2013)	NZ	Double-blind RCT	6 months	Adult (≥18 years) smokers wanting to quit (*n* = 657)	Nicotine e-cigarettes (*n* = 289)	Placebo e-cigarettes (*n* = 73) Nicotine patches (*n* = 295)	Smoking abstinence Cigarettes smoked/day Adverse events	R = low A = low Blinding of PP = low Blinding of O = low IOD = low SR = low Others = low
Caponnetto et al. (2013)	IT	Double-blind RCT	9 months	Adult (≥18 years) smokers not intending to quit (*n* = 300)	Nicotine e-cigarettes (*n* = 200)	Placebo e-cigarettes (*n* = 100)	≥50 reduction in cigarettes smoked/day Smoking abstinence Cigarettes smoked/day Adverse events	R = low A = low Blinding of PP = low Blinding of O = unclear IOD = low SR = low Others = low
Short-term pharmacotherapy studies								
Bullen et al. (2010)	NZ	Single-blind, randomized, repeated-measures crossover	1 day	Adult (≥18 years) smokers (*n* = 40)	Nicotine e-cigarettes (n = 40)	Placebo e-cigarettes (*n* = 39) Nicotine inhaler (*n* = 39) Usual cigarettes (*n* = 40)	Desire to smoke Withdrawal symptoms Adverse events	R = low A = low Blinding of PP = low Blinding of O = unclear IOD = low SR = low Others = high

Table 1 continued

References	Country	Study design	Length of follow-up	Participants (*n*)	Intervention (n)	Comparator (*n*)	Clinical outcomes	Quality assessment, risk of bias
Dawkins et al. (2012)	UK	Mixed experimental design	1 day	Adult (≥18 years) smokers ($n = 86$)	Nicotine e-cigarettes (n = 32)	Placebo e-cigarettes ($n = 27$) Just hold e-cigarettes ($n = 27$)	Desire to smoke Withdrawal symptoms Adverse events	R = unclear A = unclear Blinding of PP = low Blinding of O = unclear IOD = low SR = low Others = low
Dawkins et al. (2013)	UK	CBA trial	1 day	Adult (≥18 years) smokers ($n = 20$)	Nicotine e-cigarettes (n = 20)	Placebo e-cigarettes ($n = 20$)	Desire to smoke Withdrawal symptoms Adverse events	R = high A = high Blinding of PP = low Blinding of O = Unclear IOD = low SR = low Others = low

e-cigarette electronic cigarette, *NZ* New Zealand, *IT* Italy, *UK* United Kingdom, *RCT* randomized controlled trial, *CBA* controlled before–after, *R* random sequence generation, *A* allocation concealment, *Blinding of PP* blinding of participants and personnel, *Blinding of O* blinding of outcome assessment, *IOD* incomplete outcome data, *SR* selective reporting, *Others* source of funding

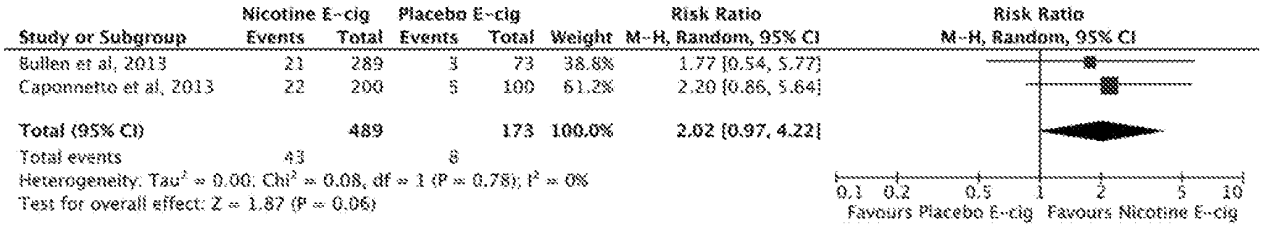


Fig. 1 Meta-analyses indicate no significant difference in smoking abstinence between the two groups

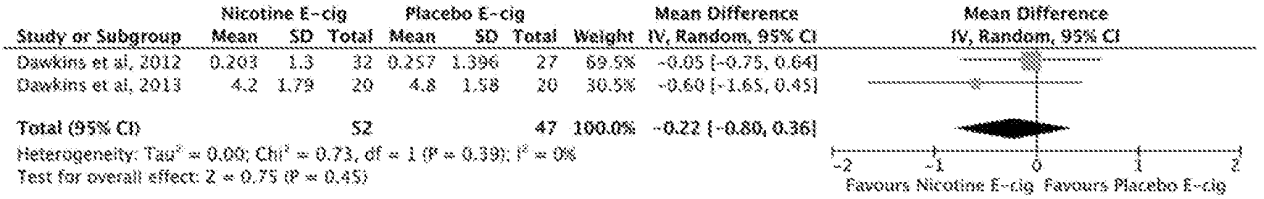


Fig. 2 Meta-analyses indicate no significant difference in desire to smoke between the two groups

Efficacy of E-cigarettes

Smoking abstinence

In two studies (Bullen et al. 2013; Caponnetto et al. 2013), there was a total of 43 (9 %) smoking abstinence events in the intervention group versus 8 (5 %) in the placebo group. The pooled relative risk (RR) was 2.02 (95 % CI 0.97, 4.21), although the effect was not statistically significantly different between groups ($p = 0.06$) (Fig. 1). The degree of heterogeneity was 0 % between the included studies. Furthermore, Bullen et al. (2013) demonstrated a total of 17 (6 %) smoking abstinence events in the nicotine patch group (risk difference for nicotine e-cigarette versus patches 1.51 [95 % CI −2.49, 5.51]), which showed insufficient statistical power to conclude the superiority of nicotine e-cigarette to patches.

Desire to smoke

The study by Bullen et al. (2010) reported a statistically significant reduction in the desire to smoke based on the mean Mood and Physical Symptoms Scale (MPSS) scores (0.82, 95 % CI 0.25,1.38; $p = 0.006$) from baseline between the nicotine (n = 39) and placebo e-cigarette groups ($n = 39$). It also reported an MPSS score of −0.10 (95 % CI −1.16, 0.95; $p = 0.99$) from baseline between nicotine e-cigarette ($n = 39$) and nicotine patches ($n = 39$). The pooled mean difference of the MPSS scores from the two studies (Dawkins et al. 2012, 2013) that reported the desire to smoke cigarettes approximately 15 min after smoking either nicotine- or placebo-containing e-cigarettes was −0.22 (95 % CI −0.80, 0.36, $p = 0.45$) (Fig. 2). The degree of heterogeneity was 0 %, demonstrating no heterogeneity between the included studies.

Cigarettes smoked per day

Two studies (Bullen et al. 2013; Caponnetto et al. 2013) reported the number of cigarettes smoked per day by participants, both in nicotine and placebo e-cigarette groups; however, it was not appropriate to pool the data, since Caponnetto et al. (2013) reported the median number and IQR of cigarettes smoked per day, whereas Bullen et al. (2013) reported the average number of cigarettes smoked per day. The median values (and IQR) of cigarettes smoked per day at week 52 in the Caponnetto et al. (2013) study was determined to be 12 (5.8–20.0) and 14 (6.30–20.0) for the 7.2 mg and 5.4 mg nicotine-containing e-cigarettes, respectively, compared to 12 (9.0–20.0) for the placebo e-cigarettes. Furthermore, Bullen et al. (2013) reported 2.8 versus 4.5 cigarettes smoked per day in the nicotine versus placebo-containing e-cigarettes, respectively. Overall, both studies showed a slight decrease in the number of cigarettes used per day among participants who were using nicotine- versus placebo-containing e-cigarettes.

Short-term effects of e-cigarettes

Withdrawal symptoms

Three out of the five studies reported withdrawal symptoms (i.e., irritability, restlessness, poor concentration, anxiety, depression, or hunger) as one of their outcomes. Two studies (Dawkins et al. 2012, 2013) used the Mood and Physical Symptoms Scale (MPSS), whereas the third study (Bullen et al. 2010) used the visual analog scale (VAS).

Bullen et al. (2010) was not included in the pooled analysis, since it reported the difference between the nicotine and placebo e-cigarette groups. This study reported no statistically significant reduced ratings for irritability

0.26 (95 % CI −0.49, 0.99; $p = 0.48$), restlessness 0.53 (95 % CI −0.11, 1.18; $p = 0.10$), and poor concentration 0.39 (95 % CI −0.30, 1.07; $p = 0.26$) from baseline between nicotine ($n = 39$) and placebo ($n = 39$) e-cigarettes.

The withdrawal symptoms reported in the nicotine and placebo e-cigarette groups in the studies by Dawkins et al. (2012) and Dawkins et al. (2013) were meta-analyzed. The mean difference of the MPSS scores of participants who received nicotine versus placebo e-cigarettes were −0.16 (95 % CI −0.40, 0.07; $p = 0.17$) for anxiety, −0.03 (95 % CI −0.38, 0.31) for irritability, −0.03 (95 % CI −0.42, 0.35) for restlessness, −0.01 (95 % CI −0.35, 0.32) for poor concentration, −0.01 (95 % CI −0.32, 0.30) for hunger, and −0.01 (95 % CI −0.22, 0.20) for depression. All pooled estimated differences were determined to be not statistically significant ($p > 0.05$). Furthermore, the I^2 value of 0 % ($p > 0.05$) was estimated for all six pooled withdrawal symptoms, demonstrating no degree of heterogeneity between the two studies (Fig. 3).

Adverse events

Adverse events were adequately reported in only two (Bullen et al. 2010, 2013) of the five studies included in the review. Bullen et al. (2013) classified and reported adverse events as serious and non-serious, whereas Bullen et al. (2010) reported only non-serious events. However, discussion with the author of the study revealed that participants did not experience any serious adverse events (unpublished data, 2014). As a result, only the non-serious events reported in both studies were pooled and meta-analyzed.

The pooled mean difference in the average number of non-serious adverse events experienced in participants who received nicotine ($n = 329$) versus placebo ($n = 112$)

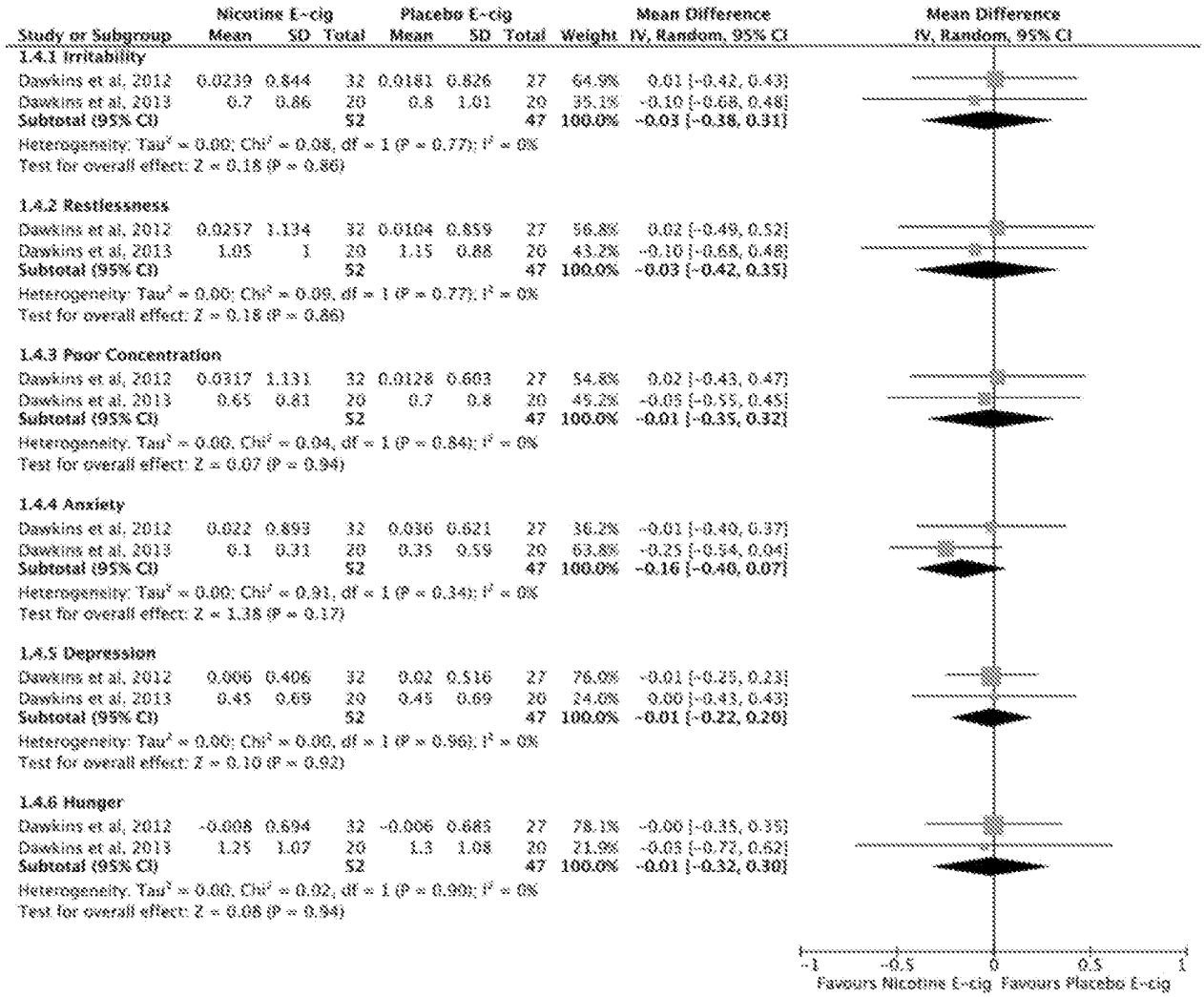


Fig. 3 Meta-analyses indicate no significant difference in withdrawal symptoms between the two groups

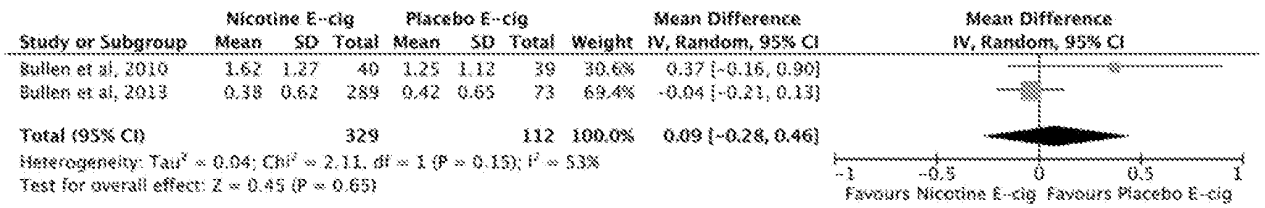


Fig. 4 Meta-analyses indicate no significant difference in non-serious adverse events between the two groups (Canada 2015)

e-cigarettes was −0.09 (95 % CI −0.28 to 0.46) (Fig. 4). However, this difference was not statistically significant ($p = 0.65$). The I^2 value was 53 %, signifying a moderate degree of heterogeneity. Due to the limited number (2 studies) of included studies, a priori subgroup analyses were not feasible to conduct to explore the reasons for the observed heterogeneity due to time to follow-up and different study design.

Serious adverse events, reported in the Bullen et al. (2013) study, were slightly higher in the nicotine e-cigarette group (27/137, 19.7 %) than in the placebo e-cigarette group (5/36, 13.9 %). Serious events by convention included death ($n = 1$, in nicotine e-cigarette group), life-threatening illness ($n = 1$, in nicotine e-cigarette group), admission to hospital or prolongation of hospital stay ($n = 17$ and $n = 4$, in nicotine and placebo e-cigarette groups, respectively), persistent or significant disability or incapacity, congenital abnormality ($n = 8$ and $n = 1$, in the nicotine and placebo e-cigarette groups, respectively).

Sensitivity analysis

Sensitivity analyses to assess the effect of missing data were not undertaken for the pooled effect estimate of smoking abstinence, since it was not statistically significant ($p = 0.06$). The a priori sensitivity analyses of assessing the influence of methodological features (low versus high risk of bias) on effect estimates was not investigated, since a maximum of two studies were pooled for each of the outcomes investigated in this review.

Discussion

This systematic review and meta-analysis synthesized all available published evidence on the efficacy, effectiveness, and safety of nicotine-containing e-cigarettes compared to other nicotine replacement therapies or placebo in healthy adult smokers. This review differs from others recently published, because it only included comparative studies and conducted meta-analyses to achieve greater statistical power for more precise estimates of the outcomes of interest.

Results from the recent trials suggest that the use of nicotine e-cigarette increased the proportion of patients who stopped smoking, although this change was not statistically significant. Importantly, the lower-bound 95 % CI of our estimate of treatment effect, or the most conservative estimate, suggested only a 3 % decrease in smoking abstinence among the intervention group. Thus, the finding of this review does not suggest that e-cigarettes are likely to be counterproductive for smoking abstinence among healthy adult smokers, whether or not they were willing to quit. The ability of an e-cigarette to mimic the psychological, cognitive, social, and behavioral elements of smoking (e.g., handling, holding and puffing actions) could be a possible explanation for the slight increase in smoking abstinence observed among nicotine and placebo e-cigarette users (Caponnetto et al. 2012). Furthermore, this review found that the desire to smoke among individuals who were using nicotine e-cigarette versus placebo was slightly lower, though again not statistically significant. No trials reported increased withdrawal symptoms or incidence of adverse events (both serious and non-serious); however, there were a limited number of studies, small sample sizes, and wide confidence intervals around effect estimates. Thus, the current evidence regarding the safety of e-cigarettes is inconclusive.

Recent reviews (Franck et al. 2014; Harrell et al. 2014; Orr and Asal 2014; Pepper and Brewer 2013) have summarized the available evidence on the efficacy and safety of e-cigarette used for smoking cessation; however, due to the limited amount of available literature and the inclusion of observational non-comparative studies, meta-analyses were not conducted. Their conclusions and the result of the recently published systematic review and meta-analysis by Cochrane Collaboration group (McRobbie et al. 2014) are consistent with the findings of this review. First, all reviews have demonstrated a slight increase in smoking abstinence among healthy adult smokers with the intervention. Second, as this review addressed, they also reported that all non-serious adverse events were self-resolved, and that the difference in the observed number of events between intervention and control groups was not significant (Franck

et al. 2014; Harrell et al. 2014; Orr and Asal 2014; Pepper and Brewer 2013). Third, they have also addressed that the serious adverse events experienced by the participants in the study by Bullen et al. (2013) were not associated with the use of e-cigarettes. Fourth, they have also suggested that no definitive conclusion can be made regarding the efficacy and safety of e-cigarettes given that the evidence faces methodological and study design limitations (Franck et al. 2014; Harrell et al. 2014; Orr and Asal 2014; Pepper and Brewer 2013).

There are several limitations of this review. Most notably, there is a paucity of completed studies in this field and of those that have been published; they differ greatly in study design, comparators, outcomes, and follow-up periods. These limitations constrained the number of studies viable for pooling data in each meta-analysis. As a result, further investigations such as subgroup analyses to explore heterogeneity, and sensitivity analyses to assess the robustness of the pooled estimates were prohibited. Furthermore, the trials by Bullen et al. (2013) and Caponnetto et al. (2013) had variable usage of behavioral support in their studies, and the results only generalize to the products used in the interventions, since not all products are manufactured similarly (Farsalinos and Polosa 2014). Hence, definitive conclusion about the efficacy and short-term effect of the use of nicotine-containing e-cigarettes cannot be confidently made. However, based on the small number of events, additional research will reduce imprecision and have an important impact on the smoking abstinence estimate and as a result may change the outcome observed.

The review showed no statistically significant effect of nicotine e-cigarettes on smoking abstinence over a long period of time, desire to smoke, withdrawal symptoms, and non-serious adverse events. However, the data upon which these conclusions have been drawn were limited. Based on the results of this review, health-care providers, regulatory agencies, and public health decision-makers should consider the uncertainty surrounding this novel intervention when deciding whether e-cigarettes should be encouraged, allowed, or restricted. This review also demonstrates the need for higher-quality studies, such as RCTs with large sample sizes. For example, for detecting an absolute difference of 5 % between nicotine e-cigarettes and placebo e-cigarettes, it will require a total of 870 individuals, assuming an alpha level of 0.05 and a power of 0.80. Additionally, there is a need to adequately report smoking abstinence over a long period of time ($\geq$6 months) and adverse events experienced by the participants to have more robust evidence of the benefits and harms associated with the use of e-cigarettes as a smoking cessation product.

Compliance with ethical standards

Conflict of interest The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author contribution statement SK and DO designed the systematic review and meta-analysis protocol. SK and KC created the search strategy. SK and TD searched for publications, and did the review and data extraction, and LL helped with the disagreements. SK, DO, and RB developed the analysis frame. SK and TD did the analysis, and SK and DO critically interpreted the results. SK drafted the article, and all authors provided critical revision of the article.

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APPENDIX I

Exported on 4/30/2019 - Tobacco

Acute Use of Nicotine Salt-based ENDS and Combusted Cigarettes

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Gal Cohen, Ph.D., JUUL Labs, US

Introduction

We report results from a pilot study which compared nicotine pharmacokinetics, exhaled CO, tolerability/safety, and subjective perceptual measures for a nicotine salt-based ENDS product (Virginia Tobacco, 5% and Cool Mint, 5%, JUUL Labs) and combusted cigarettes (Pall Mall Tobacco Flavor, British American Tobacco New Zealand; Newport Menthol Flavor, RJ Reynolds, USA). Results are presented for the JUUL Virginia Tobacco flavor ENDS and the Pall Mall Tobacco Flavor combustible cigarettes.

Methods

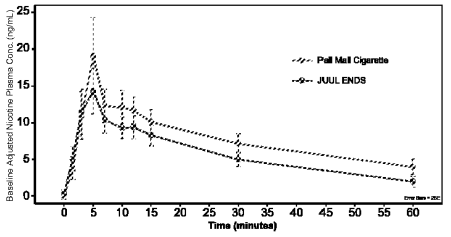
- The study was a single-center, randomized, six-way crossover design conducted in New Zealand, in 24 generally healthy, male and female adult smokers. Subjects were assigned a different product every 120 min, and consumed the products in sessions consisting of either ten, 3-sec puffs or ad libitum for 4.5 min. Venous nicotine was sampled at -5, 0, 1.5, 3, 5, 7, 10, 12, 15, 30, and 60 min.
- Exhaled carbon monoxide (CO) was collected 5 to 10 minutes before and 20 minutes after the start of each treatment session. A protocol amendment enabled CO data to be collected for the last 13 subjects.
- After each session, subjects completed an 11-item questionnaire (Product Evaluation Scale) about their subjective experience with the product, rating their responses on a 7-point scale, where 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot and 7 = extremely.

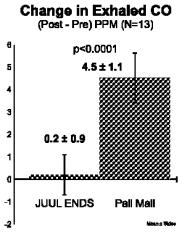
Results

No significant differences in Tmax, Cmax, AUC, baseline adjusted Cmax and baseline adjusted AUC were observed between cigarette and ENDS. This was true for both ad-lib and 10 puff sessions. Likewise, no significant differences in survey responses were observed for any of the individual survey questions ($p>0.05$)

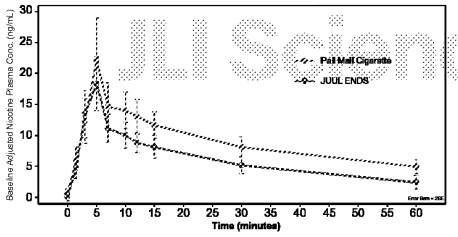
No change in exhaled CO was observed in JUUL ENDS sessions, ($p>0.92$), while a significant increase in exhaled CO was observed in cigarette sessions. ($p<0.01$). When the difference in CO (post versus pre) was compared between groups, JUUL ENDS use was associated with significantly less change in exhaled CO compared to Pall Mall cigarettes.

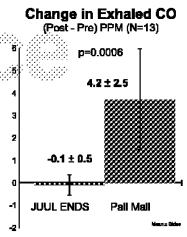
10 Puffs Sessions





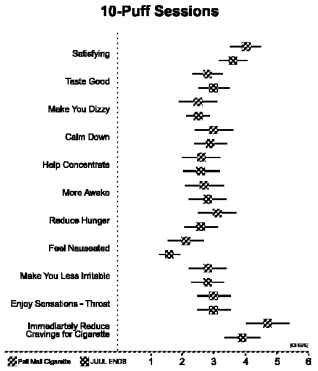
Ad Lib Sessions

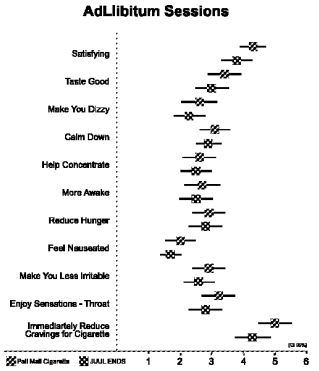




Product / session	# Puffs	C baseline (time-point -5) ng/mL	Tmax minutes	Cmax ng/mL	AUC 15min ng.hr/mL	Cmax baseline adjusted (ng/mL)	AUC 15min baseline adjusted ng.hr/mL
JUUL 10-puffs	10 ± 0 (24)	5.9 (0.99, 13.9) 6.8 ± 3.6 (24)	5.0 (1.5, 15.0) 6.5 ± 3.8 (24)	20.3 (9.3, 42.1) 21.7 ± 8.9 (24)	227 (76, 421) 236 ± 93 (23)	13.2 (7.2, 33.7) 15.4 ± 8.9 (24)	124 (61, 284) 144 ± 59 (23)
Pall Mall 10-puffs	10 ± 0 (24)	5.8 (1.3, 21.5) 6.8 ± 4.4 (24)	5.0 (3.0, 15.0) 7.5 ± 3.8 (24)	22.4 (7.5, 63.0) 27.6 ± 13.7 (24)	247 (88, 810) 273 ± 116 (23)	16.8 (4.4, 56.5) 20.1 ± 12.1 (24)	156 (42, 324) 170 ± 72 (23)
JUUL ad libitum	13.6 ± 3.3 (24)	5.1 (1.0, 17.7) 6.7 ± 4.0 (24)	5.0 (3.0, 15.0) 5.5 ± 2.4 (24)	20.9 (7.6, 49.5) 26.5 ± 12.1 (24)	216 (91, 555) 245 ± 105 (22)	15.8 (2.5, 43.7) 18.8 ± 10.7 (24)	140 (16, 342) 153 ± 75 (22)
Pall Mall ad libitum	13.7 ± 3.9 (24)	5.5 (1.0, 13.7) 5.6 ± 3.6 (24)	5.0 (5.0, 15.0) 6.8 ± 3.3 (24)	25.7 (6.6, 85.5) 26.9 ± 17.6 (24)	266 (57, 849) 289 ± 142(23)	19.9 (5.6, 79.9) 23.2 ± 18.0 (24)	193 (42, 443) 202 ± 108 (23)

Subjective Experience:





Summary

- Survey results post-use found no significant difference between JUUL ENDS and Pall Mall cigarettes, for eleven measures of subjective experience.
- No statistically significant differences were observed between Cmax, Tmax, AUC at 15 minutes, baseline-adjusted Cmax, and baseline-adjusted AUC at 15 minutes for JUUL ENDS and Pall Mall cigarettes, regardless of inhalation pattern (10 puffs over 4.5 minutes or ad libitum inhalation over 4.5 minutes).
- JUUL ENDS appeared to provide significantly lower exposure to carbon monoxide in this acute setting than Pall Mall cigarettes.
- This pilot study had several limitations. Testing commenced in New Zealand with a small sample of adult smokers who did not have significant prior experience with JUUL ENDS. Complete washout was not achieved between sessions. Sustained use of JUUL ENDS beyond 4.5 minutes and beyond first 10-14 puffs in a pod was not measured. Carbon monoxide was tested at two time points only, and this study was not designed to test for zero exposure to carbon monoxide. Additional studies will be performed to address these topics.

Consistent with FDA regulations, JUUL Labs can not and does not promote its products as less harmful or safer than cigarettes.
This document is intended for sharing data with the scientific community.

Presented at SRNT Conference, Feb 24, 2019, Baltimore, MD

REMARKS

Claims 26-30 and 32-42 are currently amended. Claims 43 to 45 are new. New and amended claims are supported throughout the application as originally filed. Illustrative support can be found in the abstract and paragraphs [0122]-[0123] and [0130]-[0136] of the published application (US20160044967A1). Additional illustrative support is noted below, also with reference to US20160044967A1. No new matter is added by these amendments. Upon entry of these amendments, claims 26-45 will be pending.

With respect to any claim amendments or cancelations, Applicant has not dedicated to the public or abandoned any unclaimed subject matter, and has not acquiesced to any rejection and/or objection made by the U.S. Patent and Trademark Office. Applicant expressly reserves the right to pursue prosecution of any presently unclaimed subject matter in one or more future continuation or divisional applications.

Rejection Under 35 U.S.C. § 103

Claims 26-42 stand rejected under 35 U.S.C. § 103 as allegedly being unpatentable over US20140000638 (hereafter "Sebastian") in view of US20070163610 (hereafter "Lindell"). In particular, the Office Action alleges that "it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the liquid formulation of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for . . . administration to a user in liquid form" (Office Action, pgs. 5-6). Applicant respectfully traverses the rejection.

MPEP § 2142 provides, "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." MPEP § 2143.01(III) provides, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 538, 417, 82 USPQ2d 1385, 1396 (2007)" (emphasis original). Moreover, "[w]hether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made" (MPEP § 2143.02(III)).

The cited references fail to teach or suggest the claimed nicotine salt liquid formulation

As amended, claims 26, 32, 37, and 38 recite "a nicotine salt liquid formulation" wherein "the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w);" and further wherein "the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1." None of the cited references, whether considered alone or in combination, teach or suggest a nicotine salt liquid formulation having a nicotine salt concentration that is from about 3% (w/w) to about 15% (w/w) in a nicotine salt liquid formulation as presently claimed.

The present application teaches that a nicotine salt liquid formulation produces heart rate effects comparable to that of a traditional burned cigarette, which is in contrast to a free base formulation (see, e.g., para. [0191] and Fig. 2). Moreover, the present application makes clear that the nicotine salt, which includes a protonated nicotine paired with an anion (such as benzoate), produces a high degree of satisfaction in the user when provided in adequate amounts. The present application teaches: "Nicotine is an alkaloid molecule that comprises two basic nitrogens. It may occur in different states of protonation. For example, if no protonation exists, nicotine is referred to as the 'free base.' If one nitrogen is protonated, then the nicotine would be 'mono-protonated'" (para. [0124]). Furthermore, "In some embodiments, monoprotonated nicotine salts produced a high degree of satisfaction in the user. For example, nicotine benzoate and nicotine salicylate are mono-protonated nicotine salts and all produce a high degree of satisfaction in the user" (para. [0130]). None of the cited art, either alone or in combination, discloses the concepts of producing comparable heart rate effects as a traditional cigarette or producing a high degree of satisfaction in the user with a nicotine salt. It was Applicant that first discovered that the use of nicotine salts at adequate levels (e.g. about 3% (w/w) to about 15% (w/w)) would produce heart rates comparable to a traditional cigarette and a high degree of satisfaction in the user.

The Office asserts that a person having ordinary skill in the art would have combined the teachings of Sebastian and Lindell. Applicant respectfully disagrees.

Sebastian states, "The present invention relates to aerosol delivery articles and uses thereof for yielding tobacco components or other materials in an inhalable form" (Sebastian, para. [0001]). By contrast, Lindell states, "Further and in contrast to other transmucosal dosage

forms the present liquid pharmaceutical formulation provides nicotine in a form being directly buccally absorbable by a subject" (Lindell, para. [0040]). Nothing in any of the cited references suggests that formulations designed for inhalation would be suitable for buccal delivery, or vice versa.

In fact, Lindell explicitly teaches away from using the components of the compositions disclosed therein for inhalation. Lindell states, "The administration to the oral cavity takes place by spraying, dropping or pipetting, preferably by spraying, most preferably by spraying under the tongue. The administration is intended for the oral cavity, not for e.g., the lungs or the upper respiratory tract" (Lindell, para. [0119]).

As such, one skilled in the art would not have combined the teachings of Sebastian and Lindell.

Even assuming *arguendo* that a person having ordinary skill in the art would have somehow been motivated to combine the teachings of Sebastian and Lindell, Applicant respectfully submits that the combination of Sebastian and Lindell fails to teach or suggest the claimed nicotine salt liquid formulation.

Sebastian fails to provide any specific discussion of the protonation state of nicotine or the presence of nicotine salts, much less the use of nicotine salts at adequate levels to produce a high degree of satisfaction in the user. In fact, nothing in Sebastian indicates formation of nicotine salts at all, much less nicotine salts at about 3% (w/w) to about 15% (w/w) as presently claimed. Moreover, in as much as a person having ordinary skill in the art would refer to Lindell for modification of Sebastian, the disclosure of Lindell is compelling evidence that Sebastian cannot be fairly read to disclose nicotine salt liquid formulations as presently claimed. Lindell states:

> Absorption of nicotine from the oral cavity to the systemic circulation is dependent on the pH of the saliva and the pKa of nicotine, which is about 7.8. Assuming a pH of the saliva of 6.8 only about 10% of the nicotine in saliva will be in the free base form. Thus, in order to promote absorption of nicotine in a free base form, which is the form predominantly absorbed through the mucosa, the pH of the saliva must be increased. (Lindell, para. [0053]).

> Hence and according to the invention, the liquid pharmaceutical formulation is alkalized by buffering and/or pH regulation. (Lindell, para. [0054]).

Thus, Lindell teaches that nicotine is preferably in the non-protonated, free base form, which cannot form a nicotine salt. Indeed, Lindell teaches that even if a nicotine salt is used as a source of nicotine, the formulation should be buffered such that the nicotine is in free base form and not a nicotine salt. Given the teachings of Lindell and the Office's assertion that a person of skill would use Lindell to modify Sebastian, it cannot be fairly asserted that the compositions of Sebastian teaches or suggests formulations containing nicotine salts (i.e. protonated nicotine) even where acids might be included "to favorably affect the organoleptic properties of the composition" (Office Action, pg. 5). Lindell clearly teaches that any effect of an acid on pH should be mitigated by also including a buffer to ensure presence of the free base form of nicotine. In fact, by expressly teaching a preference for the free base form of nicotine, Lindell teaches away from delivery of nicotine salts as claimed, to the extent a person having ordinary skill in the art would look to Lindell in modifying the teachings of Sebastian.

The Office alleges that Sebastian teaches the use of acids "to favorably affect the organoleptic properties of the composition." *See* Office Action dated September 28, 2018 at 5. As noted above, mere recitation of acids, without more, fails to provide any guidance with regard to amounts of nicotine salt in a formulation. As such, a person having ordinary skill in the art would have had no reason to modify the teachings of Lindell and/or Sebastian to arrive at a nicotine salt liquid formulation with a 1:1 benzoic acid to nicotine ratio where the nicotine salt concentration is from about 3% (w/w) to about 15% (w/w). The protonated form of nicotine (i.e. nicotine salt) was simply not a recognized results effective variable for producing a high degree of user satisfaction, or for achieving heart rate effects comparable to those of a traditional cigarette. Applicant made that discovery. As such, it would be improper to use Applicant's inventive concept as a motivation to modify the teaching of the cited art to arrive at the claimed nicotine salt liquid formulation.

In sum, the cited art fails to teach or suggest, either alone or in combination, a nicotine salt liquid formulation having a nicotine salt concentration from about 3% (w/w) to about 15% (w/w). For at least this reason, Applicant respectfully requests withdrawal of the rejection.

No reasonable expectation of success

As noted above, a person skilled in the art would not have combined Sebastian and Lindell in the first instance. Moreover, even if a person skilled in the art did have some reason to combine Sebastian and Lindell, the references fail to teach or suggest formulations including a nicotine salt liquid formulation as presently claimed. Even assuming *arguendo* that all the elements of Applicant's claims were disclosed in the cited art and that there were some reason to combine the references, neither of which is true, the claims would still be non-obvious because the modification of Sebastian and Lindell as proposed by the office would have lacked the requisite reasonable expectation of success.

Reference is made to declarations by Dr. Bradley James Ingebrethsen (originally filed in U.S. Serial No. 14/512,311; hereafter "Ingebrethsen Declaration") and Adam Bowen (originally filed in U.S. Serial No. 14/925,968; hereafter "Bowen Declaration"). Copies of these declarations were previously submitted on April 20, 2017 (Bowen Declaration) and December 4, 2017 (Ingebrethsen Declaration).

As explained by Dr. Ingebrethsen, the free base form of nicotine in basic formulations was "widely and commonly assumed over a long time period to be the form that will be most readily and rapidly absorbed from cigarette smoke in the blood upon inhalation" (Ingebrethsen Declaration, para. (4)). This belief was so ingrained among those of ordinary skill in the art that publications by Applicant did not quickly alter this attitude in the art. "Despite the publication in January 2015 of [U.S. Application No. 14/512,311], and the publication of its parent application (US 2014/0345631) in November 2014, the belief that optimum nicotine absorption occurs in nicotine formulations that have basic pHs (i.e. have nicotine present predominantly in the free base form) continues throughout industry as evidenced by El-Hellani's July publication and Gonda, at least" (Ingebrethsen Declaration, para. (5)). Lindell supports this view, as explained above. *See* Lindell at paras. [0053]-[0054], stating in part: "in order to promote absorption of nicotine in a free base form, which is the form predominantly absorbed through the mucosa, the pH of the saliva must be increased. . . . Hence and according to the invention, the liquid pharmaceutical formulation is alkalized by buffering and/or pH regulation."

In addition, Adam Bowen explains that "those of skill in the art believed that vaporized nicotine did not result in an effect on heart rate comparable to that seen with a traditional

cigarette." *See* Bowen Declaration at paragraph (7), and supporting references supplied as Exhibits C-E thereof. In contrast, the subject application teaches: "It has been unexpectedly discovered herein that certain nicotine salt formulations provide satisfaction in an individual superior to that of free base nicotine, and more comparable to the satisfaction in an individual smoking a traditional cigarette" (US20160044967A1 at [0111]).

Multiple publications describe the widely held belief that free base nicotine was most effective. El-Hellani et al., cited by Dr. Ingebrethsen, states that "Nic [free-base nicotine] is thought to be the only form that diffuses through epithelial tissues in the human body. Thus, all else being equal, an ECIG with a higher proportion of Nic will increase the rate of uptake of nicotine by the user's body" (Exhibit D of Ingebrethsen Declaration, pg. A). Thus, El-Hellani illustrates why one of ordinary skill in the art would have had no reasonable expectation that providing a nicotine salt liquid formulation, as presently claimed, would improve the performance of an electronic cigarette. On the contrary, one of ordinary skill, and indeed even experts at the time, would have expected the opposite.

El-Hellani is just one example of reports touting the importance of free base nicotine. An article detailing the history of free base nicotine in traditional cigarettes reports that "neutral, deprotonated nicotine is 'free' in that it is no longer bound to another molecule (or anion) in the form of a salt. Free nicotine is more volatile; James F. Pankow, of Oregon Health and Science University, stresses that 'increasing the proportion of the particle-phase nicotine that is in the freebase form will . . .tend to drive more nicotine into the gas phase" rendering it "more 'available' to the smoker" (Stevenson and Proctor, American Journal of Public Health, July 2008, Vol 98, No. 7; Appendix A).

The belief that favoring the free base form of nicotine with an alkaline pH dates to at least 1940. Travell et al., who reported experiments using bladder as a model for epithelial absorption, observed that nicotine compositions at acidic pH "produced no effects," and concluded that, "within a certain range the higher the pH, the more rapid is its absorption" (Travell et al., Experimental Biology and Medicine, 45(2), 552-56 (1940); Appendix B).

The perceived importance of free base nicotine was reinforced by later studies, such as Burch et al. (Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung 6(1),

45-52 (1993); Appendix C) and Shao et al. (Nicotine & Tobacco Research, 15(7), 1248-58 (December 13, 2012); Appendix D), in addition to those performed by El-Hellani noted above. Burch states, "Our data indicated that the pH of the nicotine aerosol significantly affects the absorption of nicotine. Increasing the aerosol pH produced significantly higher peak plasma nicotine levels. These results were similar to previously reported effects of pH on nicotine absorption across mucous membranes (11)" (Burch, pg. 49). Moreover, Burch refers to a previous study in which "5 mg of aerosolized nicotine with a pH of 11 . . . produced nicotine levels which were similar to those reached with cigarettes" (Burch, pg. 45; emphasis added). At a pH of 11, almost all of the nicotine would have been in the free base form (see, e.g., Lindell para. [0053]; and Ingebrethsen Declaration, Appendix D, Table 1). Taken together, a pH at which nicotine is almost completely in the free base form was the only one reported to produce nicotine levels comparable to a cigarette, and delivery was reported to go down as pH went down. Thus, Burch further illustrates why there would have been no reasonable expectation of success for using an electronic cigarette with a formulation having a pH low enough to yield a nicotine salt liquid formulation in accordance with the present claims. Indeed, Shao observed that lowering the pH of a test composition from 7.4 (mildly alkaline) to 6.8 (mildly acidic) "dramatically increased" LC_{50}, indicating "a decrease in the delivery rate and/or the bioavailability of nicotine" (Shao, pg. 1255).

Given the widespread preference for free base nicotine in the art, the express preference for free base nicotine in Lindell, and the complete lack of any results or teachings in Sebastian countering the express preferences for free base nicotine, the cited combination of references fails to supply any reason to expect that the claimed nicotine salt liquid formulation could have been successfully used within an electronic cigarette system.

Selection of benzoic acid yields unexpected results

With respect to selection of benzoic acid, the Office alleges that "it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid . . . as benzoic acid is one of many organic acids that are appropriate for use with nicotine for . . . administration to a user in liquid form" (Office Action, pgs. 5-6). Applicant respectfully disagrees. None of the cited art provides any teaching that would lead a person having ordinary skill in the art at the

relevant time to select a specific effective acid, such as ***benzoic acid***, over any other acid, much less wherein the "molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1," as claimed.

Applicant discovered, *inter alia*, that the claimed nicotine salt liquid formulation results in a rapid onset peak increase in heart rate relative to a similar free-base nicotine formulation. *See, e.g.,* FIG. 1 of the subject application. The link between effective acids such as benzoic acid and their ability to increase a physiological effect of nicotine such as an increase in heart rate was unknown before Applicant's invention. For example, benzoic acid invokes a stronger physiological response than, *e.g.*, citric acid. *See, e.g.,* paragraph (8) of the Ingebrethsen Declaration.

None of the cited art provides any teachings that would lead a person having ordinary skill in the art to predict the surprising efficacy of benzoic acid in delivering nicotine using an electronic cigarette.

Secondary considerations: Long-felt unmet need

MPEP 716.04 provides that a long-felt unmet need is established by evidence that the long-felt need (1) was "a persistent one that was recognized by those of ordinary skill in the art," (2) was not "satisfied by another before the invention by applicant," and (3) is satisfied by the claimed invention.

Attempts to address the negative consequences of smoking traditional cigarettes date from about the 1950's, and "[f]rom the 1960s onward, attention focused on the development of the safer cigarette'" and involved "decades of failed attempts at harm reduction" (Lancet 2014; Appendix E). Attempts to produce a viable electronic-cigarette alternative also date to this time (see, e.g., US3200819A). Thus, prior to Applicant's invention, there was a long felt need for effective e-cigarettes that would be an effective alternative to cigarette smoking.

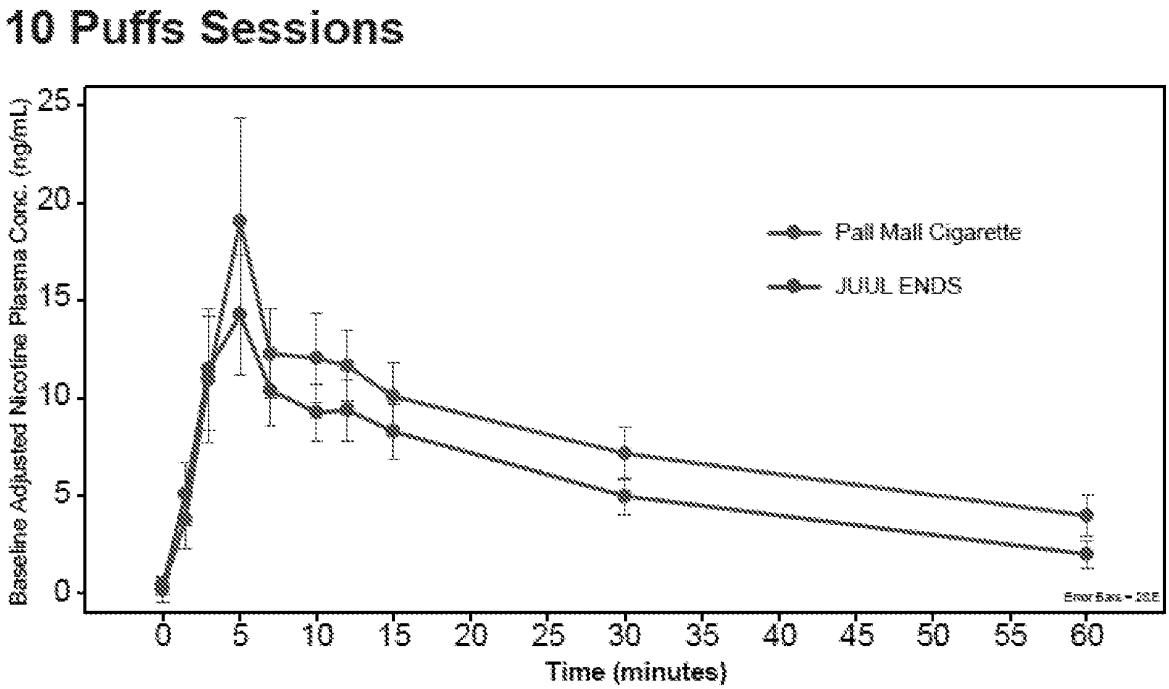
Prior to Applicant's disclosure, the long-felt need noted above was not satisfied by available electronic cigarettes. Several studies reported that previous e-cigarettes failed to perform comparably to traditional cigarettes. For example, one study in 2010 concluded that "unlike puffing from a tobacco cigarette, two 10-puff bouts with the two electronic cigarettes described here expose users to no measurable nicotine or [carbon monoxide] and do not increase

heart rate" (Vansickel et al., Cancer Epidemiol Biomarkers Prev. 2010 Aug;19(8):1945-53; Appendix F). Another study, also published in 2010, compared the effects of e-cigarettes to traditional cigarettes (Bullen et al., Tob Control. 2010 Apr;19(2):98-103; Appendix G). Bullen reports that the electronic cigarette evaluated resulted in only "modest" increases in blood nicotine levels, and that traditional cigarettes "gave a significantly higher Cmax" (Bullen, pg. 101). In fact, Table 3 shows that the Cmax for the electronic nicotine delivery device ("ENDD") in Bullens was only about one tenth that of the cigarette (*Id.*). Studies such as these illustrate that, prior to Applicant's discovery, electronic cigarettes were not able to provide physiological effects comparable to traditional cigarettes, due to low nicotine delivery.

The problems associated with smoking, and the failure of previous electronic cigarette devices to perform comparably to traditional cigarettes is further highlighted in a 2016 report by Khoudigian et al. (Appendix H). Khoudigian notes that "[a]n estimated 1.2 billion people use tobacco worldwide (World Health Organization 2014)," and that "[t]obacco-related deaths are one of the main causes of preventable early mortality, claiming 5 million lives annually (World Health Organization 2014)" (Khoudigian, at pg. 257). Moreover, "[d]espite the benefits of cessation and the desire of most smokers to quit, approximately 80% of those who attempt to quit on their own relapse within the first month of abstinence, and only 3-5% remain abstinent for 6 months or longer." (*Id.*) However, following a "systematic review" of studies comparing e-cigarettes to other nicotine replacement therapies (*Id.*, abstract), Khoudigian concludes that "[t]he review showed no statistically significant effect of nicotine e-cigarettes on smoking abstinence over a long period of time, desire to smoke, withdrawal symptoms, and non-serious adverse events" (*Id.*, pg. 266).

Results reported in the present application illustrate compositions comprising a sufficient amount of nicotine salt that performed comparably to a traditional cigarette in terms of effects on heart rate and blood nicotine (see, e.g., FIGS. 2 and 4). Moreover, clinical studies reported in 2018 further support the comparability of nicotine salt-based electronic nicotine delivery systems (ENDS) commercialized by Applicant relative to traditional cigarettes. A copy of a poster presented at the 2018 Annual Meeting of the Society for Research on Nicotine and Tobacco is attached as Appendix I (hereafter, the "SRNT Study"). The SRNT Study evaluated baseline-adjusted nicotine plasma concentration in subjects smoking a traditional cigarette or a nicotine salt-based ENDS, and concluded, "No significant difference in Tmax, Cmax, AUC, baseline

adjusted Cmax and baseline adjusted AUC were observed between cigarette and ENDS" (SRNT Study, left panel). One of the graphs from the middle panel of the SRNT Study illustrating these results is reproduced below (top plot corresponding to "Pall Mall Cigarette"):



In addition, "Survey results post-use found no significant difference between JUUL ENDS and Pall Mall cigarettes for eleven measures of subjective experience" (*Id.*, right panel).

In view of results in both the present application and the SRNT Study, the claimed compositions satisfy a long-felt unmet need in providing electronic cigarette formulations that perform comparably to a traditional cigarette. None of the cited references suggest that nicotine salts could be used to render physiological effects of e-cigarettes comparable to traditional cigarettes in general, or to increase nicotine delivery in particular. Indeed, as explained above, no such effect would have been reasonably expected at the time the present invention was made.

SUMMARY

For at least the above reasons, Sebastian and Lindell would not have been combined by one of ordinary skill in the art, and even if combined, fail to teach or suggest every element of claims 26, 32, 37, and 38, and fail to provide a reasonable expectation of success for arriving at the subject matter of these claims. Moreover, the electronic cigarette cartridge of the present

claims provides unexpected results, and satisfies a long-felt unmet need. Claims 26, 32, 37, and 38 are therefore unobvious over the cited references, as are all claims depending therefrom. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the application is in condition for allowance. If the Examiner believes that a telephone call would be useful in expediting the allowance of the application, the Examiner is invited to contact the undersigned.

The Commissioner is authorized to charge any shortage in fees due in connection with the filing of this paper, including any necessary extension of time fees, and to credit any excess fees, to Deposit Account Number 50-0311.

Dated: March 27, 2019

Respectfully submitted,

/Jeffery C. Giering/

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application.

Listing of Claims

1.-25. (Cancelled)

26. (Currently Amended) An electronic cigarette cartridge comprising:

a nicotine salt liquid formulation, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about [[4%]] 3% (w/w) to about [[12%]] 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

27. (Currently Amended) The electronic cigarette cartridge of claim 26, wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w).

28. (Currently Amended) The electronic cigarette cartridge of claim 26, wherein the nicotine salt liquid formulation further comprises a flavorant.

29. (Currently Amended) The electronic cigarette cartridge of claim 26, which is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

30. (Currently Amended) The electronic cigarette cartridge of claim 26, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

31. (Previously Presented) An electronic cigarette comprising:

the electronic cigarette cartridge of claim 26; and

a battery.

32. (Currently Amended) A method of providing nicotine to a user, the method comprising:

(i) heating a nicotine salt liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about [[4%]] 3% (w/w) to about [[12%]] 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1[[,]], and

(ii) inhalation of the aerosol by the user.

33. (Currently Amended) The method of claim 32, wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w).

34. (Currently Amended) The method of claim 32, wherein the nicotine salt liquid formulation further comprises a flavorant.

35. (Currently Amended) The method of claim 32, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

36. (Currently Amended) The method of claim 32, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

37. (Currently Amended) An electronic cigarette cartridge comprising:

a nicotine salt liquid formulation, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about [[4%]] 3% (w/w) to about [[12%]] 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol;

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1;

(d) the nicotine salt liquid formulation comprises a flavorant; and

(e) the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

38. (Currently Amended) A method of vaporizing a nicotine salt liquid formulation, the method comprising heating the nicotine salt liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about [[4%]] 3% (w/w) to about [[12%]] 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

39. (Currently Amended) The method of claim 38, wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w).

40. (Currently Amended) The method of claim 38, wherein the nicotine salt liquid formulation further comprises a flavorant.

41. (Currently Amended) The method of claim 38, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

42. (Currently Amended) The method of claim 38, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

43. (New) The method of claim 27, wherein the nicotine salt concentration is about 4% (w/w).

44. (New) The method of claim 33, wherein the nicotine salt concentration is about 4% (w/w).

45. (New) The method of claim 39, wherein the nicotine salt concentration is about 4% (w/w).

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14/925,961	10/28/2015	Adam BOWEN	52210-501C03US/713.302	1528

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Mintz/JUUL
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Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
07/11/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN et al.	
	Examiner DIONNE W MAYES	Art Unit 1747	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 3/27/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 26-45 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 26-45 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of

the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

5. Claims 26-45 are rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638) in view of Lindell et al (US. Pat. App. Pub. 2007/0163610).

Regarding independent claim 26, and dependent claims 27 and 43, Sebastian et al discloses an electronic smoking article (corresponding to the claimed “an electronic cigarette cartridge”) that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which may contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed “An electronic cigarette cartridge comprising: a nicotine…liquid formulation”).

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine

present in the aerosol precursor; hence, the nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1)(see para. [0059])(corresponding to the claimed "the nicotine…liquid formulation comprising… nicotine and…acid in a liquid carrier"…(c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1").

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (corresponding to the claimed "the liquid carrier comprises glycerol and propylene glycol"), and nicotine in an amount of about 0.1-5.0% (para. [0061]). Further, as stated above, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition, but it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference shows that it is known to use benzoic acid, in addition to a myriad of other organic acids (like pyruvic acid), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Based on the teachings of Lindell et al, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the aerosol liquid composition of Sebastian et

al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for oral administration to a user in liquid form (corresponding to the claimed “nicotine…liquid formulation comprising… nicotine and benzoic acid”).

The modified Sebastian et al reference does not clearly state that a “salt” of nicotine and benzoic acid is formed in its aerosol precursor liquid composition; however, as clearly stated above, Sebastian discloses that the nicotine and organic acid can be added in equimolar ratios. Further, as disclosed in the instant specification, Applicant states that when its nicotine is mixed equimolarly with the acid (i.e., 1:1), proper salt formation occurs - specifically, nicotine and benzoic acid (see para. [0179] of the instant published application). Hence, based on the above, it follows to reason that nicotine benzoate would presumably be formed in the aerosol liquid composition of the modified Sebastian et al invention when both nicotine and benzoic acid is mixed in equal molar ratios as disclosed (corresponding to the claimed “a salt of nicotine and benzoic acid”).

Further, Sebastian et al discloses that the combined nicotine/flavorant (organic acid), i.e. nicotine salt, weight can comprise up to about 5% to about 10% of the total weight of the aerosol precursor liquid composition, which means that the nicotine benzoate salt of the modified Sebastian et al

invention would also comprise this same weight percentage in the final composition (corresponding to the claimed “(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w); the “wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w)” recitation of claim 27; the “wherein the nicotine salt concentration is about 4% (w/w)” recitation of claim 43).

Regarding claim 28, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed “wherein the nicotine salt liquid formulation further comprises a flavorant”).

Regarding claim 29, as evident from Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “which is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation”).

Regarding claims 30, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and

about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed "wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid").

Regarding claim 31, the heating element (50 can be powered by an electrical power source, such as a battery (40)(see para. [0078] and Fig. 1)(corresponding to the claimed "the electronic cigarette cartridge of claim 26; and a battery").

Regarding claim independent claim 32, and dependent claims 33 and 44, Sebastian et al discloses improved aerosol delivery to a user using an electronic smoking article that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which may contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed "A method of providing nicotine to a user, the method comprising: (i) heating a nicotine …liquid formulation in an electronic cigarette to produce and inhalable aerosol, wherein the nicotine…liquid formulation comprises…nicotine…in a liquid carrier"…(ii) inhalation of the aerosol by the user").

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor; hence, the nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1)(see para. [0059])(corresponding to the claimed "nicotine...liquid formulation comprises a…nicotine and …acid in a liquid carrier…(c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1").

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (corresponding to the claimed "the liquid carrier comprises glycerol and propylene glycol"), and nicotine in an amount of about 0.1-5.0% (para. [0061]). Further, as stated above, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference shows that it is known to use benzoic acid, in addition to a myriad of other organic acids (like pyruvic acid), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation

designed to be delivered to a user (see abstract and Table 1). Based on the teachings of Lindell et al, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the aerosol liquid composition of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for oral administration to a user in liquid form (corresponding to the claimed "nicotine…liquid formulation comprises… nicotine and benzoic acid").

The modified Sebastian et al reference does not clearly state that a "salt" of nicotine and benzoic acid is formed in its aerosol precursor liquid composition; however, as clearly stated above, Sebastian discloses that the nicotine and organic acid can be added in equimolar ratios. Further, as disclosed in the instant specification, Applicant states that when its nicotine is mixed equimolarly with the acid (i.e., 1:1), proper salt formation occurs - specifically, nicotine and benzoic acid (see para. [0179] of the instant published application). Hence, based on the above, it follows to reason that nicotine benzoate would presumably be formed in the aerosol liquid composition of the modified Sebastian et al invention when both nicotine and benzoic acid is mixed in equal molar ratios as disclosed (corresponding to the claimed "a salt of nicotine and benzoic acid").

Further, Sebastian et al discloses that the combined nicotine/flavorant (organic acid), i.e. nicotine salt, weight can comprise up to about 5% to about 10% of the total weight of the aerosol precursor liquid composition, which means that the nicotine benzoate salt of the modified Sebastian et al invention would also comprise this same weight percentage in the final composition (corresponding to the claimed "(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w); the "wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w)" recitation of claim 33; the "wherein the nicotine salt concentration is about 4% (w/w)" recitation of claim 44).

Regarding claim 34, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed "wherein the nicotine salt liquid formulation further comprises a flavorant").

Regarding claim 35, as evident from Fig. 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed "wherein the electronic cigarette comprises a cartridge, and the

cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation").

Regarding claims 36, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed "wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid").

Regarding independent claim 37, Sebastian et al discloses an electronic smoking article (corresponding to the claimed "an electronic cigarette cartridge") that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which may contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed "An electronic cigarette cartridge comprising: a nicotine…liquid formulation, the nicotine…liquid formulation comprising… nicotine…in a liquid carrier").

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor; hence, the nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1)(see para. [0059])(corresponding to the claimed “the nicotine…liquid formulation comprising a…nicotine and…acid in a liquid carrier…(c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1”).

Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed “wherein the nicotine liquid formulation further comprises a flavorant”).

As evident from Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “which is configured to serve as a mouthpiece and a reservoir that holds the nicotine formulation”).

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (corresponding to the claimed "the liquid carrier comprises glycerol and propylene glycol"), and nicotine in an amount of about 0.1-5.0% (para. [0061]). Further, as stated above, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference shows that it is known to use benzoic acid, in addition to a myriad of other organic acids (like pyruvic acid), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Based on the teachings of Lindell et al, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the aerosol liquid composition of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for oral administration to a user in liquid form (corresponding to the claimed "nicotine…liquid formulation comprising… nicotine and benzoic acid").

The modified Sebastian et al reference does not clearly state that a "salt" of nicotine and benzoic acid is formed in its aerosol precursor liquid composition; however, as clearly stated above, Sebastian discloses that the nicotine and organic acid can be added in equimolar ratios. Further, as disclosed in the instant specification, Applicant states that when its nicotine is mixed equimolarly with the acid (i.e., 1:1), proper salt formation occurs - specifically, nicotine and benzoic acid (see para. [0179] of the instant published application). Hence, based on the above, it follows to reason that nicotine benzoate would presumably be formed in the aerosol liquid composition of the modified Sebastian et al invention when both nicotine and benzoic acid is mixed in equal molar ratios as disclosed (corresponding to the claimed "a salt of nicotine and benzoic acid").

Further, Sebastian et al discloses that the combined nicotine/flavorant (organic acid), i.e. nicotine salt, weight can comprise up to about 5% to about 10% of the total weight of the aerosol precursor liquid composition, which means that the nicotine benzoate salt of the modified Sebastian et al invention would also comprise this same weight percentage in the final composition (corresponding to the claimed "(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w).

Regarding claim independent claim 38, and dependent claims 39 and 45, Sebastian et al discloses improved aerosol delivery to a user using an electronic smoking article that provides for delivery of aerosolized components of an aerosol precursor liquid composition, which may contain nicotine, to at least one heating element which heats the aerosol precursor (corresponding to the claimed “A method of vaporizing…a nicotine…liquid formulation, the method comprising heating the nicotine…liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine…liquid formulation comprises…nicotine…in a liquid carrier”…(ii) inhalation of the aerosol by the user”).

When nicotine is chosen, organic acids can be combined with the nicotine in order to favorably affect the flavor and sensation of the composition. Organic acids, such as pyruvic acid, may be used such that the total amount of acid present is equimolar to the total amount of nicotine present in the aerosol precursor; hence, the nicotine and organic acid can be provided in equimolar ratios (i.e., 1:1)(see para. [0059])(corresponding to the claimed “(c) the molar ratio of…acid to nicotine in the nicotine formulation is about 1:1”).

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (corresponding to the claimed

"the liquid carrier comprises glycerol and propylene glycol"), and nicotine in an amount of about 0.1-5.0% (para. [0061]). Further, as stated above, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition; however, it does not specifically mention "benzoic acid", in particular, as the organic acid that can be used. However, the Lindell et al reference shows that it is known to use benzoic acid, in addition to a myriad of other organic acids (like pyruvic acid), in combination with nicotine (in a 1:1 molar ratio) in a liquid formulation designed to be delivered to a user (see abstract and Table 1). Based on the teachings of Lindell et al, it would have been obvious to one having ordinary skill in the art to have chosen benzoic acid, as an organic acid to combine with the nicotine in the aerosol liquid composition of Sebastian et al, as benzoic acid is one of many organic acids that are appropriate for use with nicotine for oral administration to a user in liquid form (corresponding to the claimed "nicotine…liquid formulation comprises… nicotine and benzoic acid").

The modified Sebastian et al reference does not clearly state that a "salt" of nicotine and benzoic acid is formed in its aerosol precursor liquid composition; however, as clearly stated above, Sebastian discloses that

the nicotine and organic acid can be added in equimolar ratios. Further, as disclosed in the instant specification, Applicant states that when its nicotine is mixed equimolarly with the acid (i.e., 1:1), proper salt formation occurs - specifically, nicotine and benzoic acid (see para. [0179] of the instant published application). Hence, based on the above, it follows to reason that nicotine benzoate would presumably be formed in the aerosol liquid composition of the modified Sebastian et al invention when both nicotine and benzoic acid is mixed in equal molar ratios as disclosed (corresponding to the claimed “a salt of nicotine and benzoic acid”).

Further, Sebastian et al discloses that the combined nicotine/flavorant (organic acid), i.e. nicotine salt, weight can comprise up to about 5% to about 10% of the total weight of the aerosol precursor liquid composition, which means that the nicotine benzoate salt of the modified Sebastian et al invention would also comprise this same weight percentage in the final composition (corresponding to the claimed “(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w); the “the nicotine salt concentration is about 4% (w/w) to about 12% (w/w)” recitation of claim 39; the wherein the nicotine salt concentration is about 4% (w/w) recitation of claim 45).

Regarding claim 40, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed “wherein the nicotine salt liquid formulation further comprises a flavorant”).

Regarding claim 41, as evident form Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation”).

Regarding claims 42, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed “wherein the nicotine salt

liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid").

Response to Applicant's Arguments

6. Applicant's arguments filed March 27, 2019 have been fully considered but are, for the most part, moot because of the new grounds of rejection, presented above, which were necessitated because of the newly amended claims. To the extent that outstanding arguments remain regarding Applicant's position that the combined references fail to teach the claimed invention, they are addressed as follows:

-Applicant argues that the teachings of Sebastian and Lindell should not have been combined because, it submits, Lindell explicitly teaches away from using the components of the compositions disclosed therein for inhalation. The Examiner disagrees with Applicant's position. Sebastian already discloses that its composition is intended to be inhaled (i.e., is an aerosol) and that its composition may include nicotine in combination with an organic acid, such as pyruvic acid, but doesn't require any particular organic acid. The Lindell reference was merely introduced to show that, like pyruvic acid, benzoic acid is also known for its use in combination with nicotine for oral administration to a user. Hence, one of ordinary skill would have been motivated to use this acid, in lieu of pyruvic acid, in combination

with nicotine in the inhalable aerosol of Sebastian. And while Lindell states that the administration of its formulation/composition is intended for the oral cavity, as opposed to the lungs/upper respiratory tract, does not mean that (some, or all of) the components of the composition are not suitable for aerosol delivery.

-Applicant argues that the combination of Sebastian and Lindell fails to teach or suggest the claimed nicotine salt liquid formulation. Specifically, Applicant states that nothing in Sebastian indicated formation of nicotine salts at all, let alone in the claimed amounts. However, as stated in the above rejection, it is admitted that the Sebastian et al reference does not clearly state that a “salt” of nicotine and benzoic acid is formed in its aerosol precursor liquid composition. However, as clearly stated above, Sebastian et al discloses that nicotine and organic acid can be added in equimolar ratios in its composition. Further, as disclosed in the instant specification, Applicant states that when its nicotine is mixed equimolarly with the acid (i.e., 1:1), proper salt formation occurs - specifically, nicotine and benzoic acid (see para. [0179] of the instant published application). Hence, based on the above, it follows to reason that nicotine benzoate would presumably be formed in the aerosol liquid composition of the modified Sebastian et al invention when both nicotine and benzoic acid is

mixed in equal molar ratios as disclosed. Lastly, Sebastian et al further discloses, in para. [0161], that its liquid composition would necessarily have comprised a nicotine/acid (salt) concentration in its total composition which is consistent with that which is claimed.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE WALLS MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Thursdays and alternate Monday and Tuesdays, 7:00A-3:00P EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael H Wilson can be reached on 571-270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE W. MAYES/
Examiner, Art Unit 1747

/Michael H. Wilson/
Supervisory Patent Examiner, Art Unit 1747

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC - Searched*		
Symbol	**Date**	**Examiner**
A24F47/008	1/11/2016	DWM
updated above	6/11/2016	DWM
updated above	5/25/2017	DWM
updated above	09/25/2018	DWM
updated above	06/27/2019	DWM

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM
Inventor Search updated	6/11/2016	DWM
Inventor Search updated	09/25/2018	DWM

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	**Art Unit**
	DIONNE W MAYES	1747

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2015/01/20 15:51

			EPO; JPO; DERWENT; IBM_TDB			
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48
S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR;	ADJ	ON	2015/01/20 16:59

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08

S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31

		(plasma or blood) and (ph near5 "7") and heat$4 and lung				
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48

		(plasma or blood)				
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	("14925961").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30
S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33
S79	225	("1067531" | "1163183" | "1299162" | "1505748" | "1552877" | "1632335" | "1706244" | "1845340" | "1972118" | "1998683" | "2031363" | "2039559" | "2104266" | "2231909" | "2327120" | "2460427" | "2483304" | "2502561" | "2765949" | "2830597" | "2860638" | "2897958" | "2935987" | "20010015209" | "20010032643" | "20010032795" | "20010052480" | "20020078951" | "20020175164" | "20030005926" | "20030089377" | "20040031495" | "20040099266" | "20040149296" | "20040149624" | "20040173229" | "20040182403" | "20040221857" | "20040237974" | "20050016549" | "20050016550" | "20050034723" | "20050061759" | "20050118545" | "20050145533" | "20050172976" | "20050244521" | "20050268911" | "20060018840" | "20060054676" | "20060102175" | "20060150991" | "20060191546" | "20060191548" | "20060254948" | "20060255105" | "20070006889" | "20070045288" | "20070062548" | "20070074734" | "20070098148" | "20070102013" | "20070144514" | "20070163610" | "20070215164" | "20070235046" | "20070267033" | "20070280652" | "20070283972" | "20080023003" | "20080029095" | "20080092912" | "20080149118" | "20080216828" | "20080241255" | "20080257367" | "20080276947" | "20090004249" | "20090095287" | "20090126745" | "20090133691" | "20090230117" | "20090255534" | "20090267252" | "20090272379" | "20090288668" | "20090288669" | "20090293892" |	US-PGPUB; USPAT	ADJ	ON	2016/12/13 13:42

		"20090293895" | "20100000672" | "20100006092" | "20100024834" | "20100031968" | "20100156193" | "20100163063" | "20100186757" | "20100236562" | "20100242974" | "20100242976" | "20100275938" | "20100276333" | "20100307116" | "20110030706" | "20110036346" | "20110041861" | "20110049226" | "20110094523" | "20110108023" | "20110155153" | "20110162667" | "20110180433" | "20110192397" | "20110226236" | "20110226266" | "20110232654" | "20110236002" | "20110265806" | "20110268809" | "20110277780" | "20110278189" | "20110315701" | "20120006342" | "20120111347" | "20120199146" | "20120204889" | "20120227753" | "20120255567" | "20120260927" | "20120267383" | "20120325227" | "20130042865" | "20130068239" | "20130140200" | "20130152922" | "20130186416" | "20130228191" | "20130247924" | "20130248385" | "20130255702" | "20130276802" | "20130312742" | "20130333700" | "20140041655" | "20140060552" | "20140190503" | "20140196731" | "20140345631" | "20140345635" | "20140366898" | "20140378790" | "20150020823" | "20150027468" | "20150128966" | "20150150308" | "20150157056" | "20150208729" | "20150313285" | "20160044968" | "3146937" | "3258015" | "3292634" | "3373915" | "3420360" | "3479561" | "3567014" | "3707017" | "3792704" | "3861523" | "3941300" | "374584" | "4020853" | "4049005" | "4066088" | "4207976" | "4215708" | "4219032" | "4506683" | "4519319" | "4595024" | "4648393" | "4708151" | "4735217" | "4771796" | "4793365" | "4794323" | "4798310" | "4813536" | "4819665" | "4830028" | "4836224" | "4846199" | "4848374" | "4848563" | "4893639" | "4907606" | "4941483" | "4944317" | "4947874" | "4947875" | "5005759" | "5020548" | "5027836" | "5050621" | "5060671" | "5065776" | "5076297" | "5105831" | "5105838" | "5123530" | "5144962" | "5183062" | "5224498" | "5249586" | "5261424" | "5269237" | "5269327" | "5322075" | "5324498" | "5372148" | "5388574" | "5591368" | "5605226" | "5641064" | "5649552" | "5666977" | "5666978").PN.				
S80	85	("5708258" | "5730118" | "5730158" | "5746587" | "5810164" | "5819756" | "5845649" | "5865185" | "5881884" | "5931828" | "5934289" | "5938018" | "5944025" | "5954979" | "5967310" | "5975415" | "5979460" | "5994025" |	US-PGPUB; USPAT	ADJ	ON	2016/12/13 13:42

		"5996589" | "576653" | "595070" | "6053176" | "6095153" | "6102036" | "6125853" | "6155268" | "6164287" | "6234169" | "6269966" | "6349728" | "6381739" | "6386371" | "6431363" | "6446793" | "6510982" | "6532965" | "6536442" | "6557708" | "6598607" | "6606998" | "6615840" | "6622867" | "6655379" | "6672762" | "6688313" | "6726006" | "6772756" | "6799576" | "6803545" | "6805545" | "6810883" | "6827573" | "6954979" | "7000775" | "7488171" | "7546703" | "7621403" | "7644823" | "7767698" | "7815332" | "7832410" | "7886507" | "7988034" | "720007" | "799844" | "8141701" | "8156944" | "8322350" | "8371310" | "8381739" | "8387612" | "8443534" | "8490629" | "8539959" | "8541401" | "8596460" | "8671952" | "8741348" | "8915254" | "8925555" | "968160" | "969076" | "D590990" | "D590991" | "D624238" | "D642330" | "D644375" | "D653803" | "D691324" | "D695450" | "D707389").PN.				
S81	1	("14925961").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/13 15:38
S82	1	("20140000638").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/13 16:16
S83	1595	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/12/14 13:14
S84	1	("9215895").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/14 13:23
S85	1998	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2017/05/25 21:46
S86	2	(adam near3 bowen).in. and (nicotine and liquid formulation and benzoic).clm.	US-PGPUB; USPAT	ADJ	OFF	2018/09/23 19:40
S87	4	(adam near3 bowen).in. and (nicotine and liquid and formulation and benzoic).clm.	US-PGPUB; USPAT	ADJ	OFF	2018/09/23 19:54
S88	4	(adam near3 bowen).in. and (benzoic).clm.	US-PGPUB; USPAT	ADJ	OFF	2018/09/23 22:05
S89	529	131/$.ccls. and (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 13:19
S90	209	131/$.ccls. and nicotine and (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 13:19
S91	58	131/$.ccls. and nicotine near50 (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 13:42
S92	91	131/$.ccls. and nicotine near50 liquid and (benzoate or benzoic)	US-PGPUB; USPAT	ADJ	OFF	2018/09/24 14:20
S93	1	(14/925961).APP.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/09/24 14:40
S94	0	(2014/0000638).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/09/24 18:36
S95	1	("20140000638").PN.	US-PGPUB;	OR	OFF	2018/09/24

			USPAT; USOCR			18:36
S96	1	("7726320").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/09/24 18:43
S97	1	("20140209105").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2018/09/24 20:02
S98	3364	(A24F47/008).cpc.	US-PGPUB; USPAT	ADJ	ON	2018/09/25 15:32
S99	4	"27760379".FMID.	US-PGPUB; USPAT; FPRS	ADJ	OFF	2018/09/25 15:41
S100	1	(14/925961).APP.	US-PGPUB; USPAT	OR	OFF	2019/06/26 15:19
S101	4301	(A24F47/008).cpc.	US-PGPUB; USPAT	ADJ	ON	2019/06/27 09:36

6/27/2019 5:26:22 PM
C:\Users\dmayes\Documents\EAST\Workspaces\14925961.wsp

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

148514 7590 10/02/2019

Mintz/JUUL
One Financial Center
Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
10/02/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com

Applicant-Initiated Interview Summary	**Application No.** 14/925,961	**Applicant(s)** BOWEN et al.	
	Examiner DIONNE W MAYES	**Art Unit** 1747	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) DIONNE WALLS. MAYES.

(2) JEFFERY GIERING.

(3) KENNETH JENKINS.

(4) _____.

Date of Interview: 26 September 2019.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☑Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: Those of Record.

Identification of prior art discussed: That of record, specifically Sebastian, Lindell and Lechuga-Ballesteros.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant's representatives provided, prior to the interview, an agenda which highlighted the various areas of discussion. The focus was the noted prior art references and their relevancy to the claims, specifically the recitation regarding nicotine salt of nicotine and benzoic acid. While no definitive agreement was reached regarding allowability of the claims, Applicant will take into consideration the substance of the interview and file amended claims, accordingly, in an AFCP 2.0 which will be filed soon..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/DIONNE W. MAYES/ Examiner, Art Unit 1747	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: Dionne W. MAYES

AGENDA FOR EXAMINER INTERVIEW

Dear Examiner Mayes,

Per your request, below is a proposed agenda for our telephonic interview scheduled for September 26, 2019 at 12:00 pm Eastern. The following topics are provided for discussion purposes only:

- Alleged inherency of salt formation in Sebastian (US20140000638)
- Alleged imputation of effects observed in Applicant's compositions to compositions of Sebastian
- Considering Lindell (US20070163610) as a whole, per MPEP 2141.02(VI)
- Consideration afforded to rebuttal evidence (declarations, appendices, and evidence of unexpected results and long-felt unmet need)

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	12/11/2019	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 23	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/NICHELE D PETERSON/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14/925,961	Filing Date	2015-10-28	Docket Number (if applicable)		Art Unit	1747
First Named Inventor	Adam BOWEN			Examiner Name	MAYES, DIONNE W.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 500311

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Jeffery C. Giering/	Date (YYYY-MM-DD)	2019-12-11
Name	Jeffery C. Giering	Registration Number	68221

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Jeffery C. Giering/Angela Olivos
Attorney Docket Number:	62210-501C03US/713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	2252	1	300	300
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	950	950
		Total in USD ($)		**1250**

Electronic Acknowledgement Receipt

EFS ID:	38003007
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Angela Olivos
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	11-DEC-2019
Filing Date:	28-OCT-2015
Time Stamp:	19:51:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1250
RAM confirmation Number	E2019BAJ52037669
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		US14925961_Response_to_Final_Office_Action.pdf	155057 a9eda02539cd7190d01a35eacbd63d80cfd23c62	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	6	8
Claims	2	5
Response After Final Action	1	1

Warnings:

Information:

2	Request for Continued Examination (RCE)	US14925961_RCE.pdf	1349939 b13f0acdfc9a922c408d790d6649c670d83c0ae0	no	3

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	32738 dbf6f099421854 5188a656c6ef9410274fd49e6c	no	2

Warnings:

Information:

Total Files Size (in bytes):	1537734

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Claims 26-31 and 37 are currently amended. Specifically, claims 26 and 37 are amended to incorporate an element of claim 31 as previously pending, with claims 27-31 amended for consistency. The amendment is supported throughout the application as originally filed. Illustrative support can be found in the abstract and paragraph [0051] of the application as originally filed. No new matter is added by these amendments. Upon entry of these amendments, claims 26-45 will be pending.

With respect to any claim amendments or cancelations, Applicant has not dedicated to the public or abandoned any unclaimed subject matter, and has not acquiesced to any rejection and/or objection made by the U.S. Patent and Trademark Office. Applicant expressly reserves the right to pursue prosecution of any presently unclaimed subject matter in one or more future continuation or divisional applications.

Interview Summary

Applicant wishes to thank Examiner Mayes for courtesies extended during a telephonic interview with Applicant's representatives Jeffery C. Giering and Kenneth E. Jenkins on September 26, 2019. The outstanding rejections were discussed, and the Examiner indicated that amendments presented herein, such that all claims expressly recite an "electronic cigarette," would facilitate expediting prosecution.

Applicant's representatives reiterated certain arguments presented in the response filed March 27, 2019, including: (a) that forming nicotine salt in the claimed amounts is not inherent to US20140000638 (hereafter "Sebastian"), (b) that the longstanding preference in the art prior to Applicant's invention was to use freebase nicotine for delivery in an electronic cigarette, as evidenced by at least Dr. Ingebrethsen's declaration and US20070163610 (hereafter "Lindell"), (c) the long-felt unmet need addressed by the presently claimed invention, (d) the surprising results obtained with formulations in accordance with the present claims, and (e) the specific advantages of benzoic acid in particular as compared to other acids, such as citric acid.

During the interview, the Examiner requested that specific support for "nicotine salt concentration" be identified. Reference is made to paragraph [0062] of the application as filed,

which provides, "In some formulations, a dilute concentration of the nicotine salt in the carrier is utilized. In some formulations, a less dilute concentration of the nicotine salt in the carrier is utilized" (emphasis added). The same paragraph goes on to provide several exemplary concentrations. Reference is also made to the abstract of the present application ("comprising nicotine salt that forms about 0.5% to about 20% nicotine"), several of the embodiments appearing at pages 43-90 (e.g., 39, 40, 104, 105, 152, 153, and so forth, reciting "the nicotine salt is in an amount that forms" various concentrations), and examples such as Example 1 (providing various "nicotine salt formulations" having one of various "nicotine free base equivalent concentration[s];" emphasis added). As such, recitation of "nicotine salt concentration" is supported throughout the application as filed.

The claims as presently amended are unobvious over the cited references for the reasons outlined above, and further detailed in the response filed March 27, 2019. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the application is in condition for allowance. If the Examiner believes that a telephone call would be useful in expediting the allowance of the application, the Examiner is invited to contact the undersigned.

This response is submitted with a Request for Continued Examination. Entry and consideration of the foregoing amendments and remarks is respectfully requested.

The Commissioner is authorized to charge any shortage in fees due in connection with the filing of this paper, including any necessary extension of time fees, and to credit any excess fees, to Deposit Account Number 50-0311.

Dated: December 11, 2019

Respectfully submitted,

/Jeffery C. Giering/

Jeffery C. Giering, Ph.D. Reg. No. 68,221

MINTZ LEVIN COHN FERRIS GLOVSKY
AND POPEO, P.C.
3580 Carmel Mountain Road, Suite 300
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Attorneys for Applicant

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application.

Listing of Claims

1.-25. (Cancelled)

26. (Currently Amended) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

27. (Currently Amended) The electronic cigarette ~~cartridge~~ of claim 26, wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w).

28. (Currently Amended) The electronic cigarette ~~cartridge~~ of claim 26, wherein the nicotine salt liquid formulation further comprises a flavorant.

29. (Currently Amended) The electronic cigarette ~~cartridge~~ of claim 26, ~~which~~ wherein the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

30. (Currently Amended) The electronic cigarette ~~cartridge~~ of claim 26, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

31. (Currently Amended) ~~An~~ The electronic cigarette of claim 26, the electronic cigarette further comprising:

~~the electronic cigarette cartridge of claim 26; and~~

a battery.

32. (Previously Presented) A method of providing nicotine to a user, the method comprising:

(i) heating a nicotine salt liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1; and

(ii) inhalation of the aerosol by the user.

33. (Previously Presented) The method of claim 32, wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w).

34. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation further comprises a flavorant.

35. (Previously Presented) The method of claim 32, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

36. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

37. (Currently Amended) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol;

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1;

(d) the nicotine salt liquid formulation comprises a flavorant; and

(e) the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

38. (Previously Presented) A method of vaporizing a nicotine salt liquid formulation, the method comprising heating the nicotine salt liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w);

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

39. (Previously Presented) The method of claim 38, wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w).

40. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation further comprises a flavorant.

41. (Previously Presented) The method of claim 38, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

42. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

43. (Previously Presented) The method of claim 27, wherein the nicotine salt concentration is about 4% (w/w).

44. (Previously Presented) The method of claim 33, wherein the nicotine salt concentration is about 4% (w/w).

45. (Previously Presented) The method of claim 39, wherein the nicotine salt concentration is about 4% (w/w).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: Dionne W. MAYES

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION

By EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This paper is filed in response to the Final Office Action dated July 11, 2019 in the above-identified application. The shortened statutory period for reply expired October 11, 2019. With this response, Applicant requests a two-month extension of time, and submits the requisite fee. Accordingly, this response is timely filed.

In addition, Applicant files herewith a Request for Continued Examination, and submits the requisite fee.

Please amend the application as set forth below, and consider the following remarks:

Amendments to the Claims begin on page **2** of this paper.

Remarks begin on page **6** of this paper

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14/925,961
	Filing Date	2015-10-28
	First Named Inventor	Adam Bowen
	Art Unit	1747
	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

U.S. PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	Attorney Docket Number	62210-501C03US/713.302

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	Art Unit	1747
	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

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	First Named Inventor	Adam Bowen
	Art Unit	1747
	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	1747
	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961 | Confirmation No.: 1528

Filed: October 28, 2015 | Art Unit: 1747

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF | Examiner: D. W. Mayes

INFORMATION DISCLOSURE STATEMENT (IDS)

FILED VIA EFS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114 (37 C.F.R. § 1.97(b)(4)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted.

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be

an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this paper. However, if a fee is due, please charge our Deposit Account No. 50-0311, from which the undersigned is authorized to draw.

Dated: December 11, 2019

Respectfully submitted,

Electronic signature: /Jeffery C. Giering/

Jeffrey C. Giering, Ph.D.
Registration No.: 68,221
MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO, P.C.
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San Diego, California 92130-6768
(858) 314-1500
(858) 314-1501 (Fax)
Attorney for Applicant

Electronic Acknowledgement Receipt

EFS ID:	38004195
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Angela Olivos
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	11-DEC-2019
Filing Date:	28-OCT-2015
Time Stamp:	19:55:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	EP_1618803_A1.pdf	692693 a96ff9f6e9c58bc2de39fdaf9daad890942b32b9	no	15

Warnings:

Information:					
2	Foreign Reference	EP_2022349_A1.pdf	308103 45f419d9871242f94e845bbeb2e28d1efd901c09	no	20
Warnings:					
Information:					
3	Foreign Reference	EP_2022350_A1.pdf	299312 cc16d63797541995a9e35799eadeb3ce47c6ca01	no	21
Warnings:					
Information:					
4	Foreign Reference	UA_67598_U.pdf	103187 235b01e9af8bd03c4f746f54e8037da2cb34b516	no	1
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5	Foreign Reference	WO_2004076289_A2.pdf	1263032 07beb6e912f2bb929fe2d10312896ecb156facb8	no	18
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6	Foreign Reference	WO_2008121610_A1.pdf	4036355 e97fc9619f020c095f03487dcfd9040319b41d86	no	71
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7	Foreign Reference	WO_2009001085_A2.pdf	1369095 e04daa29c3d3d7d731b9dcef4d148506448ceb74	no	40
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8	Foreign Reference	WO_2009079641_A2.pdf	1963842 111c93847815108572b3ecb710cad64edd23351b	no	39
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9	Foreign Reference	WO_2011034723_A1.pdf	5038889 038b34121da2fe1c1e312dfc64059fbb409a0a3a	no	92
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10	Foreign Reference	WO_2011038104_A2.pdf	1900484 04df8177285cd72c22fd81e4458037ef4a40d51c	no	46
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11	Foreign Reference	WO_2013083631_A1.pdf	1707423 cdb6811d9b5fb095940f4cf90ff37fbcd20743c0	no	28
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12	Foreign Reference	WO_2013088230_A1.pdf	691444 15b2d89ea8cb3561b9030d21a879963edc7672c9	no	17
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13	Foreign Reference	WO_2013116558_A1.pdf	2452088 7086537fdf7165a793b8b12f15cdb8ef93594974	no	60
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14	Foreign Reference	WO_2013116561_A1.pdf	1790332 c79a4372bfa8de28aefd6d0018a785e23a7deba0	no	44
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16	Foreign Reference	WO_2014150245_A1.pdf	2286209 bc9c1deb427d5a5cf17045a9741498bfceb54cc2	no	46
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17	Foreign Reference	WO_2014151434_A2.pdf	1742716 863b04a920e6cd5171438ff9141aa9bc1a3105da	no	29
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18	Foreign Reference	WO_2014159250_A1.pdf	3207806 b5c35b2666bdbdf466bb1f29e4f07a3fbe349218	no	56
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19	Foreign Reference	WO_2014177859_A1.pdf	1018620 a5afb31754c84907062057c1eff72ea48b7db7c4	no	16
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20	Foreign Reference	WO_2015091258_A1.pdf	1376650 2f21a33a4ae9c4b3bdac4c0defcdcd349ed545c7	no	26
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21	Foreign Reference	WO_2015179292_A1.pdf	3689692 c3e587bdffb1fce92592a9725516d4f5a2b88af5	no	73
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22	Foreign Reference	WO_2016071705_A1.pdf	5174523 fe9ea60d5d9a300214f732fef4e41cddbb834de6	no	37
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23	Foreign Reference	WO_2016071706_A1.pdf	2203700 0b7b691832bb12b80e0f63b19a73077bc37ae625	no	26
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24	Foreign Reference	WO2015193456A1.pdf	1150720 9f7504f662936dba87c7960fb72c9d4b44ac66a7	no	31
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25	Foreign Reference	WO2016063775A1.PDF	5612819 0a0e9348a95e0cdef1ce3d5134b57938fe139d38	no	48
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26	Non Patent Literature	Clayton.pdf	1219522 4884fa96773bb7785f53cd062af8b92e96c0e80e	no	9
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27	Non Patent Literature	Henningfield.pdf	1104154 21ab3573bc2121d9b1c16edba05af98ba4280677	no	5
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28	Non Patent Literature	Leffingwell.pdf	1518659 544d7c1b94d431863bdf48e6a28a834317eb88e0	no	20
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29	Non Patent Literature	Stepanov.pdf	544843 b815db21ea3e12b58eb049ce8bea981983dde56f	no	2
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30	Foreign Reference	WO2016012769_A1.pdf	1238270 a5114ba57675a87400115a4cd99e3f7cde899cd2	no	26
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31	Foreign Reference	WO2016020675_A1.pdf	1150779 ce7b651a19a8122e3be8cada0ed716baf34fa8d8	no	25
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33	Foreign Reference	WO2016040575_A1.pdf	1257854 565bd80f965649b979044bfa69a80e69328f71eb	no	35
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34	Foreign Reference	WO2016062777_A1.pdf	1407282 44e7d019bbee2a3ac3bf2af60538d85b35f7b843	no	32
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35	Non Patent Literature	Maier.pdf	839704 cb457de64802ed7c7a8e6514f84572fea638f0ad	no	2
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37	Information Disclosure Statement (IDS) Form (SB08)	US14925961_IDS_SB08.pdf	133953 b57f92e10540b9b7818e2fd8b68416db7228ffaf	no	7
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Information:					
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38	Transmittal Letter	US14925961_IDS_Transmittal.pdf	102114 1a9fb8c21dda9f99eec7bf887ac633f31f66ba8a	no	2
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Information:					
		Total Files Size (in bytes):	70926050		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

148514 7590 02/20/2020

Mintz/JUUL
One Financial Center
Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
02/20/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com

Office Action Summary	Application No. 14/925,961	Applicant(s) BOWEN et al.	
	Examiner DIONNE W MAYES	Art Unit 1747	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/11/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 26-45 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 26-45 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 11, 2019 has been entered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26-45 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has recited, in the independent claims, the following: "nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w)" and "the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1" (emphasis added); however, there does not appear to be sufficient support in the instant disclosure for such recitation.

First, with respect to the "nicotine salt concentration" recitation, while it is clear that Applicant has support to state that "[i]n some formulations, a dilute concentration of the nicotine salt in the carrier is utilized. In some formulation, a less dilute concentration of the nicotine salt in the carrier is utilized" (see para. [0122] of the instantly published application, emphasis

added), these are just generalizations regarding nicotine salt concentrations in the liquid formulation and there appears to be no support for the specifically-claimed nicotine salt concentrations (i.e., about 3% (w/w) to about 15% (w/w)) in the liquid formulation. The instant disclosure further indicates that "[i]n some formulations, the concentration of nicotine in the nicotine salt formulation is about 1% (w/w) to about 25% (w/w)…." (in para. [0122]). Also, in the instant "Abstract", Applicant has disclosed "A nicotine salt liquid formulation for generating an inhalable aerosol in an electronic cigarette comprising nicotine salt that forms about 0.5% to about 20% nicotine" and further in Example 1 of the instant application, "nicotine formulations with a final nicotine free base equivalent concentration of 2% (w/w)" are disclosed; however, it is clear that these concentration parameters pertain to the amount of nicotine in the nicotine salt (liquid) formulation, as opposed to the amount of nicotine ***salt*** in the nicotine salt (liquid) formulation (which is claimed). Correction is requested.

Second, with respect to the "molar ratio" recitation, in the instant specification it appears that the "molar ratio" disclosure pertains only to the stoichiometry of the nicotine salt, i.e. acid to nicotine (see, for example, paras. [0116], [0179], [0186] of the instantly published application) as opposed to the relationship of the reactants (i.e., nicotine and benzoic acid)

in the nicotine salt liquid formulation - which appears to be what Applicant is claiming. Hence, for examination purposes, it will be presumed that the intended recitation is as follows: "the molar ratio of benzoic acid to nicotine in the nicotine salt ***of the*** nicotine salt liquid formulation is about 1:1" - which is fully supported by the instant specification. Correction is requested.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

8. Claims 26-45 are rejected under 35 U.S.C. 103 as being unpatentable over Sebastian et al (US. Pat. App. Pub. 2014/0000638) in view of Lechuga-Ballesteros et al (US. Pat. App. Pub. 2006/0018840).

Regarding independent claim 26, and dependent claims 27 and 43, Sebastian et al discloses an electronic smoking article comprising a reservoir bottle (205) that contains components of an aerosol precursor liquid composition which is delivered in aerosolized form to a user. Said composition may contain one or more flavors, medicaments, or other suitable material, for example liquid nicotine, which is transported to at least one heating element that heats the aerosol precursor before being

inhaled by said user (see para. [0057]) (corresponding to the claimed “An electronic cigarette comprising an electronic cigarette cartridge”).

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (see para. [0015])(corresponding to the claimed “the liquid carrier comprises glycerol and propylene glycol”).

Also, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in the liquid precursor composition in order to favorably affect the organoleptic properties of the composition (see para. [0059]).

While the Sebastian et al reference clearly teaches a nicotine liquid formulation as its precursor composition; it may not be clear whether it teaches a nicotine ***salt*** liquid formulation. However, the Lechuga-Ballesteros et al reference teaches liquid aerosol formulations that can be administered by inhalation through the mouth. It further teaches a more palatable delivery of nicotine in a liquid formulation because it discloses that nicotine, in its free form (i.e., unprotonated) has a harsh, unpleasant taste, and is likely to cause stomach upset; however, nicotine salts are less likely to cause these problems in users (see para. [0062]). Lechuga-Ballesteros et al goes on to disclose that numerous suitable acids,

including benzoic acid, may be reacted with nicotine, preferably in 1:1 molar ratios, to form a nicotine salt (see paras. [0040]-[0042]). Hence, it would have been obvious to one having ordinary skill in the art to have chosen the "nicotine salt" of Lechuga-Ballesteros et al to replace the "nicotine" of Sebastian in order to experience a more palatable delivery of nicotine, as taught in the Lechuga-Ballesteros et al reference. Further, it would also have been obvious to one having ordinary skill in the art to have selected benzoic acid from the list of suitable acids to react with nicotine, on a 1:1 molar basis, after undergoing routine experimentation, and determining that this particular acid, when reacted with nicotine, yielded the most organoleptically-pleasing properties to the user when the nicotine salt composition was heated and inhaled (corresponding to the claimed "a nicotine salt liquid formulation comprising, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier...the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1).

Lastly, Sebastian et al discloses that the nicotine content in its liquid precursor composition can be provided in a range (up to about 5% by weight) of the liquid precursor composition (see para. [0061]). Hence, one of ordinary skill in the art would have undergone routine experimentation to

determine the optimal amount of nicotine ***benzoate*** concentration (after having reacted 1 mole of nicotine with 1 mole of benzoic acid) in the resulting liquid composition of the modified Sebastian et al invention and arrived at a point which overlaps the claimed range after determining that this nicotine benzoate concentration provided superior sensory characteristics in the resulting aerosol (corresponding to the claimed "(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w); the "wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w)" recitation of claim 27; the "wherein the nicotine salt concentration is about 4% (w/w)" recitation of claim 43).

Regarding claim 28, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed "wherein the nicotine salt liquid formulation further comprises a flavorant").

Regarding claim 29, as evident from Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to

the claimed “which is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation”).

Regarding claims 30, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic acid present can be equimolar to the total amount of nicotine present in the aerosol precursor composition (see para. [0059)(corresponding to the claimed “wherein the nicotine liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid”).

Regarding claim 31, the heating element (50 can be powered by an electrical power source, such as a battery (40)(see para. [0078] and Fig. 1) (corresponding to the claimed “The electronic cigarette of claim 26, the electronic cigarette further comprising: a battery”).

Regarding claim independent claim 32, and dependent claims 33 and 44, Sebastian et al discloses a method of providing an aerosol to a user, wherein an electronic smoking article comprising a reservoir bottle (205) that contains components of an aerosol precursor liquid composition

delivers an aerosol to a user. Said composition may contain one or more flavors, medicaments, or other suitable material, for example liquid nicotine, which is transported to at least one heating element that heats the aerosol precursor before being inhaled by said user (see para. [0057]) (corresponding to the claimed "A method of providing nicotine to a user, the method comprising: (i) heating a nicotine …liquid formulation in an electronic cigarette to produce and inhalable aerosol, wherein the nicotine…liquid formulation comprises…nicotine…in a liquid carrier"…(ii) inhalation of the aerosol by the user").

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (corresponding to the claimed "the liquid carrier comprises glycerol and propylene glycol").

Further, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition (see para. [0059]).

While the Sebastian et al reference clearly teaches a nicotine liquid formulation as its precursor composition; it may not be clear whether it teaches a nicotine ***salt*** liquid formulation. However, the Lechuga-Ballesteros et al reference teaches liquid aerosol formulations that can be administered by inhalation through the mouth. It further teaches a more

palatable delivery of nicotine in a liquid formulation because it discloses that nicotine, in its free form (i.e., unprotonated) has a harsh, unpleasant taste, and is likely to cause stomach upset; however, nicotine salts are less likely to cause these problems in users (see para. [0062]). Lechuga-Ballesteros et al goes on to disclose that numerous suitable acids, including benzoic acid, may be reacted with nicotine, preferably in 1:1 molar ratios, to form a nicotine salt (see paras. [0040]-[0042]). Hence, it would have been obvious to one having ordinary skill in the art to have chosen the “nicotine salt” of Lechuga-Ballesteros et al to replace the “nicotine” of Sebastian in order to experience a more palatable delivery of nicotine, as taught in the Lechuga-Ballesteros et al reference. Further, it would have also been obvious to one having ordinary skill in the art to have chosen benzoic acid from the list of suitable acids to react with nicotine, on a 1:1 molar basis, after undergoing routine experimentation, and determining that this particular acid, when reacted with nicotine, yielded the most organoleptically-pleasing properties to the user when the nicotine salt composition was heated and inhaled (corresponding to the claimed “(i) heating a nicotine salt liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

comprising, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier…and the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1").

Lastly, Sebastian et al discloses that the nicotine content in its liquid precursor composition can be provided in a range (up to about 5% by weight) of the liquid precursor composition (see para. [0061]). Hence, one of ordinary skill in the art would have undergone routine experimentation to determine the optimal amount of nicotine ***benzoate*** concentration (after having reacted 1 mole of nicotine with 1 mole of benzoic acid) in the resulting liquid composition of the modified Sebastian et al invention and arrived at a point which overlaps the claimed range after determining that this nicotine benzoate concentration provided superior sensory characteristics in the resulting aerosol (corresponding to the claimed "(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w); the "wherein the nicotine salt concentration is about 4% (w/w) to about 12% (w/w)" recitation of claim 33; the "wherein the nicotine salt concentration is about 4% (w/w)" recitation of claim 44).

Regarding claim 34, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice

(see para. [0053])(corresponding to the claimed “wherein the nicotine salt liquid formulation further comprises a flavorant”).

Regarding claim 35, as evident from Fig. 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation”).

Regarding claims 36, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed “wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid”).

Regarding independent claim 37, Sebastian et al discloses an electronic smoking article comprising a reservoir bottle (205) that contains components of an aerosol precursor liquid composition which is delivered in aerosolized form to a user. Said composition may contain one or more flavors, medicaments, or other suitable material, for example liquid nicotine, which is transported to at least one heating element that heats the aerosol precursor before being inhaled by said user (see para. [0057]) (corresponding to the claimed “An electronic cigarette comprising an electronic cigarette cartridge”).

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (see para. [0015])(corresponding to the claimed “the liquid carrier comprises glycerol and propylene glycol”).

Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed “wherein the nicotine liquid formulation further comprises a flavorant”).

As evident from Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle

(205) disposed therein (see para. [0081])(corresponding to the claimed "which is configured to serve as a mouthpiece and a reservoir that holds the nicotine formulation").

Also, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in the liquid precursor composition in order to favorably affect the organoleptic properties of the composition (see para. [0059]).

While the Sebastian et al reference clearly teaches a nicotine liquid formulation as its precursor composition; it may not be clear whether it teaches a nicotine ***salt*** liquid formulation. However, the Lechuga-Ballesteros et al reference teaches liquid aerosol formulations that can be administered by inhalation through the mouth. It further teaches a more palatable delivery of nicotine in a liquid formulation because it discloses that nicotine, in its free form (i.e., unprotonated) has a harsh, unpleasant taste, and is likely to cause stomach upset; however, nicotine salts are less likely to cause these problems in users (see para. [0062]). Lechuga-Ballesteros et al goes on to disclose that numerous suitable acids, including benzoic acid, may be reacted with nicotine, preferably in 1:1 molar ratios, to form a nicotine salt (see paras. [0040]-[0042]). Hence, it would have been obvious to one having ordinary skill in the art to have

chosen the “nicotine salt” of Lechuga-Ballesteros et al to replace the “nicotine” of Sebastian in order to experience a more palatable delivery of nicotine, as taught in the Lechuga-Ballesteros et al reference. Further, it would have also been obvious to one having ordinary skill in the art to have chosen benzoic acid from the list of suitable acids to react with nicotine, on a 1:1 molar basis, after undergoing routine experimentation, and determining that this particular acid, when reacted with nicotine, yielded the most organoleptically-pleasing properties to the user when the nicotine salt composition was heated and inhaled (corresponding to the claimed “a nicotine salt liquid formulation comprising, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier...the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1).

Lastly, Sebastian et al discloses that the nicotine content in its liquid precursor composition can be provided in a range (up to about 5% by weight) of the liquid precursor composition (see para. [0061]). Hence, one of ordinary skill in the art would have undergone routine experimentation to determine the optimal amount of nicotine ***benzoate*** concentration (after having reacted 1 mole of nicotine with 1 mole of benzoic acid) in the resulting liquid composition of the modified Sebastian et al invention and

arrived at a point which overlaps the claimed range after determining that this nicotine benzoate concentration provided superior sensory characteristics in the resulting aerosol (corresponding to the claimed "(a) the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w)).

Regarding claim independent claim 38, and dependent claims 39 and 45, Sebastian et al discloses a method of providing an aerosol to a user, wherein an electronic smoking article comprising a reservoir bottle (205) that contains components of an aerosol precursor liquid composition delivers an aerosol to a user. Said composition may contain one or more flavors, medicaments, or other suitable material, for example liquid nicotine, which is transported to at least one heating element that heats the aerosol precursor before being inhaled by said user (see para. [0057]) (corresponding to the claimed "A method of vaporizing a nicotine…liquid formulation, the method comprising heating the nicotine …liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine…liquid formulation comprises…nicotine…in a liquid carrier").

Sebastian et al discloses that its aerosol precursor liquid composition may include glycerol and/or propylene glycol (corresponding to the claimed "the liquid carrier comprises glycerol and propylene glycol").

Further, Sebastian et al teaches that organic acids (like pyruvic acid) can be combined with the nicotine in order to favorably affect the organoleptic properties of the composition (see para. [0059]).

While the Sebastian et al reference clearly teaches a nicotine liquid formulation as its precursor composition; it may not be clear whether it teaches a nicotine ***salt*** liquid formulation. However, the Lechuga-Ballesteros et al reference teaches liquid aerosol formulations that can be administered by inhalation through the mouth. It further teaches a more palatable delivery of nicotine in a liquid formulation because it discloses that nicotine, in its free form (i.e., unprotonated) has a harsh, unpleasant taste, and is likely to cause stomach upset; however, nicotine salts are less likely to cause these problems in users (see para. [0062]). Lechuga-Ballesteros et al goes on to disclose that numerous suitable acids, including benzoic acid, may be reacted with nicotine, preferably in 1:1 molar ratios, to form a nicotine salt (see paras. [0040]-[0042]). Hence, it would have been obvious to one having ordinary skill in the art to have chosen the “nicotine salt” of Lechuga-Ballesteros et al to replace the “nicotine” of Sebastian in order to experience a more palatable delivery of nicotine, as taught in the Lechuga-Ballesteros et al reference. Further, it would have also been obvious to one having ordinary skill in the art to have

chosen benzoic acid from the list of suitable acids to react with nicotine, on a 1:1 molar basis, after undergoing routine experimentation, and determining that this particular acid, when reacted with nicotine, yielded the most organoleptically-pleasing properties to the user when the nicotine salt composition was heated and inhaled (corresponding to the claimed "heating a nicotine salt liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein (c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1").

Lastly, Sebastian et al discloses that the nicotine content in its liquid precursor composition can be provided in a range (up to about 5% by weight) of the liquid precursor composition (see para. [0061]). Hence, one of ordinary skill in the art would have undergone routine experimentation to determine the optimal amount of nicotine ***benzoate*** concentration (after having reacted 1 mole of nicotine with 1 mole of benzoic acid) in the resulting liquid composition of the modified Sebastian et al invention and arrived at a point which overlaps the claimed range after determining that this nicotine benzoate concentration provided superior sensory characteristics in the resulting aerosol (corresponding to the claimed "(a)

the nicotine salt concentration in the nicotine salt liquid formulation is from about 3% (w/w) to about 15% (w/w); the “the nicotine salt concentration is about 4% (w/w) to about 12% (w/w)” recitation of claim 39; the wherein the nicotine salt concentration is about 4% (w/w) recitation of claim 45).

Regarding claim 40, Sebastian et al discloses that its liquid nicotine formulation can further include flavoring agents, such as cocoa and licorice (see para. [0053])(corresponding to the claimed “wherein the nicotine salt liquid formulation further comprises a flavorant”).

Regarding claim 41, as evident form Fig., 1, Sebastian et al discloses that its electronic smoking article may include a mouth-end (11) which is substantially an open cavity with a resistive heating element (50) and a reservoir bottle (205) disposed therein (see para. [0081])(corresponding to the claimed “wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation”).

Regarding claims 42, Sebastian et al discloses, as a non-limiting example, that its aerosol precursor composition can comprises 75-80% by weight glycerol; about 13-15% by weight water; about 4-6% by weight propylene glycol (i.e., the liquid carrier); about 2-3% by weight nicotine and

about 0.1-0.5% by weight flavorant (see para. [0061]), and it has already been established (above) that the total amount of organic present can be equimolar to the total amount of nicotine present in the aerosol precursor (see para. [0059)(corresponding to the claimed "wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier and the benzoic acid").

Response to Applicant's Arguments

9. Applicant's arguments with respect to the prior art rejection of the instant claims have been considered but are moot in view of the new prior art grounds for rejection, presented above. The outstanding arguments, filed on December 11, 2019, pertaining to support, in the instant specification, for the "nicotine salt concentration" recitation is believed to be sufficiently and adequately addressed in the above-stated rejection of the claims under 35 USC 112(a).

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE WALLS MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Thursdays and alternate Monday and Tuesdays, 7:00A-3:00P EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael H Wilson can be reached on 571-270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE W. MAYES/
Examiner, Art Unit 1747

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC - Searched*		
Symbol	**Date**	**Examiner**
A24F47/008	1/11/2016	DWM
updated above	6/11/2016	DWM
updated above	5/25/2017	DWM
updated above	09/25/2018	DWM
updated above	06/27/2019	DWM
updated above	02/16/2020	DWM

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM
Inventor Search updated	6/11/2016	DWM
Inventor Search updated	09/25/2018	DWM
updated above	02/16/2020	DWM

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25 (peak or max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2015/01/20 15:51

			EPO; JPO; DERWENT; IBM_TDB			
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54
S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48
S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR;	ADJ	ON	2015/01/20 16:59

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33
S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08

S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31

		(plasma or blood) and (ph near5 "7") and heat$4 and lung				
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48

		(plasma or blood)				
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	("14925961").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30
S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33
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	Application Number	14/925,961
	Filing Date	2015-10-28
	First Named Inventor	Adam Bowen
	Art Unit	1747
	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

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	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14/925,961
	Filing Date	2015-10-28
	First Named Inventor	Adam Bowen
	Art Unit	1747
	Examiner Name	DIONNE WALLS MAYES
	Attorney Docket Number	62210-501C03US/713.302

		CLAYTON, et al., "Spectroscopic investigations into the acid-base properties of nicotine at different temperatures", Analytical Methods, 2013, pp. 81-88, Vol. 5.	
		HENNINGFIELD, et al., "Tobacco Control", 1995, pp. 57-61, Vol. 4.	
		LEFFINGWELL, et al., "Basic chemical constituents of tobacco: production, chemistry and Technology", Blackwell Science, 1999.	
		MAIER, et al., "Polypropylene: the defintive user's guide and databook", 1998.	
		STEPANOV, et al., "Bringing attention to e-cigarette pH as an important element for research and regulation", Tob. Control, May 14, 2014, Vol. 24, No. 4.	

EXAMINER SIGNATURE

Examiner Signature	/DIONNE W. MAYES/	Date Considered	02/16/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

148514 7590 04/24/2020

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Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
04/24/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com
mintzdocketing@cpaglobal.com

PTOL-90A (Rev. 04/07)

Applicant-Initiated Interview Summary	**Application No.** 14/925,961	**Applicant(s)** BOWEN et al.	
	Examiner DIONNE W MAYES	**Art Unit** 1747	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) DIONNE WALLS. MAYES.

(2) KENNETH JENKINS.

(3) JEFFERY GIERING.

(4) _____.

Date of Interview: 21 April 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☑112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: Those of Record.

Identification of prior art discussed: Sebastian, LeChuga-Ballesteros, Lindell.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant's representatives, Mr. Jeffery Giering and Kenneth Jenkins, provided an "Agenda for Examiner Interview" so that they could discuss the outstanding Office Action with Examiner Mayes. Mr Jenkins and Mr Giering addressed the 35 USC 112-a and 103 rejections and provided reasonable arguments and a proposed claim amendment (to address the 35 USC 112-a issues) for which Examiner Mayes said that she would favorably consider upon the filing of an official response..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/DIONNE W. MAYES/ Examiner, Art Unit 1747	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961	Confirmation No.: 1528
Filed: October 28, 2015	Art Unit: 1747
For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	Examiner: Dionne W. MAYES

AGENDA FOR EXAMINER INTERVIEW

Dear Examiner Mayes,

Per your request, below is a proposed agenda for our telephonic interview scheduled for April 21, 2020 at 1:00 pm Eastern. The following topics are provided for discussion purposes only:

- Illustrative support for recited nicotine salt concentrations
- Teaching and guidance missing from Lechuga (US20060018840)
- Consideration of rebuttal evidence (declarations, appendices, and evidence of unexpected results and long-felt unmet need; see, e.g., response dated March 27, 2019)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Adam Bowen et al.	
Application No.: 14/925,961	Confirmation No.: 1528
Filed: October 28, 2015	Art Unit: 1747
For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	Examiner: Dionne W. MAYES

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION

By EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This paper is filed in response to the Non-Final Office Action dated February 20, 2020 in the above-identified application. The shortened statutory period for reply expired May 20, 2020. With this response, Applicant requests a three-month extension of time, and submits the requisite fee. Accordingly, this response is timely filed.

Please amend the application as set forth below, and consider the following remarks:

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **6** of this paper

Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Jeffery C. Giering/Angela Olivos
Attorney Docket Number:	62210-501C03US/713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
		Total in USD ($)		**700**

Electronic Acknowledgement Receipt

EFS ID:	40330442
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Angela Olivos
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	19-AUG-2020
Filing Date:	28-OCT-2015
Time Stamp:	17:43:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$700
RAM confirmation Number	E20208IH43484029
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		062210-501C03US_Response_to_Non-Final_Office_Action.pdf	326157 9724d4aa366c1210d1f70ba99d32dc7a62c47063	yes	18

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	6	18
	Claims	2	5
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	31047 a08a138a1fe59227ff2b6b59112f5c9a4568bbd7	no	2

Warnings:

Information:

Total Files Size (in bytes):	357204

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Claims 26, 27, 31-33, 37-39, and 43-45 are currently amended. Claims 1-25 were previously canceled. Amendments are supported throughout the application as originally filed. Illustrative support can be found in the abstract and paragraphs [0269], [0270], [0334], [0335], [0382], [0383] of US20160044967A1. No new matter is added by these amendments. Upon entry of these amendments, claims 26-45 will be pending.

With respect to any claim amendments or cancelations, Applicant has not dedicated to the public or abandoned any unclaimed subject matter, and has not acquiesced to any rejection and/or objection made by the U.S. Patent and Trademark Office. Applicant expressly reserves the right to pursue prosecution of any presently unclaimed subject matter in one or more future continuation or divisional applications.

Interview Summary

Applicant wishes to thank Examiner Mayes for courtesies extended during a telephonic interview with Applicant's representatives Jeffery C. Giering and Kenneth E. Jenkins on April 21, 2020. The outstanding rejections were discussed, as were amendments relating to recitations of nicotine concentration, adopted herein. No agreement was reached, but the examiner indicated that these amendments would be favorably considered.

Rejection Under 35 U.S.C. § 112

Claims 26-45 stand rejected under 35 U.S.C. 112(a) as allegedly lacking written description in the application as filed. Specifically, the Office alleges that there is no written support for (1) the recited nicotine salt concentrations, or (2) the molar ratio in the liquid formulation. Applicant respectfully traverses the rejection.

Recited concentrations are supported

The Office acknowledged disclosure relating to statements concerning concentrations of nicotine salt. However, regarding particular concentrations, the Office alleges that "it is clear

that these concentration parameters pertain to the amount of nicotine in the nicotine salt (liquid) formulation, as opposed to the amount of the nicotine ***salt*** in the nicotine salt (liquid) formulation (which is claimed)" (Office Action, pg. 4; emphasis original).

Without agreeing with the Office's interpretation, and solely for the sake of expediting prosecution, claims 26, 32, 37, and 38 are amended to recite, in part, "the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine" (emphasis added). Corresponding amendments are made in dependent claims 27, 33, 39, and 43-45. As such, the concentrations now expressly refer to concentrations of nicotine, while also specifying that it is the nicotine salt "is present in an amount that forms" such nicotine concentration.

These amendments are fully supported by the application as filed. For example, the abstract of the present application refers to a "nicotine salt liquid formulation" that comprises "nicotine salt that forms about 0.5% to about 20% nicotine" (emphasis added). Similar descriptions also appear in paragraphs [0269], [0270], [0334], [0335], [0382], [0383] of US20160044967A1, reciting "the nicotine salt is in an amount that forms" various concentrations. As a further illustration, Example 1 provides various "nicotine salt formulations" having one of various "nicotine free base equivalent concentration[s]" (emphasis added). Taken together, the application clearly discloses nicotine concentrations resulting from amounts of nicotine salts present in the liquid formulations. The application provides several exemplary concentrations, including those presently claimed. Illustrative support can be found at paragraph [0122] of US20160044967A1.

Recited molar ratios are supported

The Office alleges that "it appears that the 'molar ratio' disclosure pertains only to the stoichiometry of the nicotine salt . . . as opposed to the relationship of the reactants (i.e., nicotine and benzoic acid) in the nicotine salt liquid formulation" (Office Action, pgs. 4-5; emphasis original). On the basis of this interpretation, the Office "presumed that the intended recitation is as follows: 'the molar ratio of benzoic acid to nicotine in the nicotine salt ***of the*** nicotine salt liquid formulation is about 1:1" (Office Action, pg. 5; emphasis original). Applicant respectfully

disagrees with the Office's reading of the specification, and the imposed construction of the present claims.

As a practical matter, it does not make sense to restrict "molar ratio" as limited to salt stoichiometry in a liquid formulation because individual species are transient in equilibrium, and may fluctuate molecule to molecule at any given point in time. Moreover, relationships will be a consequence of amounts in the formulation. For example, all other conditions being equal, the fraction of nicotine molecules associating with benzoic acid molecules at any given point in time in solution will be higher when the molar ratio in the liquid formulation is 1:1 as opposed to when it is 4:1 (nicotine:acid). However, as already stated, such associations on a molecule-by-molecule basis are transient in equilibrium. It therefore makes more sense to interpret this claim element ("molar ratio . . . . in the nicotine salt liquid formulation") as presently worded, referring to relative amounts in the formulation.

Construction in accordance with the claims as presently worded (without the modification as proposed by the Office) is also supported in the application. Paragraph [0130] of US20160044967A1 provides a helpful explanation, using pyruvic acid as an example:

> *For example, nicotine pyruvate is a nicotine salt with 1:2 nicotine:acid ratio. The formulation containing nicotine pyruvate (1:2) may deliver more satisfaction to the user than the one containing same amount of nicotine but only half amount of pyruvic acid, i.e. nicotine pyruvate (1:1). This may be explained as 1 mole of nicotine produces a salt with 2 moles of pyruvic acid. When there is not enough pyruvic acid to associate with all nicotine molecules, the free base nicotine left unprotonated in the formulation may reduce the satisfaction the formulation provides.*

Thus a "formulation containing" nicotine and acid in a ratio of 1:2 is contrasted with one containing nicotine and acid in a 1:1 ratio, even though individual molecules are noted as associating is a 1:2 stoichiometric relationship in both cases. Thus, a distinction is drawn in the present application between the stoichiometric relationships of individual molecules, and molar ratios of components in the formulation.

Likewise, paragraph [0123] provides a variety of exemplary molar ratios contemplated "[i]n some formulations." Consistent with these disclosures, various formulations described in the examples are prepared with nicotine and acid in amount to achieve a desired molar ratio in

the formulation. Example 1 describes a formulation in which 0.15g of benzoic acid is mixed with 0.2g nicotine, which is a 1:1 molar ratio of the components in the formulation.

Taken together, there is ample descriptive support in the application for reciting a "molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1," and one of ordinary skill in the art would properly understand this phrase to refer to the relative amounts of the components in the formulation, rather than being limited to the stoichiometry of individual molecules.

For at least the above reasons, the application as filed provides full written description support for the claims as presently amended. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 26-45 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over US20140000638 ("Sebastian") in view of US20060018840 ("Lechuga"). Applicant respectfully traverses the rejection.

MPEP § 2142 provides, "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." MPEP § 2143.01(III) provides, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 538, 417, 82 USPQ2d 1385, 1396 (2007)" (emphasis original). Moreover, "[w]hether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made" (MPEP § 2143.02(III)).

"Whether a rejection is based on combining disclosures from multiple references, combining multiple embodiments from a single reference, or selecting from large lists of elements in a single reference, there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan

would not arrive at the claimed combination." *In re Stepan Co*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (emphasis added).

Each of claims 26, 32, 37, and 38 recite nicotine salt liquid formulations in an electronic cigarette. Sebastian is directed to an "electronic smoking article" with "one or more heaters" for aerosolizing the contents (Sebastian, abstract). Acknowledging that "it may not be clear whether [Sebastian] teaches a nicotine ***salt*** liquid formulation," the Office cites to Lechuga for this element. However, Lechuga fails to provide the requisite reasonable expectation of success for the delivery of nicotine in an electronic cigarette, and no motivation for the specific selection of benzoic acid. In addition, the presently claimed nicotine salt liquid formulations provide unexpected advantages that could not have been predicted based on the cited references.

No reasonable expectation of success provided by the references

Lechuga does not disclose electronic cigarettes. Instead, Lechuga describes formulations for delivery in metered dose inhaler (MDI) systems (see, e.g., Lechuga, paragraphs [0035] and [0036]). In particular, MDI's of Lechuga are described as typically comprising "a propellant" in a canister that keeps its contents "under pressure," with contents being "propelled toward the mouthpiece" in a "metered dose." As such, substantial modification would have been required to adapt the formulations of Lechuga for delivery in the "electronic smoking article" of Sebastian. In particular, neither reference provides any basis to predict how heating such compositions might affect nicotine delivery. Indeed, Lechuga does not even demonstrate nicotine delivery in the inhaler context. Instead, Lechuga only provides a "prediction" based on models (see, e.g., FIG. 4). There is no evidence that the formulations of Lechuga were actually operable in inhalers, much less any guidance as to what if any effect would be achieved with nicotine salts in an electronic cigarette. Therefore, a person of ordinary skill in the art could not have predicted the effects of the alleged combination.

No reasonable expectation of success in the art at the time of invention

The lack of evidence in Lechuga that the stated objective had actually been achieved is significant when considering the long-held belief that nicotine freebase was the preferred form for delivery with an electronic cigarette.

Reference is made to declarations by Dr. Bradley James Ingebrethsen (originally filed in U.S. Serial No. 14/512,311; hereafter "Ingebrethsen Declaration") and Adam Bowen (originally filed in U.S. Serial No. 14/925,968; hereafter "Bowen Declaration"). Copies of these declarations were previously submitted on April 20, 2017 (Bowen Declaration) and December 4, 2017 (Ingebrethsen Declaration). Reference is also made to Appendices filed with Applicant's response dated March 27, 2019.

As explained by Dr. Ingebrethsen, the free base form of nicotine in basic formulations was "widely and commonly assumed over a long time period to be the form that will be most readily and rapidly absorbed from cigarette smoke in the blood upon inhalation" (Ingebrethsen Declaration, para. (4)). This belief was so ingrained among those of ordinary skill in the art that publications by Applicant did not quickly alter this attitude in the art. "Despite the publication in January 2015 of [U.S. Application No. 14/512,311], and the publication of its parent application (US 2014/0345631) in November 2014, the belief that optimum nicotine absorption occurs in nicotine formulations that have basic pHs (i.e. have nicotine present predominantly in the free base form) continues throughout industry as evidenced by El-Hellani's July publication and Gonda, at least" (Ingebrethsen Declaration, para. (5)).

In addition, Adam Bowen explains that "those of skill in the art believed that vaporized nicotine did not result in an effect on heart rate comparable to that seen with a traditional cigarette." *See* Bowen Declaration at paragraph (7), and supporting references supplied as Exhibits C-E thereof. In contrast, the subject application teaches: "It has been unexpectedly discovered herein that certain nicotine salt formulations provide satisfaction in an individual superior to that of free base nicotine, and more comparable to the satisfaction in an individual smoking a traditional cigarette" (US20160044967A1 at [0111]).

Multiple publications describe the widely held belief that free base nicotine was most effective. El-Hellani et al., cited by Dr. Ingebrethsen, states that "Nic [free-base nicotine] is

thought to be the only form that diffuses through epithelial tissues in the human body. Thus, all else being equal, an ECIG with a higher proportion of Nic will increase the rate of uptake of nicotine by the user's body" (Exhibit D of Ingebrethsen Declaration, pg. A). Thus, El-Hellani illustrates why one of ordinary skill in the art would have had no reasonable expectation that providing a nicotine salt liquid formulation, as presently claimed, would improve the performance of an electronic cigarette. On the contrary, one of ordinary skill, and indeed even experts at the time, would have expected the opposite.

El-Hellani is just one example of reports touting the importance of free base nicotine. An article detailing the history of free base nicotine in traditional cigarettes reports that "neutral, deprotonated nicotine is 'free' in that it is no longer bound to another molecule (or anion) in the form of a salt. Free nicotine is more volatile; James F. Pankow, of Oregon Health and Science University, stresses that 'increasing the proportion of the particle-phase nicotine that is in the freebase form will . . .tend to drive more nicotine into the gas phase" rendering it "more 'available' to the smoker" (Stevenson and Proctor, American Journal of Public Health, July 2008, Vol 98, No. 7; Appendix A).

The belief that favoring the free base form of nicotine with an alkaline pH dates to at least 1940. Travell et al., who reported experiments using bladder as a model for epithelial absorption, observed that nicotine compositions at acidic pH "produced no effects," and concluded that, "within a certain range the higher the pH, the more rapid is its absorption" (Travell et al., Experimental Biology and Medicine, 45(2), 552-56 (1940); Appendix B).

The perceived importance of free base nicotine was reinforced by later studies, such as Burch et al. (Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung 6(1), 45-52 (1993); Appendix C) and Shao et al. (Nicotine & Tobacco Research, 15(7), 1248-58 (December 13, 2012); Appendix D), in addition to those performed by El-Hellani noted above. Burch states, "Our data indicated that the pH of the nicotine aerosol significantly affects the absorption of nicotine. Increasing the aerosol pH produced significantly higher peak plasma nicotine levels. These results were similar to previously reported effects of pH on nicotine absorption across mucous membranes (11)" (Burch, pg. 49). Moreover, Burch refers to a previous study in which "5 mg of aerosolized nicotine with a pH of 11 . . . produced nicotine

levels which were similar to those reached with cigarettes" (Burch, pg. 45; emphasis added). At a pH of 11, almost all of the nicotine would have been in the free base form (see, e.g., Ingebrethsen Declaration, Appendix D, Table 1). Taken together, a pH at which nicotine is almost completely in the free base form was the only one reported to produce nicotine levels comparable to a cigarette, and delivery was reported to go down as pH went down. Thus, Burch further illustrates why there would have been no reasonable expectation of success for using an electronic cigarette with a formulation having a pH low enough to yield a nicotine salt liquid formulation in accordance with the present claims. Indeed, Shao (published six years after Lechuga) observed that lowering the pH of a test composition from 7.4 (mildly alkaline) to 6.8 (mildly acidic) "dramatically increased" LC_{50}, indicating "a decrease in the delivery rate and/or the bioavailability of nicotine" (Shao, pg. 1255).

Given the widespread preference in the art for free base nicotine, and the complete lack of any results or teachings in Sebastian or Lechuga countering the express preferences for free base nicotine for electronic cigarettes, the cited combination of references fails to supply any reason to expect that the claimed nicotine salt liquid formulation could have been successfully used within an electronic cigarette system.

No reason to select benzoic acid

Sebastian does not disclose benzoic acid. Lechuga only discloses benzoic acid in a list of twenty-nine other acids (Lechuga, para. [0042]). Moreover, Lechuga considers all of these organic acids to be equivalent to one another and to any number of other organic acids. For example, Lechuga states "Numerous suitable organic acids may be used in the formulations of the present invention" (Lechuga, para. [0042]). Thus, neither reference provides any motivation or suggestion to specifically select benzoic acid, nor reason to expect the advantages thereof.

The Office also does not provide any motivation for the selection of benzoic acid from among the at least twenty-nine options offered by Lechuga. Rather, the Office alleges that such selection would have been obvious "after undergoing routine experimentation, and determining that this particular acid, when reacted with nicotine, yielded the most organoleptically-pleasing properties to the user when the nicotine salt composition was heated and inhaled" (Office Action,

pg. 8). Even if one of ordinary skill were to have embarked on such a speculative research project, there is absolutely no indication in either of the references which acid would yield "the most organoleptically pleasing properties." Sebastian does not list benzoic acid as among the organic acids considered to have such properties, and draws no distinctions between those that are listed. Lechuga does not address organoleptic properties at all. While Lechuga lists benzoic acid, such listing is one among several others all deemed to be equivalent (Lechuga, para. [0042]). As such, the references do not even suggest that any particular acid would be "most organoleptically-pleasing," and therefore give no reason for one of ordinary skill in the art to embark on the allegedly "routine experimentation" postulated by the Office. Moreover, even if undertaking such experimentation, there would have been no reason to believe that benzoic acid would have been identified as the preferred acid. Any conclusion to the contrary can derive only from impermissible hindsight. It was Applicant who first discovered the unexpected benefits of using sufficient amounts of nicotine salts formed with particular acids in an electronic cigarette, and the advantages of benzoic acid in particular.

Selection of benzoic acid provides unexpected results

For at least the above reasons, a *prima facie* case of obviousness has not been established. However, even if a *prima facie* case had been established, it can be rebutted by unexpected results. MPEP 716.02(a)(II) states, "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. 'Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness.' No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) . . . . See also *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria)."

As explained above, none of the cited references provide any teaching that would lead a person having ordinary skill in the art at the relevant time to select a specific effective acid, such

as ***benzoic acid***, over any other acid, much less wherein the "molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1," as claimed.

Applicant discovered, *inter alia*, that the claimed nicotine salt liquid formulation results in a rapid onset peak increase in heart rate relative to a similar free-base nicotine formulation. *See, e.g.,* FIG. 1 of the subject application. The link between effective acids such as benzoic acid and their ability to increase a physiological effect of nicotine such as an increase in heart rate was unknown before Applicant's invention. For example, benzoic acid invokes a stronger physiological response than, *e.g.*, citric acid. *See, e.g.,* paragraph (8) of the Ingebrethsen Declaration.

None of the cited art provides any teachings that would lead a person having ordinary skill in the art to predict the surprising efficacy of benzoic acid in delivering nicotine using an electronic cigarette.

Secondary considerations: Long-felt unmet need

MPEP 716.04 provides that a long-felt unmet need is established by evidence that the long-felt need (1) was "a persistent one that was recognized by those of ordinary skill in the art," (2) was not "satisfied by another before the invention by applicant," and (3) is satisfied by the claimed invention.

Attempts to address the negative consequences of smoking traditional cigarettes date from about the 1950's, and "[f]rom the 1960s onward, attention focused on the development of the safer cigarette'" and involved "decades of failed attempts at harm reduction" (Lancet 2014; Appendix E). Attempts to produce a viable electronic-cigarette alternative also date to this time (see, e.g., US3200819A). Thus, prior to Applicant's invention, there was a long felt need for effective e-cigarettes that would be an effective alternative to cigarette smoking.

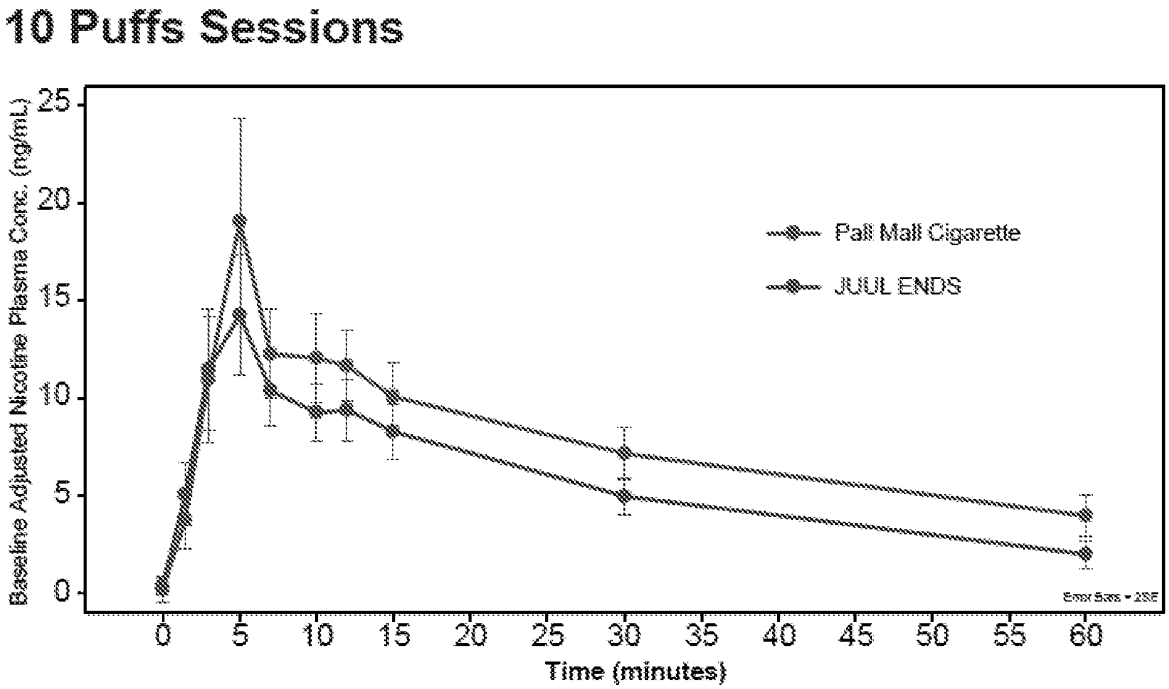
Prior to Applicant's disclosure, the long-felt need noted above was not satisfied by available electronic cigarettes. Several studies reported that previous e-cigarettes failed to perform comparably to traditional cigarettes. For example, one study in 2010 (four years after Lechuga) concluded that "unlike puffing from a tobacco cigarette, two 10-puff bouts with the two electronic cigarettes described here expose users to no measurable nicotine or [carbon monoxide] and do not increase heart rate" (Vansickel et al., Cancer Epidemiol Biomarkers Prev.

2010 Aug;19(8):1945-53; Appendix F). Another study, also published in 2010, compared the effects of e-cigarettes to traditional cigarettes (Bullen et al., Tob Control. 2010 Apr;19(2):98-103; Appendix G). Bullen reports that the electronic cigarette evaluated resulted in only "modest" increases in blood nicotine levels, and that traditional cigarettes "gave a significantly higher Cmax" (Bullen, pg. 101). In fact, Table 3 shows that the Cmax for the electronic nicotine delivery device ("ENDD") in Bullens was only about one tenth that of the cigarette (*Id.*). Studies such as these illustrate that, prior to Applicant's discovery, electronic cigarettes were not able to provide physiological effects comparable to traditional cigarettes, due to low nicotine delivery.

The problems associated with smoking, and the failure of previous electronic cigarette devices to perform comparably to traditional cigarettes is further highlighted in a 2016 report by Khoudigian et al. (Appendix H). Khoudigian notes that "[a]n estimated 1.2 billion people use tobacco worldwide (World Health Organization 2014)," and that "[t]obacco-related deaths are one of the main causes of preventable early mortality, claiming 5 million lives annually (World Health Organization 2014)" (Khoudigian, at pg. 257). Moreover, "[d]espite the benefits of cessation and the desire of most smokers to quit, approximately 80% of those who attempt to quit on their own relapse within the first month of abstinence, and only 3-5% remain abstinent for 6 months or longer." (*Id.*) However, following a "systematic review" of studies comparing e-cigarettes to other nicotine replacement therapies (*Id.*, abstract), Khoudigian concludes that "[t]he review showed no statistically significant effect of nicotine e-cigarettes on smoking abstinence over a long period of time, desire to smoke, withdrawal symptoms, and non-serious adverse events" (*Id.*, pg. 266).

Results reported in the present application illustrate compositions comprising a sufficient amount of nicotine salt that performed comparably to a traditional cigarette in terms of effects on heart rate and blood nicotine (see, e.g., FIGS. 2 and 4). Moreover, clinical studies reported in 2018 further support the unexpected effects of nicotine salt-based electronic nicotine delivery systems (ENDS) commercialized by Applicant, by comparison to traditional cigarettes. A copy of a poster presented at the 2018 Annual Meeting of the Society for Research on Nicotine and Tobacco is attached as Appendix I (hereafter, the "SRNT Study"). The SRNT Study evaluated baseline-adjusted nicotine plasma concentration in subjects smoking a traditional cigarette or a nicotine salt-based ENDS, and concluded, "No significant difference in Tmax, Cmax, AUC, baseline adjusted Cmax and baseline adjusted AUC were observed between cigarette and ENDS"

(SRNT Study, left panel). One of the graphs from the middle panel of the SRNT Study illustrating these results is reproduced below (top plot corresponding to "Pall Mall Cigarette"):



In addition, "Survey results post-use found no significant difference between JUUL ENDS and Pall Mall cigarettes for eleven measures of subjective experience" (*Id.*, right panel).

In view of results in both the present application and the SRNT Study, the claimed compositions satisfy a long-felt unmet need in providing significantly improved formulations for delivery of nicotine in electronic cigarettes. None of the cited references suggest that nicotine salts could be used to render physiological effects of e-cigarettes comparable to traditional cigarettes in general, or to increase nicotine delivery in particular. Indeed, as explained above, no such effect would have been reasonably expected at the time the present invention was made.

SUMMARY

For at least the above reasons, Sebastian and Lechuga would not have been combined by one of ordinary skill in the art, and even if combined, fail to provide a reasonable expectation of success for arriving at the subject matter of the present claims. Moreover, the nicotine salt liquid formulations of the present claims provide unexpected results, and satisfy a long-felt unmet need.

Claims 26, 32, 37, and 38 are therefore unobvious over the cited references, as are all claims depending therefrom. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the application is in condition for allowance. If the Examiner believes that a telephone call would be useful in expediting the allowance of the application, the Examiner is invited to contact the undersigned.

The Commissioner is authorized to charge any shortage in fees due in connection with the filing of this paper, including any necessary extension of time fees, and to credit any excess fees, to Deposit Account Number 50-0311.

Dated: August 19, 2020

Respectfully submitted,

/Jeffery C. Giering/

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application.

Listing of Claims

1.-25. (Cancelled)

26. (Currently Amended) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt ~~concentration~~ in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

27. (Currently Amended) The electronic cigarette of claim 26, wherein the nicotine salt ~~concentration~~ is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine.

28. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt liquid formulation further comprises a flavorant.

29. (Previously Presented) The electronic cigarette of claim 26, wherein the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

30. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

31. (Currently Amended) The electronic cigarette of claim 26, the electronic cigarette further comprising**[[**:**]]** a battery.

32. (Currently Amended) A method of providing nicotine to a user, the method comprising:

(i) heating a nicotine salt liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt ~~concentration~~ in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1; and

(ii) inhalation of the aerosol by the user.

33. (Currently Amended) The method of claim 32, wherein the nicotine salt ~~concentration~~ is present in an amount that forms about 4% (w/w) to about 12% (w/w).

34. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation further comprises a flavorant.

35. (Previously Presented) The method of claim 32, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

36. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

37. (Currently Amended) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation, the nicotine salt liquid formulation comprising a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt ~~concentration~~ in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine;

(b) the liquid carrier comprises glycerol and propylene glycol;

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1;

(d) the nicotine salt liquid formulation comprises a flavorant; and

(e) the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

38. (Currently Amended) A method of vaporizing a nicotine salt liquid formulation, the method comprising heating the nicotine salt liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a salt of nicotine and benzoic acid in a liquid carrier, wherein

(a) the nicotine salt ~~concentration~~ in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

39. (Currently Amended) The method of claim 38, wherein the nicotine salt ~~concentration~~ is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine.

40. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation further comprises a flavorant.

41. (Previously Presented) The method of claim 38, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

42. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

43. (Currently Amended) The method of claim 27, wherein the nicotine salt ~~concentration~~ is present in an amount that forms about 4% (w/w) nicotine.

44. (Currently Amended) The method of claim 33, wherein the nicotine salt ~~concentration~~ is present in an amount that forms about 4% (w/w) nicotine.

45. (Currently Amended) The method of claim 39, wherein the nicotine salt ~~concentration~~ is present in an amount that forms about 4% (w/w) nicotine.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/925,961	Filing Date 10/28/2015	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/19/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 23	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/NICHELE D PETERSON/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/925,961
				Filing Date	October 28, 2015
				First Named Inventor	Adam Bowen
				Art Unit	1747
(Use as many sheets as necessary)				Examiner Name	D. W. Mayes
Sheet	1	of	1	Attorney Docket Number	

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A	US-20160270451-A1	09-22-2016	HON	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	A	CN-105263345-A	01-20-2016	Ploom Inc		
	B	JP-2006524494-A	11-02-2006			
	C	JP-S61254170-A	11-11-1986	Advanced Tobacco Prod Inc		
	D	WO-2011109849-A1	09-15-2011	Buchberger, Helmut		
	E	WO-2014182736-A1	11-13-2014	Ploom, Inc		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	BURN et al., "ACTION OF NICOTINE ON THE HEART", Excretion of Piperazine Salts, British Medical Journal, Jan. 18, 1958, pp. 137-139.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

102699706v.1

Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Jeffery C. Giering/Meghan Breault
Attorney Docket Number:	62210-501C03US/713.302

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	120	120
		Total in USD ($)		**120**

Electronic Acknowledgement Receipt

EFS ID:	40356152
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Meghan Breault
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	21-AUG-2020
Filing Date:	28-OCT-2015
Time Stamp:	20:15:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$120
RAM confirmation Number	E20208KK15532116
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Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	062210-501C03_IDS_Transmittal.pdf	101510 f95232008cd99686738fda3681a27fe07081dc9c	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	062210-501C03_SB08.pdf	149798 aaa675388ca4bb0f1b562ee2aeba3b2ca1eaf0e6	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	CN105263345.pdf	5546342 b781fa685c5d0bba9bc1b8400d77b372dd20b382	no	71
Warnings:					
Information:					
4	Foreign Reference	JP2006524494.pdf	1280748 4081d9e7e33dfc783e41b4f1bed368ecdc571661	no	28
Warnings:					
Information:					
5	Foreign Reference	JPS61254170.pdf	3062111 4dba6101931c2092a5debf3549d11f15fef8bea7	no	8
Warnings:					
Information:					
6	Foreign Reference	WO2011109849A1.pdf	367937 a03d78dc57ee99fcc2c672c4ff0f129f9760facc	no	40
Warnings:					

Information:					
7	Non Patent Literature	Burn_1958_Nicotine-on-the-heart.pdf	1820338 0be88cc024cf0304d61da317a65153dc76694086	no	3
Warnings:					
Information:					
8	Foreign Reference	WO2014182736A1.pdf	5536829 3eb37dbb5c382d0cc4385ee50f82e431b5943f69	no	99
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	30567 09b946cbe84e267aa4b06ebc728e774ebb942f90	no	2
Warnings:					
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Adam Bowen et al.

Application No.: 14/925,961	Confirmation No.: 1528
Filed: October 28, 2015	Art Unit: 1747
For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	Examiner: D. W. Mayes

INFORMATION DISCLOSURE STATEMENT (IDS)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), a copy of a U.S. patent application publication is not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 50-0311 in the amount of $120.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in fees due in connection with the filing of this document to our Deposit Account No. 50-0311, under Application No. 14/925,961.

Dated: August 21, 2020

Respectfully submitted,

Electronic signature: /Jeffery C. Giering/

Jeffery C. Giering, J.D., Ph.D.
Registration No.: 68,221
MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO, P.C.
3580 Carmel Mountain Road
Suite 300
San Diego, California 92130-6768
(858) 314-1500
(858) 314-1501 (Fax)
Attorney for Applicant

102699697v.1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

148514 7590 11/25/2020

Mintz/JUUL
One Financial Center
Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

DATE MAILED: 11/25/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

TITLE OF INVENTION: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	02/25/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

148514 7590 11/25/2020

Mintz/JUUL
One Financial Center
Boston, MA 02111

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

TITLE OF INVENTION: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	02/25/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
MAYES, DIONNE WALLS	1747	131-328000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

148514 7590 11/25/2020

Mintz/JUUL
One Financial Center
Boston, MA 02111

EXAMINER	
MAYES, DIONNE WALLS	
ART UNIT	PAPER NUMBER
1747	

DATE MAILED: 11/25/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/925,961	Applicant(s) BOWEN et al.	
	Examiner DIONNE W MAYES	Art Unit 1747	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Amendment filed on August 19, 2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 26-45 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/DIONNE W. MAYES/ Examiner, Art Unit 1747	/Michael H. Wilson/ Supervisory Patent Examiner, Art Unit 1747

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Mr. Jeffery Giering on Thursday, November 19, 2020.

The application has been amended as follows:

IN THE CLAIMS:

In claim 26,

-line 3, after "a nicotine salt liquid formulation", the phrase -- for generating an inhalable aerosol upon heating in the electronic cigarette -- has been added.

-line 3, after "the nicotine salt liquid formulation comprising", the phrase -- a nicotine salt in a liquid carrier, wherein the nicotine salt comprises -- has been added.

-in line 4, after "a salt of nicotine and benzoic acid", the phrase "in a liquid carrier" has been deleted.

-in line 6, after "nicotine", the phrase -- in the inhalable aerosol -- has been added.

In claim 27,

-in line 2, after "nicotine", the phrase -- in the inhalable aerosol -- has been added.

In claim 32,

-in line 3, after “wherein the nicotine salt liquid formulation comprises”, the phrase -- a nicotine salt in a liquid carrier, wherein the nicotine salt comprises -- has been added,

-in lines 3- 4, after “a salt of nicotine and benzoic acid”, the phrase “in a liquid carrier” has been deleted.

-in line 6, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

In claim 33,

-in line 2, after “present in an amount that forms about 4% (w/w) to about 12% (w/w)”, the phrase -- in the inhalable aerosol -- has been added.

In claim 37,

-line 3, after “a nicotine salt liquid formulation”, the phrase -- for generating an inhalable aerosol upon heating in the electronic cigarette -- has been added.

-line 3, after “the nicotine salt liquid formulation comprising”, the phrase -- a nicotine salt in a liquid carrier, wherein the nicotine salt comprises -- has been added.

-in lines 3-4, after “a salt of nicotine and benzoic acid”, the phrase “in a liquid carrier” has been deleted.

-in line 6, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

In claim 38,

-in line 3, after “wherein the nicotine salt liquid formulation comprises”, the phrase -- a nicotine salt in a liquid carrier, wherein the nicotine salt comprises -- has been added,

-in lines 3-4, after “a salt of nicotine and benzoic acid”, the phrase “in a liquid carrier” has been deleted.

-in line 6, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

In claim 39,

-in line 2, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

In claim 43,

-in line 2, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

In claim 44,

-in line 2, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

In claim 45,

-in line 2, after “nicotine”, the phrase -- in the inhalable aerosol -- has been added.

Reasons for Allowance

2. The following is an examiner’s statement of reasons for allowance:

The prior art of record neither teaches nor reasonably suggests an electronic cigarette, or a method of providing nicotine to a user, wherein a nicotine salt liquid formulation contains a nicotine salt comprised of nicotine and benzoic acid in a 1:1 molar ratio, and in a liquid carrier which includes glycerol and propylene glycol, wherein the nicotine salt is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol which is generated when the nicotine salt liquid formulation is heated in the electronic cigarette. Hence, the claims are allowable over the prior art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DIONNE WALLS MAYES whose telephone number is (571)272-5836. The examiner can normally be reached on Thursdays and alternate Monday and Tuesdays, 7:00A-3:00P EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Michael H Wilson can be reached on 571-270-3882. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DIONNE W. MAYES/
Examiner, Art Unit 1747

/Michael H. Wilson/
Supervisory Patent Examiner, Art Unit 1747

Examiner-Initiated Interview Summary	Application No. 14/925,961	Applicant(s) BOWEN et al.	
	Examiner DIONNE W MAYES	Art Unit 1747	AIA (FITF) Status Yes

All participants (applicant, applicant's representative, PTO personnel):

(1) DIONNE WALLS. MAYES. (3) _____.

(2) JEFERY GEIRING. (4) _____.

Date of Interview: 19 November 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: Those of Record.

Identification of prior art discussed: Nonne.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/DIONNE W. MAYES/ Examiner, Art Unit 1747	

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Examiner Mayes contacted Applicant's representative, Mr. Jeffery Giering, to suggest claim amendments that would place the application in condition for allowance after it was determined that the claims, as currently amended, raised potential issues under 35 USC 112a, even though it appeared to define over the prior art of record. After some discussion as to the proper claim terminology, an agreement was reached between Applicant and Examiner Mayes and such is reflected in the attached "Examiner's Amendment".

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC							
Symbol						Type	Version
A24F	/	47	/	008		F	2020-01-01
A24B	/	15	/	16		I	2013-01-01
A61K	/	31	/	465		I	2013-01-01
A24B	/	15	/	167		I	2016-11-01
A61K	/	9	/	12		I	2013-01-01
A61K	/	9	/	007		I	2013-01-01
A61K	/	31	/	60		I	2013-01-01
A61K	/	47	/	10		I	2013-01-01

CPC Combination Sets								
Symbol						Type	Set	Ranking	Version
	/		/						

/DIONNE W. MAYES/ Examiner, Art Unit 1747 (Assistant Examiner)	19 November 2020 (Date)	Total Claims Allowed: 20	
/Michael H. Wilson/ Supervisory Patent Examiner, Art Unit 1747 (Primary Examiner)	20 November 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20201119

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A24F	/	47	/	00

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/DIONNE W. MAYES/ Examiner, Art Unit 1747 (Assistant Examiner)	19 November 2020 (Date)	**Total Claims Allowed:** 20	
/Michael H. Wilson/ Supervisory Patent Examiner, Art Unit 1747 (Primary Examiner)	20 November 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20201119

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	**Art Unit**
	DIONNE W MAYES	1747

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	26	12	35	10	44										
2	27	13	36	17	45										
4	28	14	37												
5	29	15	38												
6	30	16	39												
7	31	18	40												
8	32	19	41												
9	33	20	42												
11	34	3	43												

/DIONNE W. MAYES/ Examiner, Art Unit 1747	19 November 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/Michael H. Wilson/ Supervisory Patent Examiner, Art Unit 1747	20 November 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20201119

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

CPC - Searched*		
Symbol	**Date**	**Examiner**
A24F47/008	1/11/2016	DWM
updated above	6/11/2016	DWM
updated above	5/25/2017	DWM
updated above	09/25/2018	DWM
updated above	06/27/2019	DWM
updated above	02/16/2020	DWM
A24F47/00; A24F40/00; A24B15/16 - cursory overview	11/19/2020	DWM

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/925,961	BOWEN et al.
	Examiner	Art Unit
	DIONNE W MAYES	1747

Search Notes		
Search Notes	**Date**	**Examiner**
EAST search conducted (see attached search strategy)	1/11/2016	DWM
Inventor search conducted	1/11/2016	DWM
Inventor Search updated	6/11/2016	DWM
Inventor Search updated	09/25/2018	DWM
updated above	02/16/2020	DWM
updated above	11/19/2020	DWM

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A24F	47/00; 40/00	11/19/2020	DWM
A24B	15/16		

Used in Lieu of PTO/SB/08A/B
(Based on PTO 11-07 version)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	14/925,961
				Filing Date	October 28, 2015
				First Named Inventor	Adam Bowen
				Art Unit	1747
(Use as many sheets as necessary)				Examiner Name	D. W. Mayes
Sheet	1	of	1	Attorney Docket Number	

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A	US-20160270451-A1	09-22-2016	HON	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	A	CN-105263345-A	01-20-2016	Ploom Inc		
	B	JP-2006524494-A	11-02-2006			
	C	JP-S61254170-A	11-11-1986	Advanced Tobacco Prod Inc		
	D	WO-2011109849-A1	09-15-2011	Buchberger, Helmut		
	E	WO-2014182736-A1	11-13-2014	Ploom, Inc		

Examiner Signature	/DIONNE W. MAYES/	Date Considered	11/17/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	BURN et al., "ACTION OF NICOTINE ON THE HEART", Excretion of Piperazine Salts, British Medical Journal, Jan. 18, 1958, pp. 137-139.	

Examiner Signature	/DIONNE W. MAYES/	Date Considered	11/17/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

102699706v.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.W.M/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	("14925961").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2020/11/19 20:56
L2	1	(14/925961).APP.	US-PGPUB; USPAT; USOCR	OR	OFF	2020/11/19 20:56
L3	1,472	(A24F47/00 or A24F40/00 or A24B15/16).cpc.	US-PGPUB; USPAT	ADJ	OFF	2020/11/19 21:04
L4	20	(A24F47/00 or A24F40/00 or A24B15/16).cpc. and inhal$5 near25 (gas or gas$1phase or aerosol) near25 (amount or level or content or concentration) near15 nicotin$3	US-PGPUB; USPAT	ADJ	OFF	2020/11/19 21:04
S1	3	(("20060195518") or ("20120256567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S2	3	(("20060195518") or ("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:41
S3	2	(("20120255567") or ("20080241255")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 11:42
S4	0	("2006").pn. and (hon).in.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:42
S5	42	(hon).in. and cigarette	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 11:44
S6	25	("131"/$ or "128"/$).ccls. and electronic cigarette and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S7	6	("131"/$ or "128"/$).ccls. and (fuisz).in. and nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:06
S8	91	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:15
S9	25	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and plasma and ((max or maxim$3) near25 time)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:16
S10	23	("131"/$ or "128"/$).ccls. and inhal$5 near15 nicotine and (plasma near25	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25

		(peak or max or maxim$3) near25 time)				
S11	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 15:25
S12	9	("131"/$ or "128"/$).ccls. and inhal$5 same (nicotine same (plasma near25 (peak or max or maxim$3) near25 time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:26
S13	32	("131"/$ or "128"/$).ccls. and inhal$5 and (nicotine same (plasma near25 (peak or max or maxim$3) same time))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:28
S14	2	("131"/$ or "128"/$).ccls. and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:51
S15	2	(vaporiz$3 or electronic cigarette) and nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:52
S16	346	("131"/$ or "128"/$).ccls. and (salt near5 nicotine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:53
S17	230	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) same (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:54

S18	210	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 15:55
S19	17	("131"/$ or "128"/$).ccls. and (salt near5 nicotine) near35 (carboxylic or citric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:08
S20	1	("2356185").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:32
S21	1	("2356185").PN.	USOCR	OR	OFF	2015/01/20 16:33
S22	4	nicotine benzoate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:38
S23	1	("20010029959").PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 16:43
S24	0	electronic cigarette and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:47
S25	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/01/20 16:48
S26	1	nicotine and inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 16:59
S27	53	inhal$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:33

S28	222	puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:37
S29	207	("131"/$ or "128"/$ or cigarette) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S30	179	("131"/$ or "128"/$) and puff$4 near25 every near15 (seconds or secs)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/20 17:40
S31	28	(("20070163610") or ("20090293895") or ("20130186416") or ("7832410") or ("8,156,944") or ("8,511,318") or ("20140345631") or ("20140345635") or ("20040191322") or ("20060018840") or ("20060196518") or ("20080241255") or ("20090004249") or ("20100242976") or ("20110268809") or ("20120255567") or ("4,830,028") or ("4,836,224") or ("6,102,036") or ("6,234,169") or ("6,799,576") or ("6,874,507") or ("7,767,698") or ("8,079,371") or ("8,322,350") or ("8,375,957") or ("8,381,739") or ("8,741,348")).PN.	US-PGPUB; USPAT	OR	OFF	2015/01/20 20:10
S32	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/03/23 22:03
S33	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 15:25
S34	1,605	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:07
S35	237	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08

S36	221	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S37	191	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:08
S38	163	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:09
S39	108	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:10
S40	87	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5 or mouth or oral$4) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:11
S41	77	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 16:12
S42	4	("2004076289").PN.	FPRS; EPO; JPO	OR	OFF	2015/05/14 18:13
S43	15	ANDERSSON near3 SVEN-BORJE	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S44	13	ANDERSSON near3 SVEN-BORJE and nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:15
S45	71	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and ph and ((drop$4 or vapor$4	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:26

		or aerosol$4 or particle) near25 size) and heat$4 and lung				
S46	21	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and ((drop$4 or vapor$4 or aerosol$4 or particle) near25 size) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:27
S47	26	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:28
S48	38	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and benzoic and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/14 18:31
S49	1	("20060196518").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/14 19:32
S50	34	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (salicylic or sorbic or lauric or levulinic or citric or benzoic or pyruvic) and (inhal$5) and ((plasma or blood or peek or peak) near10 concentration) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 08:30
S51	1	("8831739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S52	1	("8381739").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/15 08:43
S53	14	(igor near3 gonda) and nicotine and ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S54	13	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:42
S55	0	(igor near3 gonda) and nicotine near50 concentration near50 ng/ml near50 salt	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:43
S56	64	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46

S57	13	(igor near3 gonda) and ((blood or plasma or nicotine) near50 concentration) same nicotine	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/05/15 10:46
S58	1	("20030136404").PN.	US-PGPUB; USPAT	OR	OFF	2015/05/17 15:16
S59	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 09:12
S60	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2015/07/14 10:27
S61	1	("14512311").PN.	US-PGPUB; USPAT	OR	OFF	2015/09/17 14:40
S62	934	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S63	78	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and (ph near5 "7") and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:46
S64	367	("128"/$ or "131"/$ or "424"/$ or "514"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and acid and (inhal$5) and (plasma or blood) and heat$4 and lung	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:47
S65	283	("128"/$ or "131"/$ or "424"/$).ccls. and nicotine near25 (formulation or solution or liquid or solvent) and (levulinic or pyruvic or salicylic or sorbic or lauric or benzoic) and (inhal$5 or mouth or oral$4) and (plasma or blood)	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/17 14:48
S69	2	(("20060196518") or ("20140261474")).PN.	US-PGPUB; USPAT	OR	OFF	2015/12/10 16:09
S70	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/01/11 15:23
S71	1,069	(A24F47/008).cpc.	US-PGPUB; USPAT; USOCR	ADJ	ON	2016/01/11 23:26
S73	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 18:50
S74	1	("14925961").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:19
S75	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/07 19:30

S76	1	("9,215,895").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:28
S77	1	("20140261474").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:32
S78	1	("20130255702").PN.	US-PGPUB; USPAT	OR	OFF	2016/06/10 15:33
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Adam Bowen et al.

Application No.: 14/925,961	Confirmation No.: 1528
Filed: October 28, 2015	Art Unit: 1747
For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF	Examiner: Dionne W. MAYES

AMENDMENT UNDER 37 C.F.R. § 1.312

By EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This paper is submitted after a Notice of Allowance issued in connection with the above-referenced application on November 25, 2020. Applicant respectfully requests entry of the following amendments and remarks under 37 C.F.R. § 1.312:

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **6** of this paper

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application.

Listing of Claims

1.-25. (Cancelled)

26. (Previously Presented) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

27. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine in the inhalable aerosol.

28. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt liquid formulation further comprises a flavorant.

29. (Previously Presented) The electronic cigarette of claim 26, wherein the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

30. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

31. (Previously Presented) The electronic cigarette of claim 26, the electronic cigarette further comprising a battery.

32. (Previously Presented) A method of providing nicotine to a user, the method comprising:

(i) heating a nicotine salt liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1; and

(ii) inhalation of the aerosol by the user.

33. (Currently Amended) The method of claim 32, wherein the nicotine salt is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine in the inhalable aerosol.

34. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation further comprises a flavorant.

35. (Previously Presented) The method of claim 32, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

36. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

37. (Previously Presented) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol;

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1;

(d) the nicotine salt liquid formulation comprises a flavorant; and

(e) the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

38. (Previously Presented) A method of vaporizing a nicotine salt liquid formulation, the method comprising heating the nicotine salt liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

39. (Previously Presented) The method of claim 38, wherein the nicotine salt is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine in the inhalable aerosol.

40. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation further comprises a flavorant.

41. (Previously Presented) The method of claim 38, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

42. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

43. (Previously Presented) The method of claim 27, wherein the nicotine salt is present in an amount that forms about 4% (w/w) nicotine in the inhalable aerosol.

44. (Previously Presented) The method of claim 33, wherein the nicotine salt is present in an amount that forms about 4% (w/w) nicotine in the inhalable aerosol.

45. (Previously Presented) The method of claim 39, wherein the nicotine salt is present in an amount that forms about 4% (w/w) nicotine in the inhalable aerosol.

REMARKS

Claims 26-45 were allowed in the Notice of Allowance dated November 25, 2020, which included an Examiner's Amendment to claims 26, 27, 32, 33, 37, 38, 39, and 43-45. Claims 1-25 were previously canceled. The claim listing presented herein reflects amendments with respect to the claims as allowed, including the Examiner's Amendment.

Claim 33 is amended herein. Amendment is directed to a clarification, specifying that the recited nicotine salt forms the recited percentage of nicotine in the inhalable aerosol. This amendment is consistent with claim 32, from which claim 33 depends, and which recites that the nicotine salt "forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol." Amendment to claim 33 is also consistent with allowed claims 27 and 39, and is similarly supported.

No new matter is added by this amendment, which does not require additional search and does not enlarge the scope of the claims as previously allowed. As such, the amended claims are supported and allowable for the same reasons, and no new search is required. Entry of these amendments is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the amendments to the claims under 37 C.F.R. § 1.312 and notice thereof. If it is determined that a telephone conference would expedite the entry of this Amendment After Allowance, the Examiner is invited to telephone the undersigned at the number given below.

No fee is believed to be due in connection with the filing of this amendment.

Dated: February 9, 2021

Respectfully submitted,

/Jeffery C. Giering/

Jeffery C. Giering, Ph.D. Reg. No. 68,221

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(858) 314-1500
Attorneys for Applicant

Electronic Acknowledgement Receipt

EFS ID:	41877466
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Angela Olivos
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	09-FEB-2021
Filing Date:	28-OCT-2015
Time Stamp:	16:16:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		062210-501C03US_312_Amendment.pdf	151615 73104dcb52595091b7ca37ba96be41c16fe4d49a	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	7
Warnings:			
Information:			
	Total Files Size (in bytes):	151615	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

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148514 7590 11/25/2020

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Angela Olivos-Blackburn	(Typed or printed name)
/Angela Olivos-Blackburn/	(Signature)
February 9, 2021	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

TITLE OF INVENTION: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	~~SMALL~~ Undiscounted	~~$600~~ $1,200	$0.00	$0.00	~~$600~~ $1,200	02/25/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
MAYES, DIONNE WALLS	1747	131-328000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Mintz, Levin, Cohn, Ferris, Glovsky, and Popeo, P.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: JUUL LABS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): San Francisco, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-0311

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☒ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Jeffery C. Giering/ Date February 9, 2021

Typed or printed name Jeffery C. Giering Registration No. 68,221

Electronic Patent Application Fee Transmittal

Application Number:	14925961
Filing Date:	28-Oct-2015
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Filer:	Jeffery C. Giering/Angela Olivos
Attorney Docket Number:	62210-501C03US/713.302

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1200**

Electronic Acknowledgement Receipt

EFS ID:	41881495
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Jeffery C. Giering/Angela Olivos
Filer Authorized By:	Jeffery C. Giering
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	09-FEB-2021
Filing Date:	28-OCT-2015
Time Stamp:	18:16:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1200
RAM confirmation Number	E202129I17044713
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	62210-501C03US_2021-02-09_Issue_Fee_Transmittal.pdf	121917 b988fcb837e28fc07e9035333457768c36bfcc8a	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30690 29a6dff88c9a409b06548d11c9ae82d976293b6b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	152607		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	10/28/2015	Adam BOWEN	62210-501C03US/713.302	1528

148514 7590 02/26/2021

Mintz/JUUL
One Financial Center
Boston, MA 02111

EXAMINER
MAYES, DIONNE WALLS

ART UNIT	PAPER NUMBER
1747	

NOTIFICATION DATE	DELIVERY MODE
02/26/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketingBOS@mintz.com
IPFileroombos@mintz.com
mintzdocketing@cpaglobal.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	14/925,961	BOWEN et al.	
	Examiner	Art Unit	AIA (FITF) Status
	DIONNE W MAYES	1747	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 09 February 2021 under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☑ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/DIONNE W. MAYES/ Examiner, Art Unit 1747	/Michael H. Wilson/ Supervisory Patent Examiner, Art Unit 1747

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application.

Listing of Claims

1.-25. (Cancelled)

26. (Previously Presented) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

27. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine in the inhalable aerosol.

28. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt liquid formulation further comprises a flavorant.

29. (Previously Presented) The electronic cigarette of claim 26, wherein the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

30. (Previously Presented) The electronic cigarette of claim 26, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

31. (Previously Presented) The electronic cigarette of claim 26, the electronic cigarette further comprising a battery.

32. (Previously Presented) A method of providing nicotine to a user, the method comprising:

(i) heating a nicotine salt liquid formulation in an electronic cigarette to produce an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1; and

(ii) inhalation of the aerosol by the user.

33. (Currently Amended) The method of claim 32, wherein the nicotine salt is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine in the inhalable aerosol.

34. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation further comprises a flavorant.

35. (Previously Presented) The method of claim 32, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

36. (Previously Presented) The method of claim 32, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

37. (Previously Presented) An electronic cigarette comprising an electronic cigarette cartridge, the electronic cigarette cartridge comprising:

a nicotine salt liquid formulation for generating an inhalable aerosol upon heating in the electronic cigarette, the nicotine salt liquid formulation comprising a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol;

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1;

(d) the nicotine salt liquid formulation comprises a flavorant; and

(e) the electronic cigarette cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

38. (Previously Presented) A method of vaporizing a nicotine salt liquid formulation, the method comprising heating the nicotine salt liquid formulation using an electronic cigarette to provide an inhalable aerosol, wherein the nicotine salt liquid formulation comprises a nicotine salt in a liquid carrier, wherein the nicotine salt comprises a salt of nicotine and benzoic acid, wherein

(a) the nicotine salt in the nicotine salt liquid formulation is present in an amount that forms from about 3% (w/w) to about 15% (w/w) nicotine in the inhalable aerosol;

(b) the liquid carrier comprises glycerol and propylene glycol; and

(c) the molar ratio of benzoic acid to nicotine in the nicotine salt liquid formulation is about 1:1.

39. (Previously Presented) The method of claim 38, wherein the nicotine salt is present in an amount that forms about 4% (w/w) to about 12% (w/w) nicotine in the inhalable aerosol.

40. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation further comprises a flavorant.

41. (Previously Presented) The method of claim 38, wherein the electronic cigarette comprises a cartridge, and the cartridge is configured to serve as a mouthpiece and a reservoir that holds the nicotine salt liquid formulation.

42. (Previously Presented) The method of claim 38, wherein the nicotine salt liquid formulation consists essentially of the nicotine, the liquid carrier, and the benzoic acid.

43. (Previously Presented) The method of claim 27, wherein the nicotine salt is present in an amount that forms about 4% (w/w) nicotine in the inhalable aerosol.

44. (Previously Presented) The method of claim 33, wherein the nicotine salt is present in an amount that forms about 4% (w/w) nicotine in the inhalable aerosol.

45. (Previously Presented) The method of claim 39, wherein the nicotine salt is present in an amount that forms about 4% (w/w) nicotine in the inhalable aerosol.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/925,961	03/23/2021	10952468	62210-501C03US/713.302	1528

148514 7590 03/03/2021

Mintz/JUUL
One Financial Center
Boston, MA 02111

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Adam BOWEN, San Francisco, CA;
JUUL Labs, Inc., San Francisco, CA;
Chenyue XING, San Francisco, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IR103 (Rev. 10/09)

Docket No.: 14/925,961
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Adam Bowen et al.

Patent No.: 10,952,468

Issued: March 23, 2021

For: NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.322

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §1.322, Applicant submits a Request for Certificate of Correction, correcting a typographical error made at the time of printing the above-referenced patent to correct the following errors:

On page 48 of the patent, at column 60, please revise as follows:

In Claim 1, line 52-53, delete "in a liquid carrier," and

In Claim 3, line 64, the word "method" should be replaced with the words "electronic cigarette".

The omission now sought to be corrected is an inadvertent typographical error, the correction of which does not involve new matter or require reexamination. Transmitted herewith is a proposed Certificate of Correction effecting such amendment. A Certificate of Correction is respectfully requested.

The error was not in the application as filed by applicant; accordingly no fee is required. However, if any fee is due, the Director is hereby authorized to charge our Deposit Account No. 50-0311, under Order No. 14/925,961.

Dated: July 7, 2021

Respectfully submitted,

Electronic signature: /Victor Behar/
Victor Behar
Registration No.: 60,691
MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO, P.C.
3580 Carmel Mountain Road, Suite 300
San Diego, California 92130-6768
(858) 314-1500
(858) 314-1501 (Fax)
Attorney for Applicant

114049649v.1

PTO/SB/44 (09-07)
Approved for use through 01/31/2020. OMB 0651-0033
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	10,952,468
APPLICATION NO.	:	14/925,961
ISSUE DATE	:	March 23, 2021
INVENTOR(S)	:	Adam Bowen et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Claim 1, line 52-53, delete “in a liquid carrier,” and

In Claim 3, line 64, the word “method” should be replaced with the words “electronic cigarette”

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Victor Behar
MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO, P.C.
3580 Carmel Mountain Road
Suite 300
San Diego, CA 92130-6768

1

Electronic Acknowledgement Receipt

EFS ID:	43192752
Application Number:	14925961
International Application Number:	
Confirmation Number:	1528
Title of Invention:	NICOTINE SALT FORMULATIONS FOR AEROSOL DEVICES AND METHODS THEREOF
First Named Inventor/Applicant Name:	Adam BOWEN
Customer Number:	148514
Filer:	Victor Behar/Jeremy Johnston
Filer Authorized By:	Victor Behar
Attorney Docket Number:	62210-501C03US/713.302
Receipt Date:	07-JUL-2021
Filing Date:	28-OCT-2015
Time Stamp:	18:48:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	62210-501C03US-Request-for-Certificate-of-Correction-SIGNED.pdf	268236 7b034db633b95f937e7d44232f451df46b648260	no	3

Warnings:

Information:	
Total Files Size (in bytes):	268236

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,952,468 B2
APPLICATION NO. : 14/925961
DATED : March 23, 2021
INVENTOR(S) : Adam Bowen et al.

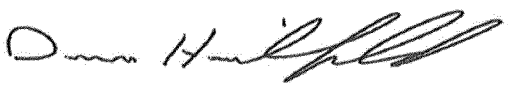
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 60, In Claim 1, Line 52-53, delete "in a liquid carrier," and

Column 60, In Claim 3, Line 64, the word "method" should be replaced with the words "electronic cigarette"

Signed and Sealed this
Third Day of August, 2021



Drew Hirshfeld
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office