liquid from the chamber if and when the corresponding resistor is energized by a short electrical pulse. The resistors thus function as ejection means. Within a few microseconds liquid in contact with the resistor is vapourised and forms a bubble. The vapour bubble grows rapidly and imparts momentum to liquid above the bubble. Some of this liquid is ejected as a droplet from the adjacent nozzle at a velocity typically exceeding 10 meters/second. The ejected volume of liquid is automatically replaced in the chamber from a reservoir by capillary action or by atmospheric pressure acting on collapsible reservoir bladder, a piston or the like. Devices of this kind when used for printing eject a typical drop of about 50 micron diameter at velocities in excess of 10 meters/second and are capable of drop ejection frequencies of up to several thousand droplets per second. The piezoelectric device generates a droplet by means of a pressure wave in the fluid produced by applying a voltage pulse to a piezoelectric ceramic which in this device acts as the ejection means. As with the thermal device, the droplet is ejected through a fine aperture. The fluid is ejected in the form of a fine droplet whose velocity depends on the energy contained in the voltage pulse. In conventional ink jet applications, ejection velocities in excess of 2 meters/second with droplet diameters of around 150

microns and droplet ejection rates of in excess of 6,000 droplets per second can be achieved.

Although conventional "droplet on demand" or "droplet ejection" devices such as used in ink jet printers may be employed in embodiments of the invention, the droplet ejection devices for use in the invention preferably differ from those used for printing. With printheads the ejection orifices are typically arranged as a rectangular matrix of, for example, 2 x 6 or 4 x 6 orifices the droplets being expelled in parallel direction from various combinations of orifice to form characters on a paper moving past the printhead at a distance of from 0.7 mm to 1.0 mm from the orifice. Droplet size is chosen to provide optimum print quality and high dot resolution. For use in the present invention there may be a smaller or greater number of orifices than used for printing and there is no need for the orifices to be arranged in a rectangular matrix with parallel orifice axes. The droplet ejection orifices may, for example, be arranged in a circle and/or may be directed at a converging or diverging angle to the axis of each other. Also for use in the present invention it is often preferred to eject much smaller droplets than are useful for printing. Additionally, the droplet ejection orifices may differ in diameter one from another so that the particle size of the

active agent sprayed from the device may be controlled programmatically by selecting which orifices are used for droplet ejection and particle size may be varied from one time interval to another. Because the size of droplet ejected from the device in response to a predetermined signal is predetermined for a given liquid and device, and because the number and frequency of droplets ejected can be controlled with great precision, it is possible to closely control the total volume of liquid (dose) delivered in a given time interval. For example the device might deliver 1,000 droplets of 50 micron diameter in a second. This volume can in principle be increased or decreased in increments of one droplet.

In preferred embodiments of devices according to the invention the DED is provided with orifices of an aperture size selected to eject a droplet of less than 10 microns diameter and, more preferably, of from 1 to 5 microns diameter. Droplets may be emitted from the DED from a selected orifice in succession or from a plurality of orifices simultaneously.

In preferred embodiments the droplet delivery device or devices may be manually actuated or may actuate in response to an inhalation detector signal or other signal. The apparatus is provided with control means programmed to eject a predetermined number of droplets. The number may be varied in

response to stored data and/or other input signals and programme logic may control such factors as the number of droplets ejected in a predetermined time interval, frequency of droplet ejection, the total number of droplets of active substance issued within a time period, or the like. The control means may be programmed to provide many other desirable functions as hereinafter described.

The means for directing the ejected droplets at or into the subject may for example be a simple mouth piece provided with an air inlet, a nasal shroud, face mask or other spray directing means. The active agent is typically in solution and is emitted from the DED as a fine spray which may be combined with air and/or may be heated prior to inhalation.

BRIEF DESCRIPTION OF DRAWINGS

Various embodiments of the invention will now be described by way of example only and with reference to the accompanying drawings in which:

Figure 1 is a schematic part sectional perspective view of one embodiment of a dispenser (cigarette substitute) according to the invention; and

Figure 2 is a schematic section in an axial plane of the dispenser of Figure 1; and

Figures 3A, 3B and 3C are graphs showing the dispensation of an active ingredient (hatched) as a function of inhalation time in use of the embodiment

of Figure 1, and

Figure 4 is a schematic perspective view of a second embodiment of the invention, and

Figure 5 is a schematic diagram of a third embodiment of the invention.

DESCRIPTION OF PREFERRED EMBODIMENTS

With reference to Figures 1 and 2 there is shown a first embodiment of the invention consisting of a nicotine dispenser comprising a cigarette-shaped hollow tubular body 1 comprising connected body parts 2, 3. Body part 2 has a sidewall 4, a mouthpiece 5 at or adjacent one end and a threaded other end 6. A plurality of axially extending slots 7 penetrate side wall 4. Body part 3 is screw threaded at one end for connection with threaded end 6 of body part 2. Body part 3 is closed or constricted at the end 9 remote from mouthpiece 5.

Nicotine in a suitable solvent (for example water) is provided in a container 10 which is adapted by means of a spiggot shaped outlet and coupling 11, for fluid connection to an inlet port 12 of a droplet ejection device 14. In the present example, device 14 is of the kind used in a bubble jet printer and is provided with one or more droplet ejection orifices 15. Device 14 is controlled by control means 16, for example a microelectronic circuit or microprocessor means. Device 14 and control means 16 as well as

other electrically-powered parts are energised by means of a hollow cylindrical battery 17 via an on-off switch 18 extending through side wall 14 and operable by the user. When a user inhales at mouthpiece 5, a stream of air "A" is drawn into body 1 via slots 7, through body part 2, and mouthpiece 5 into the user's lungs. Slots 7 may be provided with a damper or the like (not illustrated) to control airflow or the device may be provided with a porus plug to control airflow ("draw") on inhalation at mouthpiece 5. A pressure sensor 19 detects a change in pressure in the device due to inhalation or suction at mouthpiece 5 and issues an actuation signal via cables (not illustrated) to control means 16. Control means 16 responds to the actuation signal by issuing an output signal or signals via cables (not illustrated) to device 14 according to pre-programmed parameters or algorithms as hereinafter described. The output or "dose" signal is, or includes, a set of "eject" signals for example a train of voltage pulses. Device 14 responds to the output signal or signals by issuing a plurality of droplets of nicotine solution from orifices 15 of device 14. The liquid containing nicotine issues from device 14 as a fine spray of droplets which are entrained in the inhalation airflow from slots 7 towards mouthpiece 5. The spray typically comprises fine droplets which tend to

vaporise in the airflow. Optionally, heating means 20 are provided. In that case the combination of air with nicotine droplets may be brought into thermally conductive contact with heating means 20 prior to leaving mouthpiece 5. This not only produces a sensation on inhalation similar to that obtained by smoking a combustible cigarette, but also serves to enhance the vaporisation of active substance droplets in the gas stream reducing droplet size.

In the embodiment illustrated in Figs. 1, 2 the active substance container 10 is a collapsible bladder which is housed within a protective hollow cylindrical cartridge 21 having an air vent 22. However other forms of container (for example a cylinder fitted with a piston) could be used. Cartridge 21 is optional and serves to shield bladder 10. Container 10 is disposable or replaceable and may be adapted for fluid communication with inlet 12 of device 14 by means of a threaded, bayonet, or other suitably sealing connection.

Optionally, battery 17 may be of annular form and adapted to sleeve cartridge 21 to save space. Heating means 20 may be infrared heating plates or elements, resistance elements or the like.

Control means 16 desirably comprises a programmable logic circuit for example a microprocessor together with associated Read Only

Memory (ROM), Read and Write Memory (RAM), clocks, power supply and the like and is programmed to control the quantity of nicotine delivered by the DED upon inhalation, subject to predetermined criteria.

In normal operation of the device a drop of pressure at mouthpiece 5 is detected by pressure sensor 19 which issues a signal indicative of inhalation ("actuation" signal) to control means 16 (via cables not illustrated). Control means 16 responds by issuing a "dose" signal to device 14 resulting in a spray of droplets from the device.

The dose signal typically comprises a predetermined set of drop "eject" signals which causes one or more orifices 15 of device 14 to eject a predetermined number of droplets. The dose signal may, for example, be a train of pulses (each pulse being a droplet eject signal) directed serially to one resistance heater of a thermal bubble jet device, or may be a sequence of pulses directed in parallel to a number of such resistance heaters. Since the volume of a droplet issued from a selected orifice 15 is predetermined for a given liquid and orifice, and the number of droplets ejected is controlled by the dose signal, the total volume of nicotine-containing liquid ejected in response to the actuation signal is precisely determined.

Control means 16 controls the pulse spacing,

pulse width, and pulse frequency of the "dose" signal as well as the number of pulses or droplet "eject" signals and therefore determines the time interval during which droplets enter the inhalation air stream i.e. the dose rate. The number of droplets issued and/or the droplet issue frequency may be altered by changing data stored in a control memory. Control means 16 may also be programmed to address specific resistance heaters so as to emit droplets from selected orifices which may differ one from another for example in respect of diameter or orientation.

Control means 16 may also be programmed to provide a time delay between receipt of an actuation signal indicative of inhalation from pressure sensor 19 and the issuance of a "dose signal". The time delay may be varied by changing data stored in a control memory. By controlling the time delay between the leading edge of an actuation signal and issue of the dose signal, and by controlling the frequency of droplet "eject" pulses in the dose signal, the active substance can, for example, be injected into an inhaled air stream as a spike near the start (Fig. 3A) or start and end (Fig. 3B) of an inhalation "puff", or can be spread over the puff duration (Fig. 3C), or may be confined to the leading or trailing portion of a puff. This enables the change in concentration of nicotine during a puff of a cigarette to be more

closely mimicked.

The control means can also be programmed to prevent a dose signal from issue until a predetermined "non repeat" time has elapsed after a preceding dose signal has been issued, notwithstanding receipt of a inhalation signal. This provides a minimum delay between successive doses.

The control means may also be provided with means for counting and storing the total number of dose signals issued within a predetermined time interval and if the total exceeds a predetermined limit (for example 30 doses in a 30 minute period) then the control circuit prevents further dose issue until a further period (e.g. 1 hour) has elapsed. This limits the maximum dose issued within an extended period.

In preferred embodiments of the invention the control means enters a minimum energy drain mode to conserve battery power if for example more than 5 minutes have elapsed since an inhalation was detected.

The apparatus of Fig. 1 may optionally be provided with means for signalling the doses remaining in the device for example by means of a plurality of LEDs 30 which progressively extinguish. Each LED may for example correspond to a dose equivalent to smoking one cigarette and the apparatus might initially store a dose corresponding to one (or several) packets of cigarettes. Other indicator means e.g. an LCD display

could be used.

In summary the control means allows programmable control of factors such as:

(1) Predetermined number of droplets of nicotine issued in a single dose (dose volume).

(2) Frequency of drop issue within a dose (dose rate).

(3) Synchronization of the dose relative to commencement of inhalation.

(4) Injection of dose as a function of time from commencement of inhalation. (Pulse spacing and frequency).

(5) Control of maximum frequency of issue of successive doses or non repeat time (e.g. successive doses
available at not less than 60 second intervals).

(6) Control of maximum number of doses available in a given period i.e. maximum dose rate (e.g. no more than 20 doses available per hour).

(7) Programmed variation of dose from one actuation to another (e.g. successive reduction in dose to reduce drug dependence).

(8) Programmed variation from time to time (e.g. dose to decrease from day to day).

(9) Control of nozzles from which the droplets

issue (and hence spray pattern).

(10) Discrimination for adequacy of inhalation (No dose unless accompanied by sufficient inhalation air).

It will be apparent from the above that the device can be programmed in other ways and to perform other functions by the addition of other sensors - for example temperature or humidity sensors.

In addition the control means may be provided with means by which control parameters may be altered or by which the device may be reprogrammed, for example by interfacing with a keyboard or an external computer.

As will be appreciated, the microprocessor may be pre-programmed or may be user-programmable to control the operation of various DED nozzles, the heater, the airflow or the like in various other combinations, sequences, or as functions of time, temperature, or the like.

Tubular body 1 may be made of any suitable material e.g. plastics, ceramics, precious metals or the like. Mouthpiece 5 may be integral or may be soft-tip, for example of rubber or plastics cardboard, or paper and may be independently disposable. The battery may be replaceable or rechargeable. The dispenser as a whole may be provided as a disposable item or may be reusable. In the latter case, the

product container and DED device will normally be replaceable or may be provided as a combined unit. In that case, the body portion will be separable e.g. via screw-threaded or bayonet coupling into sections to facilitate installation and removal of the product cartridge and/or battery. The product to be dispensed may be for example an aqueous solution of nicotine and may contain additional substances such as glycols, flavours or essences, for example menthol. The active substance may be in the form of a gel, melt, solution or suspension.

If desired, more than one DED 14 may be incorporated whereby to produce droplet streams of different droplet size and in this case, one stream may be fully vapourised by heating plates 20 while a second stream may be directed so that the user receives the sensation of a wet vapour in combination with a dry vapour as occurs when smoking conventional cigarettes.

It is not essential that the spray of active ingredient be combined with air prior to heating and if preferred the spray and/or the air may be separately heated and subsequently combined or the active ingredient may be preheated e.g. by heating means in thermal communication with storage container 10. By selective programming of the controller the smoking instrument can be adjusted to simulate "light"

or "ultralight" cigarette nicotine levels or can be selectively adjustable therebetween. In other embodiments the air intake may be adjusted to vary the air to active substance ratio thus further to facilitate simulation of the sensation of smoking different kinds of cigarettes. The invention is of particular application for assisting those wishing to withdraw from cigarette smoking being programmable to progressively reduce the dose of nicotine obtainable. Devices according to the invention may either be pre-programmed, may be provided with simple means enabling the user to adjust dose within predetermined limits of safety or may be adapted to be programmed by a user e.g. by connection via an interface to a computer.

Although use of a battery is preferred other energization means for example photo cells, may be employed.

It will be understood that the apparatus described may be provided in a different form, for example with a mouthpiece which is flexible whereby the body may be held in a different orientation from the mouthpiece. Similarly the battery need not be annular and may be of any suitable shape.

With reference to Figure 4, there is shown another embodiment of the invention intended to dispense a bronchodilator. Parts in Figure 4 which

correspond in function to parts in Figure 1 are identified with the same numerals. If the substance to be dispensed is heat sensitive it is preferred to use a piezoelectric DED. Disposable cartridge 10 of the embodiment of Figure 4 contains for example, salbutamol. The embodiment of Figure 4 differs from that of Figure 1 in that the body is of rectangular cross-section and in that of the shape and arrangement of components differs.

A further difference is that in the embodiment of Figure 4 the mouthpiece portion 5 is moveable hingedly between a storage position "A" in which it is in alignment with the body (shown in ghost outline in Figure 4) and an active position "B" in which it is inclined at an angle to the body portion.

The mouthpiece may swivel about a swivel pin 40 and the swivel motion may itself actuate an on/off switch to energize the electronic control systems 16.

If desired the apparatus may be provided with manual actuation (e.g. a push-button switch, not illustrated) instead of a pressure-sensitive switch, to control the operation and initiate a "actuation" signal.

In cigarette substitute apparatus according to figure 1, droplet sizes of the order of 1-10 micron diameter or more are acceptable. For pulmonary administration of drugs a small droplet size is

preferred. For this purpose droplet size distribution is normally described as mass median aerodynamic diameter (MMAD), with a standard deviation to indicate the degree of poly dispersity. Particles with MMAD > 5 micron tend to impact on the delivery system and do not readily follow respiratory passages.

For practical purposes droplets of below 10 micron diameter and more preferably of below 5 micron diameter are therefore preferred. If necessary, droplet size can be reduced after ejection from the DED device by directing droplets at each other or at a suitable target designed to further fragment the droplets, or by injecting the droplets into an inhaled stream in a suitable manner. Optionally heating devices can be employed to vapourise the liquid and reduce droplet size.

Suitable drugs for delivery by the apparatus described include, by way of example only, analgesics, peptides and proteins. Other suitable agents include

(i) $ß_2$-bronchodilators - salbutamol, terbutaline sulphate, fenoterol hydrobromide, pirbuterol, reproterol hydrochloride, rimiterol hydrobromide, salmeterol (used extensively for treatment of acute asthma attacks and in prophylactic asthma therapy).

(ii) Antimuscarinic bronchodilators - Ipratropium bromide, oxitropium bromide (used in management of chronic bronchitis).

(iii) Corticosteroids - beclomethasone dipropionate, budesonide: used in prophylactic asthma therapy.

(iv) Sodium chromoglycate, nedocromil sodium (used in prophylactic asthma therapy).Antibiotic Therapy:

(v) Pentamidine isethionate - (antibiotic for the prophylaxis and treatment of pneumonia due to Pneumocystis carinii, a common secondary infection in HIV/AIDS patients).

Local Action:

(vi) Range of proprietary 'Over the Counter' nasal decongestant sprays for common cold symptoms,

(vii) Corticosteroids - beclomethasone dipropionate, betamethasone sodium phosphate, budesonide, fluticasone propionate (used in prophylaxis and treatment of allergic rhinitis).

(viii) Sodium chromoglycate (used in prophylaxis of allergic rhinitis).

(ix) Anti-infective agents - e.g. dexamethasone, fusafungine, chlorhexadine hydrochloride (used in treatment of infection due to nasal

staphylococci).

Systemic Action

(x) Nasal administration of peptides related to antidiuretic hormone - desmopressin, lypressin (used in management of diabetes insipidus).

Apparatus for use in dispensing certain drugs may comprise programmed control means which issues a predetemined dose into each of a plurality of successive inhalations and in that case may be provided with a "dose complete" signal for example via LED 31 to indicate to a user when a full dose has been dispensed. The dose can be varied according to the composition being dispensed and the prescription for each user.

With reference to fig. 5, there is shown a further embodiment of the invention which is adapted to dispense an active substance such as an anaesthetic, antiseptic or a liquid medication by topical application rather than by inhalation.

In surgery or medical treatment it is sometimes necessary to apply an anaesthetic, antiseptic or other fluid over a local area by means of an aerosol sprayed from a pressurised container. However it is difficult to control the amount and location of spray application. Moreover the use of CFC propellant as used in the aerosol is environmentally undesirable.

Parts of Fig. 5 corresponding in function to parts in the embodiment of Fig. 1 are identified by the same numerals.

With reference to Figure 5 there is shown a dispenser comprising a pen shaped hollow tubular body 1 assembled from hollow body parts 2, 3. Body part 2 has a nozzle opening 25 at one end while body part 3 is closed at the dispenser end remote from nozzle opening 4. Body parts 2, 3 are separably connected at 6, for example by interengaging thread formations. A cartridge 10 is situated within body 1 and contains a liquid. Cartridge 10 is in fluid communication with one or more droplet ejector devices 14 via one or more conduits 11. In the present example DED 14 is a piezoelectric crystal or thermal resistor bubble jet device such as used in an ink jet print head. Device 14 can be energized from a battery 17 via an on off control switch 18 adapted for finger operation while the device is hand held. For example the device may be held between thumb and middle finger and may carry a push button switch 18 which is operable by the first finger. In the embodiment of Figure 5 when control 18 is actuated, device 14 delivers liquid from cartridge 10 as a spray directed outwardly from the dispenser via nozzle 25. The duration of the spray is determined by whether the switch 8 is "on" or "off".

In a more highly preferred embodiment of the

invention the volume sprayed per unit time is also be controlled. For example, the dispenser 1 is provided with one or more switches 26 (for example touch pad switches) which condition control means 16 (for example a microprocessor circuit) which in turn controls a number of bubble jet orifices 15 of device 14 through which spray droplets are emitted and/or which controls the repetition rate of device 14 and thus the number of droplets delivered in a unit of time. Thus the spray rate may be selectively light or heavy depending on the number of orifices emitting droplets and depending on the repetition rate of droplet emission.

If the device 14 is provided with a plurality of emitting orifices which are directed at preselected angles to the axis of the body, droplets of liquid may be directed in the axial direction or selectively at predetermined angles to the axial direction by circuit actuation of a selected jet orifice 15, or a selected combination of droplet ejection device jet orifices 15. In this manner a spray pattern may be selected by means of a suitable finger control forming part of a suitable micro-electric circuit controlling means 16. If all emitting orifices 15 are directed axially the spray pattern may be made selectively narrow or broad.

Alternatively control switch 26 may be adapted to select between a number of predetermined total dose

dispensations or an additional control means may be provided to select total dose. In such manner, if the cartridge contains for example a liquid local anaesthetic, a surgeon can select a preset quantity and spray pattern of local anaesthetic to be applied during surgery. The surgeon could thus select between application of a small, medium or large dose, at each actuation of a switch 26 and could preselect between a narrow, medium, or broad spray pattern.

If desired the control circuit 16 may be provided with means to prevent inadvertent excessive use, for example by limiting the maximum dose of liquid which can be applied within a prespecified time period.

Also, if desired, the control circuit can be provided with security locking which overrides the on/off switch. For example the device might be provided with a programmable security code and might be incapable of issuing its contents unless and until a corresponding code is entered by an intending user.

For this purpose the device may have a plug 28, socket or transmitter/receiver which permits the device to interface with an external computer. The external computer might then also record data indicative of use, doses issued, user identification, patient identification, or similar data. The external computer may also re-enter new data in one or more memories in the control circuit of the dispenser for

example dose values, time parameters, security codes. This data is then used in controlling response of the device to actuation by the user.

Other forms of hand control, for example touch sensitive switches or rotary switches may be employed instead of touch pads 26.

Control circuit 26 may utilise digital or analogue control and may employ a microprocessor, or discrete circuit components. In preferred embodiments the circuit includes a memory, preferably of type which is not erased due to lack of battery power such as a ramtron chip. The circuit further desirably includes a display screen such as a single line LCD 27. The circuit may also employ a clock and be able to utilise and display date and time data and may have a key pad or equivalent input device or may rely for input upon communication with an external key pad. The LCD could be used to display data such as number of remaining doses or time and date of last dose.

Although the embodiment of fig. 5 has been described with reference to dispensation of a liquid it will be appreciated that the material to be dispensed can be in the form of a gel, colloid, powder suspension or any other form suitable for dispensation via the device 14.

In a further embodiment of the invention (not illustrated) the dispenser is provided with a

plurality of cartridges or chambers each adapted to contain a respective medication in liquid or solution form. The control means may be programmed to provide an alarm (for example a beeper or flashing LED) at predetermined times or at predetermined times and dates. On next actuation of the device, it then delivers a predetermined dose of one medication or a combination or succession of medications each in a respective predetermined dose.

This embodiment is thus ideally suited for pre-programmed treatment of persons suffering from dementia or the like and for persons having to take a number of different medications each according to a schedule and who find self-administration confusing.

The device itself prompts the user to accept a dose and issues the appropriate doses of prescribed medication.

As will be apparent to those skilled in the art, features described in relation to one of the described embodiments may be combined with those of another.

Although the control signals have been described as pulses, those skilled in the art will appreciate that the signals can take a great variety of forms and may employ voltage or current signals, AC or DC signals, digital or analogue signals or the like, as required for operation of the DED selected. It is not necessary literally to count signals to eject a

predetermined number of droplets and it will be understood that such expediencies as issuing eject signals at a predetermined frequency for a selected time interval are considered equivalent and within the scope hereof. Although the invention has been described in terms of electronic devices, fluidic devices and non electronic means of control may be employed.

Those skilled in the printing art will appreciate that with many DED devices a principal ejected droplet sometimes has trailing satellite droplets which are very much smaller. References herein to a predetermined number of droplets refer to the number of principal droplets ejected, but if necessary the DED can be calibrated to issue a desired dose taking account of satellite drops without departing from the inventive concept hereof. Likewise it will be understood that the control of liquid viscosity is important and that therefore the volume of one substance issued in response to a given set of "eject" signals will not necessarily be the same as for another substance. However those skilled in the art will have no difficulty based on the teaching hereof in programming devices according to the invention to take account of these factors.

As will be apparent to those skilled in the art from the description herein contained, the device may

be embodied in other forms or arrangements and using other construction materials without departing from the scope of the invention herein disclosed.

CLAIMS:

1. A method for administering a substance to a human or animal subject by inhalation, said method comprising the steps of:

(i) ejecting a predetermined number of discrete droplets of the substance from at least one droplet ejection device in response to an actuation signal, and

(ii) entraining the droplets in an inhalation airstream.

2. A method for topical application of a substance to a human or animal subject comprising the steps of:

(1) ejecting a predetermined number of discrete droplets of the substance from at least one droplet ejection device in response to an actuation signal, and

(2) directing the droplets at a selected area or region of the subject.

3. A method according to Claim 1 or 2 further comprising the step of controlling the frequency of issue of droplets of the predetermined number.

4. A method according to any one of the preceding claims comprising the step of ejecting a second predetermined number of droplets after ejecting a first predetermined number of droplets and controlling a time interval between ejection of the first and the second predetermined number of droplets.

5. A method according to any one of the preceding claims wherein the at least one droplet ejection device has a plurality of ejection orifices.

6. A method according to Claim 5 wherein the device or devices collectively have ejection orifice which differs in diameter from another and the size of the droplets is controlled by selectively issuing the droplets from an orifice of selected diameter.

7. A method according to any one of the preceding claims wherein the device or devices collectively have ejection orifices directed in differing directions, further comprising the step of controlling a spray pattern by selectively issuing droplets from a selected set of said orifices.

8. A method according to any one of the preceding claims further comprising the step of measuring a "non repeat" time interval commencing after issue of a first predetermined number of droplets and controlling the droplet ejection device to prevent issue of droplets in response to an actuation signal during said "non repeat" time interval.

9. A method according to any one of the preceding claims further comprising controlling the droplet ejection device so that the total number of droplets issued during a predetermined time period does not exceed a predetermined "maximum dose" number of droplets.

10. A method according to Claim 1 wherein the actuation signal is a signal indicative of inhalation by the subject.

11. A method according to Claim 10 wherein the ejection of a predetermined number of droplets is synchronised with an inhalation by the subject.

12. A method according to Claims 10 or 11 further comprising the step of ejecting the predetermined number of droplets in a time interval which is shorter than an inhalation period, and delaying the ejection of the droplets relative to the commencement of inhalation.

13. A method according to any one of Claims 10 to 12 wherein the droplets are selected to have a size of less than 10 microns.

14. A method according to any one of Claims 10 to 13 wherein the droplets are selected to have a size of from 1 to 5 microns.

15. A method according to any one of Claims 10 to 13 wherein the airstream is heated.

16. A method according to any one of Claims 10 to 15 wherein the substance is, or contains, nicotine.

17. A method according to any one of Claims 10 to 16 wherein the substance is selected from the group consisting of peptides, proteins, analgesics and saline solutions.

18. A method according to any one of Claims 10 to 16

wherein the substance is selected for systemic therapy via pulmonary absorption.

19. A method substantially as herein described with reference to any one of the examples.

20. Apparatus for administering a substance to a human or animal subject, said apparatus comprising:

a droplet ejection device containing a substance to be administered, means responsive to an actuation signal to eject a predetermined number of discrete droplets of the substance, and

means for directing the ejected droplets at, or into, the subject.

21. Apparatus according to Claim 20 wherein the droplet ejection device comprises at least one droplet ejection orifice and ejection means responsive to an "eject" signal to eject a droplet from said orifice.

22. Apparatus according to Claim 20 or 21 wherein the droplet ejection device is a thermal bubble jet device.

23. Apparatus according to Claim 20 or 21 wherein the droplet ejection device is a piezoelectric device.

24. Apparatus according to any one of Claims 20 to 23 wherein the means responsive to an actuation signal comprises control means for issue of a set of "eject" signals the set consisting of a predetermined number of droplet "eject" signals each eject signal being effective to issue a droplet.

25. Apparatus according to any one of Claims 21 to 24 comprising control means adapted to vary the number of discrete droplets ejected in accordance with a predetermined programme.

26. Apparatus according to any one of Claims 20 to 25 comprising control means adapted to vary the frequency of issue of discrete droplets in accordance with a predetermined programme.

27. Apparatus according to any one of Claims 20 to 26 wherein the droplet ejection device has a plurality of droplet ejection orifices.

28. Apparatus according to Claim 27 wherein the droplet ejection device has a droplet ejection means associated with each ejection orifice.

29. Apparatus according to Claim 28 wherein a set of eject signals is directed to more than one ejection means.

30. Apparatus according to any one of Claims 20 to 29 wherein the droplet ejection device has at least one droplet ejection orifice having dimensions selected so as to eject a droplet of less than 10 micron diameter of the substance.

31. Apparatus according to any one of Claims 20 to 30 having a plurality of droplet ejection orifices defined by one or by a plurality of droplet ejection devices and wherein the direction of ejection of droplets from one orifice is not coaxial with that of

another.

32. Apparatus according to any one of Claims 20 to 31 having a plurality of droplet ejection orifices defined by one or more droplet ejection devices each orifice being associated with ejection means and wherein the dimensions of one orifice differ from that of another whereby the size of a droplet ejected is programmatically selectable by issuing an eject signal to a selected ejection means.

33. Apparatus according to any one of Claims 20 to 32 comprising a reservoir containing the substance and in fluid communication with a droplet ejection device.

34. Apparatus according to any one of Claims 20 to 33 wherein the means for directing the ejected droplet comprises a mouthpiece.

35. Apparatus according to any one of Claims 20 to 34 wherein the means for directing the ejected droplets comprises a nasal shroud or mask.

36. An apparatus according to any one of Claims 20 to 34 having at least one air admission vent and wherein the droplet or droplets are entrained an airstream flowing from the vent to the means for directing ejected droplets.

37. An apparatus according to any one of Claims 20 to 36 further comprising means to detect an inhalation of the subject and for issuing an actuation signal in response to a detected inhalation.

38. An apparatus according to any one of Claims 20 to 37 wherein the number of droplets is selected in accordance with a desired therapeutic dose volume of the substance.

39. An apparatus according to any one of Claims 20 to 38 comprising means for directing ejected drops into the bronchial tract of a subject, means for detecting in use of the apparatus a pressure drop due to inhalation by the subject, and means for synchronising issue of a set of "eject" signals with the detected inhalation.

40. An apparatus according to any one of Claims 20 to 39 comprising inhalation detection means and control means including timer means for delaying the issue of droplets so as to occur during a predetermined period after the commencement of and during an inhalation.

41. An apparatus according to any one of Claims 20 to 40 comprising the control means including counter means adapted to limit the maximum frequency of issue of successive doses.

42. Apparatus according to any one of Claims 20 to 41 comprising means for selecting orifices of the droplet ejection device from which droplets are ejected so as to vary the spray pattern.

43. Apparatus according to any one of Claims 20 to 42 adapted for use as an inhalation device and having heating means adapted to raise the temperature of an

airstream to be inhaled.

44. Apparatus according to any one of Claims 20 to 43 comprising means adapted to store a security code and provided with means for rendering the device inoperable to issue the substance unless and until a corresponding code is entered.

45. Apparatus according to any one of Claims 20 to 44 wherein the means for directing comprise a nozzle.

46. Apparatus according to claim 45 adapted to be hand-held and comprising one or more actuators providing signals for control of droplet ejection, said one or more actuators being positioned for use by a hand holding the apparatus.

47. Apparatus according to any one of Claims 20 to 46 comprising a plurality of reservoirs each containing a respective active agent, each reservoir communicating with a respective droplet ejection device, and control means for controlling the number of droplets issued from each droplet ejection device according to a predetermined programme.

48. Apparatus substantially as herein described with reference to any one of the drawings.

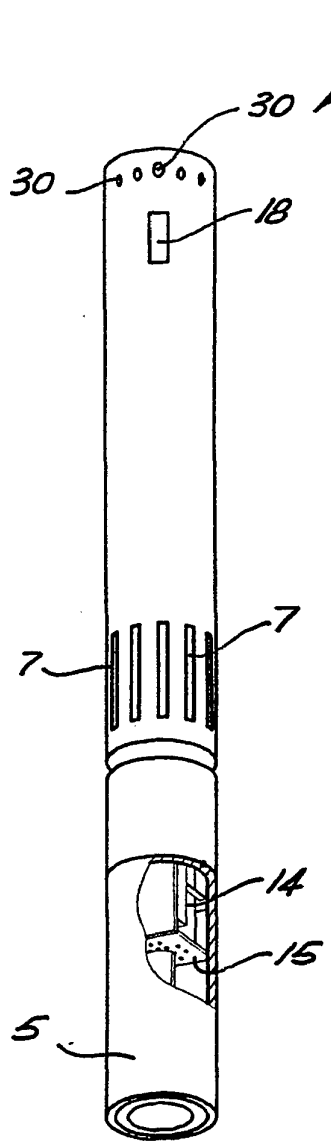

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FIG. 1

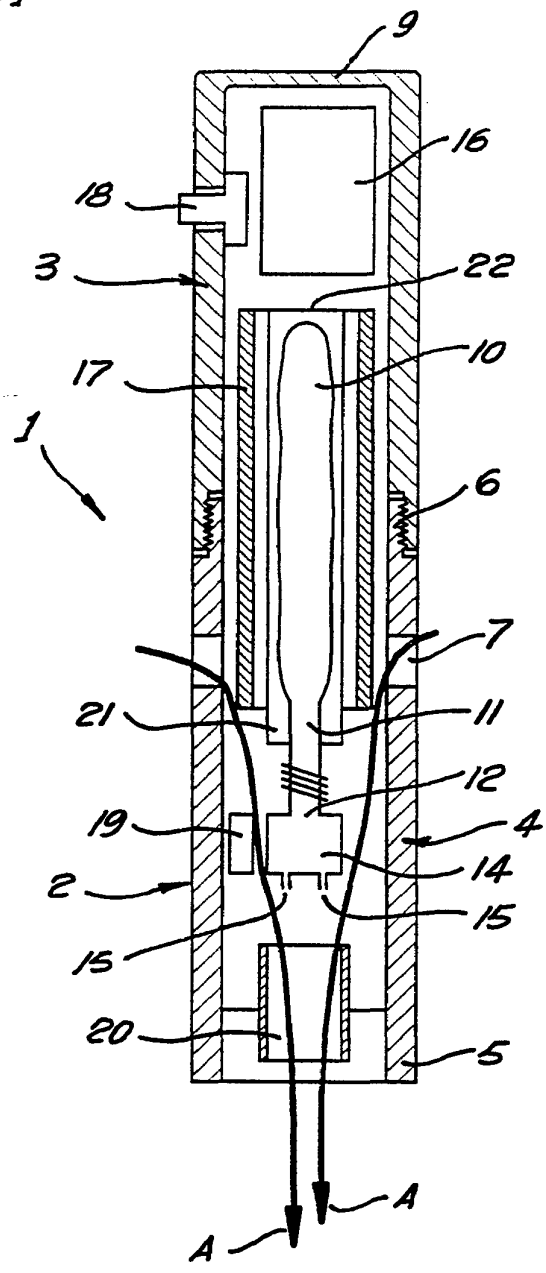

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FIG. 2

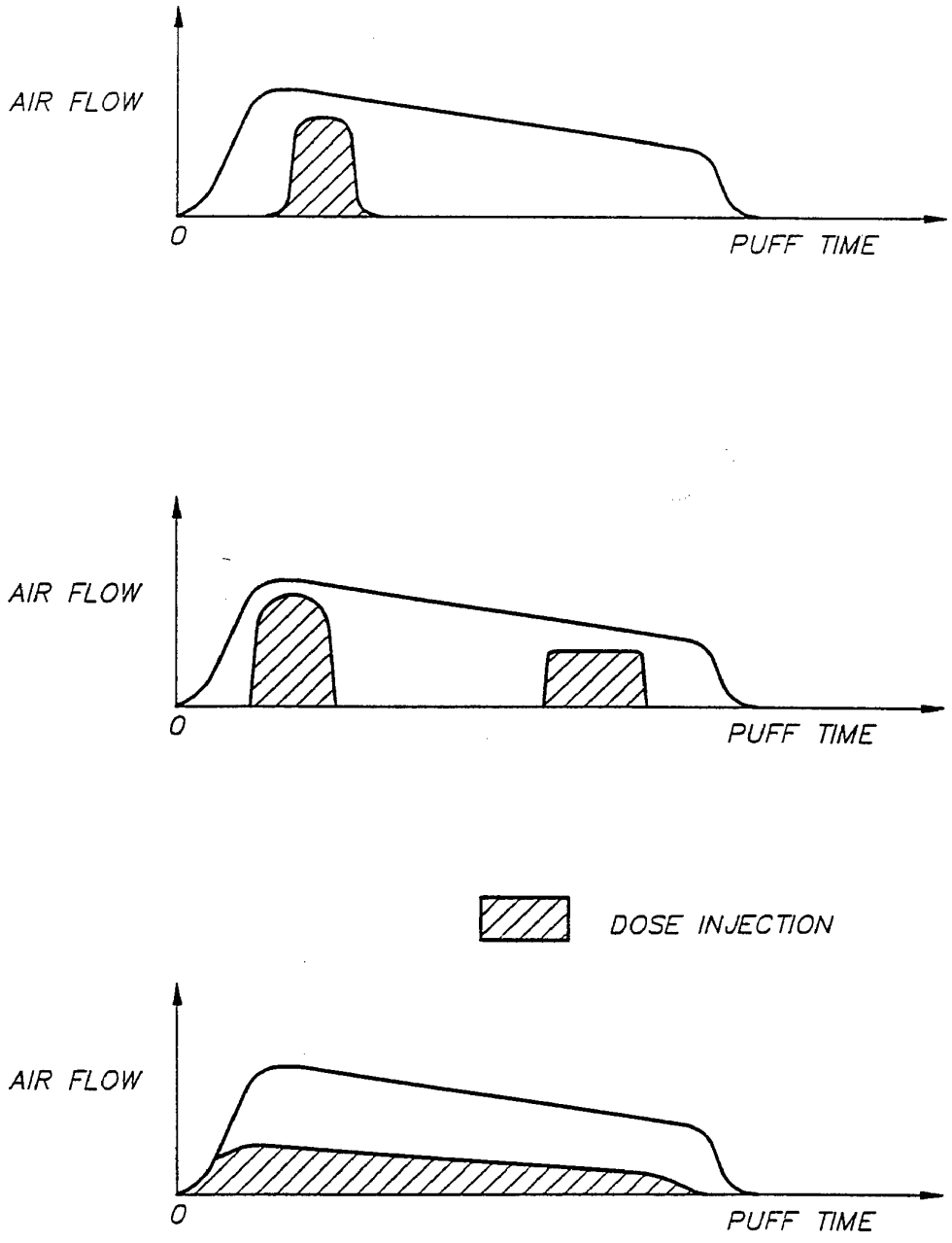

AIR FLOW
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AIR FLOW
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PUFF TIME
DOSE INJECTION
AIR FLOW
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PUFF TIME

FIG. 3

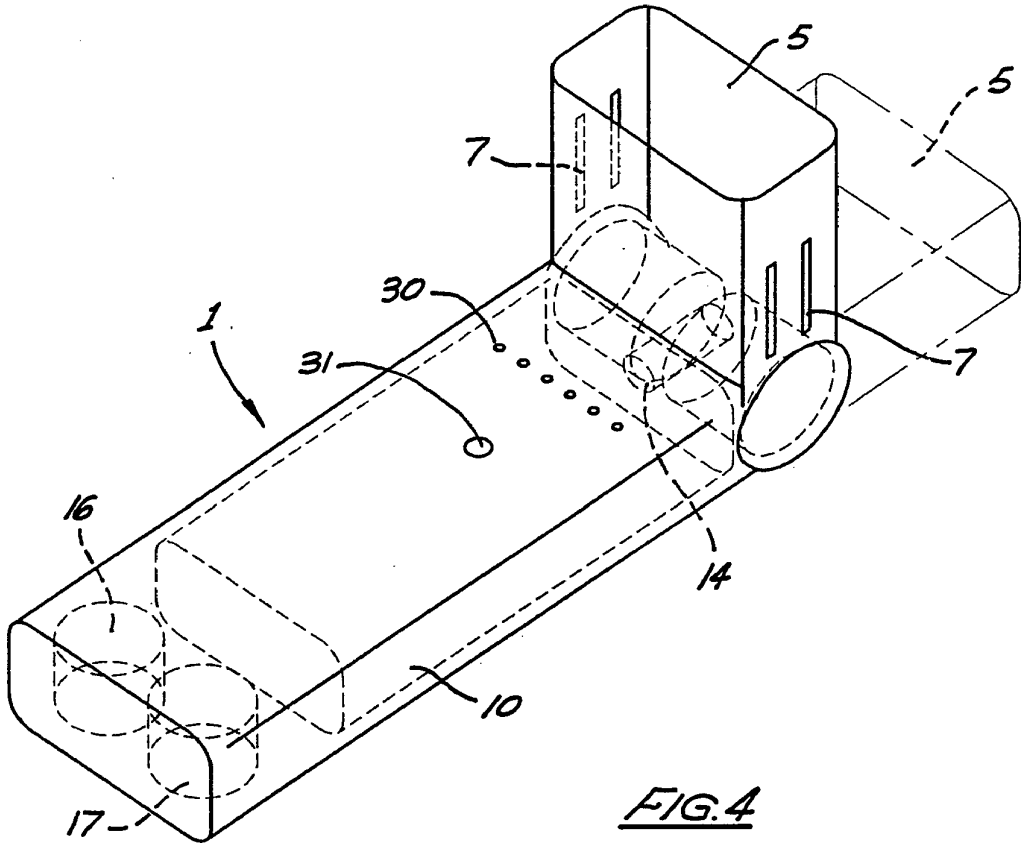



FIG. 4

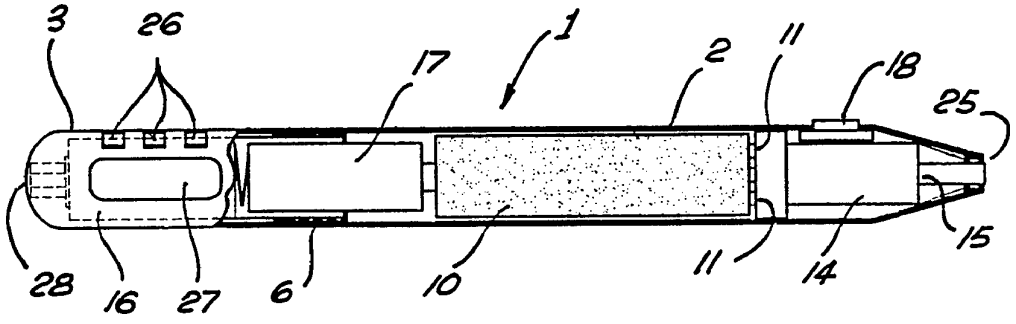



FIG. 5

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 94/00355

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl.[5] A61D 7/00, 7/04, A61M 11/00, 15/00, 15/06, 35/00

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: A61D 7/00, 7/04, A61M 11/00, 11/06, 11/08, 15/00, 15/06, 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| P,X | US,A,5284133 (BURNS et al) 8 February 1994 (08.02.94)<br>Entire document | 1,3-4,8-11,13-14, 16-18,20-21,23,25-26, 30,33-39,41,44-46 |
| X | WO,A,87/04354 (AKTIEBOLAGET DRACO) 30 July 1987 (30.07.87)<br>Page 2 lines 20-31, page 7 lines 23-33 | 1,3-4,8-11,13-14, 16-18,20-21,25-26,30, 33-39,41,44-46 |
| Y | | 12,15,40,43 |

[X] Further documents are listed in the continuation of Box C.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 September 1994 (07.09.94) | 19 Sept 1994 (19.09.94) |


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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|---|
| **Category*** | **Citation of document, with indication, where appropriate of the relevant passages** | **Relevant to Claim No.** |
| | EP,A,432992 (BESPAK PLC) 19 June 1991 (19.06.91) | |
| X | Column 3 lines 29-36, column 3 line 52 - column 8 line 13, column 9 lines 5-13 | 1,3-5,8-9,20-21,23, 25-27,30-31,33-36,38, 41,45-46 |
| Y | | 12,15,40,43 |
| | WO,A,89/06147 (ETELAHAMEEN KEUHKOVAMMAYHDISTYS R.Y.) 13 July 1989 (13.07.89) | |
| X | Entire document | 1,3-4,9-11,13-14, 16-18,20-21,23, 25-26,30,33-39, 41,45-46 |
| Y | | 12,15,40,43 |
| | WO,A,92/11050 (MINNESOTA MINING AND MANUFACTURING CO.) 9 July 1992 (09.07.92) | |
| X | Page 3 line 36 - page 5 line 33 | 1,3-5,9-11,13-14, 16-18,20-21,23,25-28, 30-31,33-39,41,45-46 |
| Y | | 12,15,40,43 |
| | EP,A,42468 (JAEGER) 30 December 1981 (30.12.81) | |
| X | Entire document | 1,3-4,10-14,16-18, 20-21,25-26,30,33-37, 39-40,45,47 |
| Y | | 12,15,40,43 |
| | DD,A,205820 (GRZONKA) 11 January 1984 (11.01.84) | |
| X | Entire document | 2-5,20-21,25-28,30-31, 33,36,38,45 |
| | DE,A,3908909 (SCHUMACHER) 20 September 1990 (20.09.90) | |
| X | Entire document | 1,20,33-36,43,45,47 |
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| P,X | 22 July 1993 (22.07.93) | 1,3-5,20-21,25,28, 30-31,33-36,38,43, 45,47 |
| | US,A,4934358 (NILSSON et al) 19 June 1990 (19.06.90) | |
| X | Figure 2, column 2 lines 23-34, column 4 lines 21-30 | 1,3-4,8-9,20-21,25-26, 30,33-35,38,41,45,47 |
| Y | | 12,15,40,43 |
| | WO,A,93/03856 (HABLEY MEDICAL TECHNOLOGY CORP.) 4 March 1993 (04.03.93) | |
| X | | 2-4,9,20-21,33,36, 38,45-46 |

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| | | DK | 4665/87 | EP | 232235 | EP | 252147 |
| | | FI | 874221 | IL | 81368 | JP | 62249656 |
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| | | DK | 165/87 | | | | |
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| | | EP | 542723 | ES | 2030348 | ES | 2043293 |
| | | FI | 906089 | FI | 931780 | FR | 2655572 |
| | | GB | 8928086 | GB | 2240494 | GB | 9225004 |
| | | GB | 2263076 | IL | 96597 | IT | 9022344 |
| | | JP | 4100557 | JP | 6040984 | NO | 905350 |
| | | NZ | 236418 | PT | 96169 | US | 5152456 |
| | | US | 5261601 | ZA | 9009776 | GB | 9017563 |
| | | GB | 9026804 | | | | |
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| | | GB | 2219512 | JP | 2502791 | SE | 8902851 |
| | | US | 5063922 | | | | |
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| | | GB | 9101527 | | | | |
| EP | 42468 | AT | 19939 | DE | 3023648 | DE | 3174689 |
| | | US | 4558710 | | | | |
| DD | 205820 | | | | | | |
| DE | 3908909 | | | | | | |
| US | 4987861 | | | | | | |
| EP | 213753 | AT | 56607 | CA | 1256338 | DE | 3674299 |
| | | IL | 76001 | US | 4674490 | IL | 78589 |
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| | | FI | 884384 | JP | 63502885 | NO | 874873 |
| | | NO | 163670 | SE | 8601351 | WO | 87/05813 |
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**END OF ANNEX**

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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|---|---|---|
| | | (43) International Publication Date: 10 April 1997 (10.04.97) |

(21) International Application Number: PCT/CA95/00562

(22) International Filing Date: 3 October 1995 (03.10.95)

(71)(72) Applicants and Inventors: SLUTSKY, Arthur [CA/CA]; 61 Glen Cedar Road, Toronto, Ontario M3C 3G4 (CA). ZAMEL, Noe [CA/CA]; 252 Otonabee Avenue, Willowdale, Ontario M2M 2T1 (CA).

(74) Agent: BERESKIN & PARR; 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).

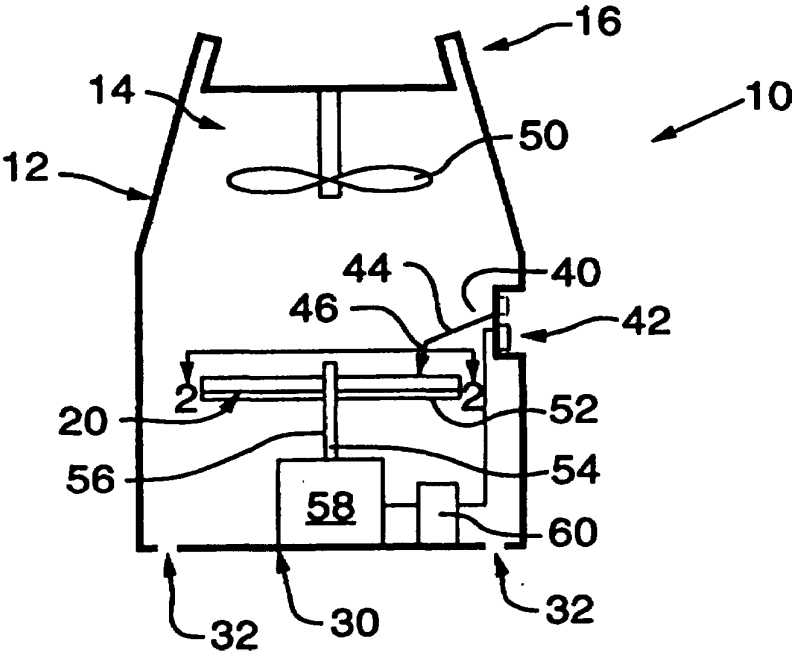
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
*With international search report.*

(54) Title: MEDICAMENT INHALER

(57) Abstract

A method of delivering a predetermined dose of a nicotine formulation through the lung alveoli and small airways into the bloodstream of a patient utilizes a portable inhaler containing the nicotine formulation. The portable inhaler may be used as a tobacco (e.g. cigarette) substitute. In one embodiment, individual dose capsules for a portable powder inhaler and their fabrication are also described.



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# Title: MEDICAMENT INHALER

## FIELD OF THE INVENTION

The present invention relates to an inhaler for dispensing a medicament into the lung. The invention also relates to a method for introducing nicotine into the lungs of a patient. The method may be used to assist the patient to withdraw from tobacco induced nicotine dependency. The invention further relates to the use of nicotine inhaled from a portable inhaler as a tobacco substitute (e.g. cigarette, cigar, pipe).

## BACKGROUND OF THE INVENTION

In industrialized countries about one third of the adult population smokes cigarettes, resulting in a major avoidable cause of morbidity and mortality. Smoking is a contributory or causative factor in a number of diseases including respiratory diseases such as emphysema, chronic bronchitis, lung infections, and lung cancer; cardiovascular disease; gastric and duodenal ulcers; and cancer of the lung, oral cavity, larynx and oesophagus.

Most regular smokers become addicted to, or dependent upon, the pharmacological effects of nicotine in tobacco smoke. Nicotine is rapidly absorbed across the blood brain barrier and exerts a direct action on nicotine receptors in the spinal cord, autonomic ganglia and adrenal medulla. For more detailed information on the pharmacologic effects of nicotine see, for example, Oates and Wood, New Eng. J. Med. 319:1318, 1988.

Although nicotine is responsible for the addictive nature of cigarette smoking, most of the harmful health effects of smoking are attributable to other constituents in cigarette smoke (The Lancet, 337:1191, May 18, 1991). The combustion of tobacco in cigarettes results

in the production of up to 4,000 compounds and the inhalation of such unwanted by-products as tar, combustion gases and a range of carcinogens. Nicotine may be nitrosated to form highly carcinogenic tobacco-specific N-nitrosamines in tobacco smoke, or in the cured smokeless tobacco for use as chewing tobacco or snuff. It is an unfortunate feature of cigarette smoking that the negative consequences of nicotine addiction are largely manifested by the inhalation of toxic and carcinogenic materials generated by the combustion of tobacco.

The habit of smoking is based upon a pharmacological dependence on nicotine, an addiction comparable to that arising from the use of heroin. There are a number of acute symptoms of smoking cessation relating to nicotine withdrawal including irritability, anxiety, insomnia and a craving for nicotine. The addictive nature of nicotine poses a major obstacle to those who wish to quit smoking and a number of approaches have been developed to aid individuals in their efforts to stop smoking. The more successful of these involve therapy with nicotine substitutes such as chewing gum, nicotine patches, nicotine nasal sprays, nicotine vapour and the like. However, as discussed in more detail below, these approaches have met with limited user acceptance and limited success. In addition, there are individuals who are unable to stop despite repeated attempts, due to the addictive nature of nicotine. These individuals could benefit from a product which fulfilled their craving for nicotine, but did not have the same detrimental health consequences as cigarettes.

Smoking is a uniquely effective form of systemic drug administration. As nicotine enters the blood stream via the pulmonary circulation, it is speedily transported to the brain. Smokers achieve a rapid peak in nicotine levels in the blood within one or two minutes after finishing a cigarette. Nicotine substitutes generally contain nicotine in solid form, in a vapour or in solution. As nicotine is a base, these preparations are alkaline. The alkalinity of nicotine

substitutes is frequently increased, for example to pH 10, because at high pH nicotine is not ionized and ionization is known to impede the passage of nicotine across biological membranes (Burch et al., Am. Rev. Respir. Dis. 1989, 140:955).

With respect to nicotine gum, it is known that nicotine, even at an alkaline pH, is absorbed slowly across the mucous membranes of the oral cavity, so absorption by this route does not produce the very rapid increase in nicotine levels associated with cigarette smoking. Therefore, buccal absorption has proved to have limited use in simulating the effects of cigarette smoking and lessening the adverse symptoms of nicotine withdrawal. The rate of rise of nicotine levels in the blood which is achieved with chewing nicotine gum is much lower then that achieved by smoking cigarettes and the gum has been associated with gastrointestinal side effects, hiccups, mouth ulcers and sore throat. The amount of nicotine absorbed is also highly variable and is dependent upon the chewing and swallowing actions of the user over a prolonged period of time.

Nicotine patches are associated with skin irritation at the application site. The rate of absorption can vary with blood flow to the region where the patch is applied, which in turn can vary with temperature or the rate at which the user exercises. Both nicotine gum and dermal patches result in slow absorption of nicotine which is frequently not effective in satisfying the patient's craving for cigarettes. This may be one of the reasons for the lack of success of these forms of therapy in weaning subjects from smoking.

Self-propelled aerosols (also know as "pressurized aerosols") which contain nicotine in solution and a pressurized propellant have also been proposed as cigarette substitutes. An example is the self-propelled aerosol formulation of Jacobs in U.S. Patent No. 4,635,651. Such formulations are packaged in pressurized metered dose delivery systems. As shown in Jacobs, these delivery systems contain a water based aerosol formulation and a propellant,

such as pressurized freon, which are stored in a pressurized storage container. When the device is activated, the aerosol formulation is released at high speed from the pressurized storage container. The pressurized storage container is in flow communication with a delivery system. When the device is used by an individual, the user aims the delivery system into their mouth. The user then causes a valve of the pressurized storage container to be opened. When this valve is opened, the pressure inside the container forces a dose of medicament to be expelled at high speed from the container and into the user's mouth.

There are a number of problems with such pressurized aerosols. Pressurized aerosols require coordination on the part of the user who ideally should inhale at exactly the same time as the device is actuated in order to deliver the drug into the respiratory system of the user.

Failure to coordinate actuation of an aerosol inhaler and inhalation results in deposition of the aerosol in the oral cavities and upper respiratory tracts. In addition, even if the user properly aims the delivery device and coordinates the inhalation, the speed with which the aerosol is expelled from the device and enters the mouth causes much of the aerosol to impact on the throat and upper airways of the user. For the foregoing reason, the amount of nicotine entering the lower airways by using pressurized aerosols can not be accurately controlled. For example, devices such as the device disclosed in Jacobs in U.S. Patent No. 4,635,651 tend to expel some particles of about 40 μm. These particles would comprise agglomerations of particles and solvents. As the particles travel from the inhaler into the airway of the user, the particles would break up into smaller particles and some of the solvent would evaporate. However, even these smaller particles would still be at least about 10 μm as they travelled through the mouth of the user and would accordingly impact on the throat and upper airways of the user. Aerosols utilize nicotine which is in

solution. Since nicotine in solution has an alkaline pH which irritates the throat and upper airways, aerosols have poor acceptance by smokers (Burch et al., 1989, Am. Rev. Respir. Dis. 140:955).

Further, it is problematic to produce particles of an optimal size for absorption in the alveoli with a self-propelled aerosol. Jacobs in U.S. Patent No. 4,635,651 included a solid particulate component of defined size into a pressurized aerosol formulation of an inhalable nicotine solution.

## SUMMARY OF THE INVENTION

It has been determined that a controlled dose of a medicament comprising at least one pharmaceutically acceptable nicotine preparation suitable for absorption into the blood stream of a person through the alveoli and lower airways of the person's lungs can be delivered to the alveoli and lower airways of the person's lungs by using a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs in a portable inhaler while causing only minimal noticeable irritation to the throat and upper airways of the person and, preferably without causing any noticeable or significant irritation. It has also been determined that a controlled dose of a medicament comprising a pharmaceutically acceptable nicotine preparation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the lungs can be delivered into the alveoli and lower airways of a person's lungs by an inhaler pursuant to this invention to mimic the pharmacologic effects of the nicotine administered by a cigarette, cigar, pipe or the like (hereinafter generally referred to as "cigarette") while minimizing or preventing the delivery of extraneous irritants or toxins into the oral cavity and respiratory airways. Preferably, the pharmaceutically acceptable nicotine preparation is suitable for absorption into the blood stream of a person through the alveoli and small airways of the person's lungs.

The present invention relates to a method of delivering a medicament including at least one nicotine formulation to a person comprising introducing a predetermined dose of a medicament including at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, and preferably through the alveoli and small airways of the person's lungs, from an inhaler, into the alveoli and lower airways of the person's lungs, and preferably into the alveoli and small airways of the person's lungs.

The portable inhaler may comprise a housing, an air conduit within the housing adapted to conduct air flow to the person, a medicament comprising at least one pharmaceutically acceptable nicotine preparation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, and preferably through the alveoli and small airways of the person's lungs and means for introducing a predetermined dose of the medicament into the air conduit, whereby on activation of the inhaler and inhalation by the person, the medicament is introduced to the person's lungs.

The individual medicament particles, when they enter the air passageway of the user, may be up to about 10 μm in size, preferably up to about 7 μm, more preferably up to about 5 μm and most preferably up to about 3 μm. The nicotine formulation can be in the form of a powder or a liquid solution. The liquid solution must be converted to an aerosol. The nicotine powder may have a tendency to join together to form larger particles (eg. greater than about 10 μm) by various mechanisms (eg aggregation, agglomeration). If this is the case, then the force applied to the joined particles on inhalation may not be sufficiently great to break up the joined particles into constituent units sufficiently small so as to be entrained in the air inhaled by the user. Therefore, mechanical assistance is preferably provided to break up

such joined particles to constituent units sufficiently small so as to be entrained in the air inhaled by the user.

The nicotine formulation may be stored at atmospheric pressure as a powder or as a liquid solution. The liquid solution may be aerosolized using compressed fluid (preferably a gas). The compressed fluid that disperses the powder or that produces a liquid aerosol from the liquid solution of nicotine, may be contained in a reservoir chamber or be compressed by any mechanical means just prior to the dispersion of the powder or the aerosolization of the liquid solution. Further, the medicament may be stored under pressure provided that velocity reducing means is provided so that the momentum of the medicament particles upon inhalation is sufficiently low so as to permit the medicament to travel past the glottis and preferably to the small airways, which inhalers are referred to as non-pressurized inhalers. Such inhalers are in contrast to the pressurized portable inhaler of Jacobs wherein the medicament particles impact on the upper airway and cause excessive irritation to the user. The generation of the powder dispersion or of the liquid aerosol may be activated prior to the person taking the breath. Very high energy devices, such as ultra-sound, could be used to disperse the powder or to generate a liquid aerosol. Alternately, the nicotine formulation may be stored under high pressure.

The predetermined dose of nicotine may be from about 0.1 to about 10 mg and preferably from about 0.2 to about 2 mg of nicotine. In order to more closely mimic the pharmacologic effects of the nicotine administered by a cigarette, the inhaler may be adapted to provide a series of small doses of the nicotine preparation, such as from about 0.1 mg. to about 0.5 mg., over the period of time in which an individual would smoke a cigarette.

In an embodiment of the invention, the medicament may additionally comprise a pharmaceutically acceptable carrier,

binder, excipient, surface active agent, diluent, or a combination thereof.

In one embodiment, the medicament is dispersed by the person's breath. The inhaler may include means to mechanically assist the dispersion of the medicament. The means to mechanically assist the dispersion may include mixing means. The mixing means may comprise a non-rotatably mounted impeller. As the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past the impeller to assist in the dispersion of the medicament. Alternately, the mixing means may comprise a rotatably mounted impeller. As the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past the rotating impeller to assist in the dispersion of the medicament. The rotation of the impeller may be assisted by mechanical means such as by a battery operated motor.

Alternately, the medicament may be stored under pressure. Upon activation of the inhaler, the medicament is released from a pressurized container into the air. Depending upon the velocity at which the medicament is expelled from the container, the inhaler may include velocity reduction means so that, when the medicament is inhaled, the medicament is at a velocity sufficiently slow to be entrained in the air inhaled by the user. The velocity reduction means may comprise the use of air (in a chamber or otherwise) to create frictional drag on the medicament particles to slow the speed of these particles.

The nicotine may be any nicotine salt such as a sulphate or a bitartrate or a nicotine base, such as a nicotine oil formulation or mixtures thereof. These nicotine formulations may be absorbed, adsorbed or aggregated onto a suitable carrier or excipient. Alternately, the nicotine oil formulation may be encapsulated.

The invention also relates to a method of introducing a medicament comprising at least one nicotine formulation into the

lungs of a person using an inhaler having a housing having a first opening and a second opening, one of the first opening and the second opening being adapted to deliver the medicament to the mouth of the person and storage means for storing a medicament suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, the method comprising the steps of:

(a) releasing the medicament from the storage means and dispersing the medicament for inhalation by the person; and,

(b) inhaling the medicament.

The invention further relates to a method of introducing a medicament comprising at least one nicotine formulation into the lungs of a person using an portable inhaler having a housing having a first opening and a second opening, one of the first opening and the second opening being adapted to deliver the medicament to the mouth of the person and container means for receiving a medicament suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, the method comprising the steps of:

(a) delivering the medicament to the container means and dispersing the medicament for inhalation by the person; and,

(b) inhaling the medicament.

The method may be used to assist a person to withdraw from cigarette induced nicotine dependency through the introduction of a predetermined dose of the medicament into the alveoli and small airways of the person's lungs. In a preferred embodiment, the method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal. In a further preferred embodiment, where a person appears to be unable to stop smoking, the inhaler may be used as a cigarette substitute.

The inhaler according to this aspect of the invention may contain a single dose of a medicament which is intended to be inhaled

by the person in a single breath. Alternately, if the dosage which is required by a person is sufficiently great that it would cause irritation to the throat and upper airways of the person, a full dose may be located in the inhaler and the inhaler is preferably provided with by-pass air feed means for supplying air to dilute the air passing through the housing so as to reduce the concentration of the medicament in the air which is inhaled by the person.

Preferably, the by-pass air feed means is located near the opening which is adapted to deliver the medicament to the mouth of the person.

## BRIEF DESCRIPTION OF THE DRAWINGS

These and other advantages of the instant invention will be more fully and completely understood by reference to the following description of the following drawings of an exemplary embodiment of the invention in which:

Figure 1 is a cross-section of an inhaler according to the instant invention;

Figure 2 is a top plane view along the line 2-2 in Figure 1;

Figure 3A discloses a cross-section of a further inhaler according to the instant invention;

Figures 3B and 3C disclose methods of how the inhaler shown in Figure 3A may be utilized by a person;

Figures 4A - 4D show a method by which a further inhaler according to the instant invention may be manufactured.

Figures 5A - 5D show a further embodiment of the inhaler according to the instant invention and the method of use of this further embodiment of the inhaler; and,

Figure 6 is a cross section of alternate inhaler which may be used pursuant to the instant invention.

## DETAILED DESCRIPTION OF THE INVENTION

As hereinbefore mentioned the present invention relates to the use of a portable inhaler for dispensing a medicament comprising at least one nicotine formulation to the alveoli and the lower airways, and preferably into the alveoli and the small airways. In the art, "lower airways" is used to refer to the passages in the respiratory system which are downstream (upon inhalation) from the glottis. In the art, "small airways" is used to refer to the passages in the lungs which are less than about 2 mm in diameter. The inhaler may be used to deliver a predetermined dose of medicament comprising at least one nicotine formulation into the alveoli and lower airways, and preferably into the alveoli and the small airways, in a form which is sized for rapid absorption and which simulates the pharmacologic effect of a rapid increase in nicotine blood levels similar to that achieved by cigarette smoking. The rapid nicotine absorption is due to deposition of nicotine in the airways and alveoli of the lung where the medicament may be absorbed efficiently across the large surface area of the highly vascularized alveoli and the lower airways, and in particular the alveoli and the small airways.

The medicament to be drawn into the lungs may comprise one or more nicotine formulations. The medicament may be a powdered or liquid nicotine formulation. The nicotine is preferably in the form of a stable powder. The nicotine formulation may comprise a nicotine salt such as a sulphate or a bitartrate or a nicotine base, such as a nicotine oil formulation or pharmacologically active analogues or derivatives of nicotine or substances which mimic the effects of nicotine, either alone or in combination with other active substances. The medicament may be discrete particles or it may be absorbed, adsorbed or aggregated onto a suitable carrier or excipient. Alternately, if the medicament is a liquid, such as a nicotine oil formulation, the medicament may be encapsulated.

Nicotine is known to form salts with almost any acid and double salts with many metals and acids. Nicotine salts vary in their

ability to absorb water. It has been found that the ability of nicotine salts to penetrate into the distal regions of the lung, such as the lower airways and the alveoli and in particular the smaller airways and the alveoli, is based in part upon the size of the particles of the medicament and the degree of hygroscopicity of the medicament. For example, some nicotine salts are very hygroscopic. Accordingly, the particles rapidly increase in size when exposed to an airway of the person which is fully water saturated. The absorption of water by the particles increases the size of the particles and, for the reason set out herein, may alter the location of the deposition of the particles. By selecting a nicotine salt which is somewhat hygroscopic, and selecting the particles so as to be capable of being inhaled and transported to the alveoli and lower airways, and preferably to the alveoli and the small airways, a rapid increase in the blood level of nicotine may be obtained in a person. This rapid increase in blood level simulates cigarette smoking. Accordingly, the nicotine may be selected, based upon its hygroscopicity, to provide nicotine salt particles which are of the sufficient size to be transported to the distal regions of the lungs and, in particular, to the alveoli and lower airways, and preferably to the alveoli and the small airways. Preferred nicotine salts include sulphate and tartrate, chloride, bi-chloride, bitartrate, picrates, aipricrates, salicylates, picrolonates and dipicrolonates. More preferably, the salt is sulphate, bitartrate or mixtures thereof.

A medicament such as nicotine may be mixed with one or more pharmacologically acceptable binders, excipient or diluents, surface active agents, colouring or flavouring agents, suitable for inhalation. Examples of suitable solid diluents or carriers which may be used in the medicament include mannitol, dextrose and lactose.

In order to facilitate storage, handling and introduction of the medicament into the air conduit the medicament may be packaged in powdered form with a desiccant to prevent moisture absorption.

The medicament of the invention, if ionized (e.g. a nicotine salt), is poorly absorbed across the mucosa of the upper airways and is relatively non toxic to those surfaces. Surprisingly, the extensive cross-sectional area of the lower airways, and in particular the small airways, and the alveolar lining provides a large stable buffering environment for the ionized nicotine. As the nicotine is buffered in the lungs, the pH of the nicotine increases and the nicotine may be readily transported across the biological membranes in the lung. Thus, nicotine, whether acidic or basic, delivered into the distal regions of the lung is readily buffered and absorbed by the extensive airway and alveolar surfaces. It is the rapid and efficient absorption across the expansive buffered alveolar and airway surfaces which results in the steep rise in nicotine blood levels mimicking the pharmacological effect of cigarettes. The selective delivery to, and absorption across, the distal lung regions therefore mimics the pharmacologic effects of cigarette-derived nicotine while decreasing or eliminating the undesirable side effects of smoking or other nicotine substitution therapies.

The medicament doses of the present invention are intended for administration to humans and preferably contain from about 0.1 mg. to about 10 mg. of nicotine. The medicament can be prepared by known methods for the preparation of pharmaceutically acceptable compositions which can be administered to the airways of persons such that an effective quantity of nicotine is provided, which may be combined in a mixture with a pharmaceutically acceptable vehicle as hereinbefore mentioned.

In order for the nicotine in the medicament to be deposited in the alveoli and the lower airways, and preferably in the alveoli and the small airways, of the lung, the medicament enters the mouth of the user with a momentum sufficiently low to cause the medicament to be entrained in the air of the inhalation so as to follow the curvature in the pathways of the upper respiratory tract and be

carried to the lower airways, and preferably to the alveoli and the small airways of the lungs of the user. To achieve this result, the mass of the particles of the medicament (expressed in this application in terms of the size of the medicament particles given that the density of the particles is readily determinable) and the velocity of the medicament particles at the position from which it is inhaled must be in a defined range.

The nicotine is in a size range suitable for deposition on and absorption across the lower airways and the alveolar lining, and preferably the small airways and the alveolar lining, taking into account the amount of water which may be absorbed by the particles as they pass through the lungs. Larger particles, over about 7 μm, more particularly over about 10 μm (which have a higher mass) tend to be deposited in the oral cavity and upper airways. If the nicotine formulation contains a significant proportion of particles greater than about 7 μm, more particularly over about 10 μm, then the impaction of these nicotine particles on the throat and upper airways of the user during inhalation will cause irritation to the user and may make the product unacceptable to the user. It will be appreciated that some users are more sensitize than others to the irritation caused by these larger particles and, therefore, the amount of such particles which may be present in each dose will vary by user. As used herein, a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs does not include medicament particles that would cause significant irritation to the general public.

The particles grow in size as they are exposed to water in the atmosphere and in the airways of the user. For example, a 0.1 μm particle may increase to about 0.5 μm as it passes through the airways to the alveoli and smaller airways of a user. In order to have an appropriate mass, the individual medicament particles, when they enter the air passageway of the user, may vary in size up to about about

10 μm, preferably up to about 7 μm, more preferably up to about 5 μm and most preferably up to about 3 μm. However, it should be noted that the individual particles of the medicament may be joined together to form larger particles by various mechanisms (eg aggregation, agglomeration) If the medicament is a powder formulation, such joining may occur during the packing of the medicament container and/or during the storage of the medicament container. These larger particles, while they may be entrained by the air which enters the mouth of the user, may have a momentum which is too large to permit them to be transported past the glottis by the air which travels downstream from the glottis upon inhalation and will therefore tend to impact on the throat and upper airways of the user causing irritation to these areas. If the medicament contains a sufficient amount of these particles to cause such irritation, then these larger joined particles are preferably broken down into smaller component units. These smaller units may comprise individual medicament particles and/or such larger joined medicament particles from which some of the individual medicament particles have been removed so as to produce smaller joined particles. This reduction in size may be achieved when the large particles are expelled from the medicament container (eg. by the force applied to expel the particles from the medicament container) and/or by turbulence arising prior to and/or on inhalation (eg. by mixing means provided in the air flow conduit). Preferably, each dose of the medicament will contain a sufficiently small amount of particles greater than about 7 μm so as not to cause irritation or other undesirable side effects to the user. Twenty five percent of each dose may contain particles within the range up to about 7 μm, preferably more than about 35% of each dose, more preferably more than about 50% and, most preferably, more than about 70%.

To have an appropriate velocity, the air conduit of the inhaler is preferably sized to permit an air flow rate therethrough of

up to about 2 L/s, preferably up to about 1 L/s and, more preferably up to about 0.5 L/s upon inhalation by the person. Preferably, the medicament may be entrained in an air flow created by a normal or a less than normal inhalation.

Pursuant to the invention, the inhaler provides a pre-determined dose of a nicotine medicament to the lung. The dose should be physiologically acceptable for administration to humans by this route of administration. The dose of nicotine delivered to the lungs may be from about 0.1 to about 10 mg, preferably from about 0.2 to about 3 mg, more preferably from about 0.2 to about 2 mg, and most preferably about 1 mg as a total dose in any one treatment. However, one treatment may consist of multiple inhalations of a smaller dose over a period of time thus more closely simulating the act of smoking and minimizing the irritant effect of nicotine impaction in the mouth and throat. Accordingly, in order to more closely mimic the pharmacologic effects of the nicotine administered by a cigarette, the inhaler may be adapted to provide a series of small doses of the nicotine preparation, such as from about 0.1 mg. to about 0.5 mg., over the period of time in which an individual would smoke a cigarette, typically from about 1 to about 10 minutes.

The use of the instant invention allows a person to achieve a rapid increase in nicotine blood level which effectively simulates cigarette smoking.

The inhalation of the medicament is achieved by the person's own breath. This breath may also serve to stir a powdered medicament in order to disperse it, and/or to activate any kind of system that will, in turn, assist the dispersion of the medicament. The powder dispersion can be assisted by any mechanical or electrical means, such as a battery operated impeller or vibrator. The dispersion of a powder or liquid formulation can also be assisted by the application of compressed air or gas to the formulation. The means

that assists the dispersion may be activated prior to the person taking the breath.

Various types of portable inhalers are known in the art. Such inhalers may have a housing, an air conduit adapted to conduct air flow to a person, and means for introducing a medicament into the air conduit. See, for example, U.S. Patent Serial No. 4,524,769 to Wetterlin; Bell et al., J. Pharmaceut. Sci. 60:1559, 1971; Newman et al., Eur. Res. J. 2:247, 1989; and Clark, A.R., Aerosol Science and Technology, Vol. 22, No. 4, 374-391, 1995. While various portable inhalers may be used in accordance with this invention, it will be appreciated that the exact inhaler which is used is preferably chosen based on the particle size range of the individual particles of the medicament, the particle size distribution of the individual particles of the medicament, the nature of the medicament (i.e. whether the medicament in a liquid or a solid formulation) and the degree to which the individual particles join together. If the medicament is in a form wherein the individual particles do not join together to any significant degree, then the medicament must be of a particle size range and distribution suitable for travelling to the alveoli and lower airways, and preferably to the alveoli and small airways, of the lungs of the user. If the medicament is in a form wherein the individual particles tend to join together to form a significant number of large particle, or if the medicament is a liquid formulation, then according to the preferred embodiment, means is provided to produce medicament particles which, at the point the medicament reaches the airways of the user, are of a particle size range and distribution suitable for travelling to the alveoli and lower airways, and preferably to the alveoli and small airways, of the lungs of the user. It will be appreciated that, depending on the size of the individual medicament particles and the inhaler which is selected, it may not be necessary to completely break up such joined particles to provide an aerosol comprising the individual medicament particles.

For example, if the medicament when inhaled contains few particles greater than about 2 μm, and the particles generally do not join together, then a much higher rate of inhalation may be used than if the medicament when inhaled contains a large percentage of particle in the range 2 μm to 7 μm. As will be appreciated from the following discussion, a mechanically simpler inhaler may be used if the medicament when expelled from the medicament storage container contains a high percentage (eg. 50%) of the dose as relatively small particles (eg. up to about 5 μm). Such particles may be entrained in air flowing at a higher rate without significantly impacting on the throat and upper airways of the user. Thus, the inhalation may be used to assist the break up of any joined particles. If the medicament comprises individual medicament particles within the desired size range but, the dose when expelled from the medicament storage container, contains a relatively large percentage (eg. 50%) of the dose as particles which are relatively large (eg. 5-10 μm), then a low velocity release inhaler which includes means to disperse, or to assist in such dispersion is preferably used so that, when inhaled, the joined particles have been sufficiently dispersed so as to reduce to a tolerable level, or preferably eliminate, irritation to the user.

Inhalers deliver medicaments to a position from which the user may inhale the medicament. As opposed to pressurized aerosol inhalers (e.g. Jacobs), the inhalers used pursuant to the instant invention deliver the medicament to the position from which the user may inhale the medicament at a velocity which is sufficiently slow so that the medicament may be entrained in the air upon inhalation by the user and transported past the glottis by the air which travels downstream from the glottis upon inhalation. Preferably, the medicament is carried to the smaller airways. The velocity of the medicament at the position from which it may be inhaled is preferably approximately equal to or lower than the velocity of gas during a normal, or part of a normal, inhalation so that most, if not all, of the

medicament released by the inhaler is entrained in the air upon inhalation by the user and transported past the glottis. Accordingly, while the medicament may have some forward velocity (i.e. in the direction of the airways of the user) when it is inhaled, the inhalation of the medicament is achieved, at least to a large degree, by the person's own breath. Such devices are referred to as "breath-activated" inhalers.

It will be appreciated that the velocity of the medicament prior to being delivered to the position from which it may be inhaled may be substantially greater that the velocity at the position from which it may be inhaled. Accordingly, as discussed in more detail below, the medicament may be in the form of a powder that is released from a storage container and held effectively stationary in a chamber until inhalation. Alternately, the medicament may be stored at high pressure so that the medicament travels at a high velocity when expelled from the container. Pursuant to this embodiment, the high pressure is used to deliver the medicament to the position from which it may be inhaled. The inhaler includes velocity reduction means so that by the time the medicament reaches this position, its velocity has decreased to within the desired range of velocities. The velocity reduction means may comprise the use of air (in a chamber or otherwise) to create frictional drag on the medicament particles to slow the speed of these particles. As the medicament travels from the storage chamber to the position from which it may be inhaled, the high velocity assists in the dispersion (break up) of the medicament particles.

Referring to Figure 1, inhaler (10) generally comprises a hollow housing (12) with an air conduit (14). One end of the air conduit (16) is adapted for insertion into the mouth of a person. Such inhalers have means for introducing the medicament into the air conduit, for example a rotatable disc (20) having spaced containers (22) of medicament which can be rotated to introduce a single dose of

medicament into the air conduit (see Figure 2). Containers (22) may be in the form of capsules, blister packs or any other similar container. In an alternate embodiment, it will be appreciated that containers (22) may contain multiple doses of medicament. In a further alternate embodiment, a single container may contain multiple doses (eg. 100 doses) of medicament. According to such an embodiment, each activation of the device causes a predetermined dose of medicament to be delivered to the chamber in the inhaler from which the medicament may be inhaled. Referring to Figure 1 in more detail, housing (12) has a bottom surface (30). Bottom surface (30) is provided with air inlets (32). Air inlets (32) are sized to provide an appropriate amount of air into inhaler (10). As the air enters inhaler (10), it travels past rotatable disc (20) and exits through end (16). In use, the person inserts one end of the air conduit into their mouth and inhales. Conduit (10) thus acts as a chamber to hold the medicament at a position from which it may be inhaled by the user. The turbulent airstream created in the air conduit by the person's inspiration fluidizes the medicament to produce a cloud of medicament particles which are carried into the lung with the inhaled air.

Inhaler (10) also includes means (40) for opening spaced containers (22) in a controlled fashion. As shown in Figure 1, inhaler (10) includes actuator button (42). Button (42) is movable between a first position as shown in Figure 1 and a second position which is shown in dotted outline in Figure 1. Button (42) is connected to extender arm (44). Attached to the distal end of extender arm (44) is piercing member (46). Piercing member (46) has a sharpened edge so that, when actuated, it will pierce spaced container (22) thus opening the container and allowing the medicament to be fluidized by the passage of air over the disc. Extender arm (44) and piercing member (46) are configured such that the sharpened edge of piercing member (46) is positioned adjacent the circle defined by spaced containers (22). When actuator button (42) is moved to the position shown in dotted

outline, piercing member (46) is moved so as to open spaced container (22).

Such inhalers are designed to dispense the medicament to the person without the use of any mechanical assistance to assist in the dispersion of the medicament in the air which is drawn into the lungs of the person. Such inhalers may be used if the medicament particles when positioned in conduit (10) are relatively fine and have a small particle size distribution, eg. the medicament comprises a high percentage (eg. 50%) of the dose as relatively small particles (eg. up to about 5 μm). Examples of such inhalers include the ROTAHALER™, CYCLOHALER™ and INHALATOR™ inhalers. See also United States Patent No. 4,811,731 for the DISKHALER™ which is incorporated herein by reference.

Most inhalers currently in use for the treatment of respiratory disorders have low resistance so that sufficient air flow can be generated by persons having impeded respiratory capacity and obstructed airways, resulting, for example, from an asthmatic attack. However, the high flow rates generated by users not having obstructed airways could cause larger particles (approximately greater than about 5 μm to about 10 μm) to impact against the back of the upper airway. If the medicament contains a large percentage of the dose (eg. greater than about 25%) as such larger particles and these particles tend not to join together, then the inhaler preferably restricts the velocity of air exiting the inhaler so as to limit the velocity of the medicament as it enters the airways of the user.

Alternately, the medicament particles may tend to join together to produce large joined particles (approximately greater than about 5 μm to about 10 μm) requiring a lower velocity of inhalation to avoid irritation of the throat and/or requiring turbulence and/or mechanical assistance to disperse, or assist in the dispersion of, the joined particles. Accordingly, if the medicament comprises a large percentage (eg. more than about 25%) of the dose as such larger

particles, it is preferred to use an inhalation device with mechanical assistance to disperse (break up), or assist in the dispersion (break up) of, the medicament.

Accordingly, mixing means which may serve two functions may be provided. First, to restrict the cross-sectional area of the air conduit so as to reduce the flow rate of air thereby decreasing impaction at the back of the throat particularly in the case of users not having obstructed airways. Secondly, to produce turbulence in the air flow to break up joined particles of the medicament which may be present in the inhaler prior to inhalation.

For example, as shown in Figure 1, inhaler (10) may be provided with mixing means (50) which is mounted at end (16). Air passing by mixing means (50) is disrupted so that joined particles of the medicament which might be formed are disrupted. Mixing means (50) may be a non-rotatably mounted impeller or other means which will cause a disruption in the air stream as the air passes thereover thus helping to disperse the medicament. An example of such inhalers include the TURBUHALER™ inhaler (United States Patent No. 4,907,583 which is included herein by reference). Alternately, mixing means (50) may be a rotatably mounted impeller or other obstruction means which rotates as the person inhales so as to assist the dispersion of the medicament. An example of such inhalers include the SPINHALER™ inhaler. See also United States Patent No. 3,831,606 which is incorporated herein by reference.

Preferably, in order to further assist in the dispersion of the medicament, mixing means (50) may be mechanically assisted by, for example, a battery operated motor. An example of such a device is disclosed in United States Patent No. 5,327,883 which is incorporated herein by reference.

In summary, suitable inhalers include traditional dry powder metered dose inhalers such as the DISKHALER™, the ROTAHALER™, the CYCLOHALER™ and the INHALATOR

inhalers which rely only on the person's inspiratory power to deliver and break up the medicament for inhalation. More sophisticated inhalers also include dry powder inhalers which provide mechanical assistance to break up, or to assist in the break up of, the medicament. The mechanical assistance may be in the form of a fixed impeller positioned in the path of the medicament as the medicament is inhaled, such as the TURBUHALER™ inhaler. Alternately, the mechanical assistance may be in the form of a rotating member, such as an impeller (eg. the SPINHALER™ inhaler).

More preferably, the inhaler is a low velocity release inhaler. Medicaments released by such inhalers are either effectively stationary at the point from which they are inhaled, or they are travelling at a velocity sufficiently slow so that particles as large as 5 to 10 μm may be entrained in the air inhaled by a user. Medicaments which may be used with such inhalers include liquid formulations and powder formulations wherein the medicament particles are relatively small but tend to join together. Such inhalers typically include mechanical means to disperse (break up), or to assist in the dispersion (break up) of the medicament.

To achieve the dispersion of the medicament particles while maintaining the medicament particles at a low velocity, low velocity release inhalers generally rely completely, or at least substantially, upon energy which is imparted to the system other than through the movement of air caused by inhalation by the user. One means which may be used to impart energy to the system is pneumatic pressure. In such inhalers, a metered does of medicament is discharged with the aid of a small compressed air pulse. An example of such a device is Galli (Patent Application WO 93/18812). As exemplified in Figure 6, the inhaler has dosage chamber 100. Dosage chamber 100 is isolated from the medicament container 106 by spring loaded plug 102. Medicament may be loaded into dosage chamber 100 by means of broom 104. Thus, once filled, dosage chamber 100 has an air tight

separation from medicament container 106. Dosage chamber 100 is in air flow communication with compression chamber 108. Positioned beneath compression chamber 108 is piston 110 which is situated on top of spring 112. Compression of plunger 114 by the user causes spring 112 to compress. Further compression of plunger 114 releases piston 110 which snaps upward into compression chamber 108 thus producing a jet of compressed air which is channelled into dosage chamber 100. This jet of air causes the medicament to be dispersed and to pass through nozzle 116 which is provided with a check valve 118. The jet of air disperses the medicament to the air surrounding nozzle 116. Alternately, as shown in dotted outline in Figure 6, a chamber may be positioned in flow communication with nozzle 116. Pursuant to this embodiment, the user may actuate plunger 8 causing the medicament to be expelled into chamber 124. The chamber acts as a receiving chamber to collect the dispersed medicament and, in addition, to allow the medicament to slow down to a sufficiently slow velocity or, to in fact become stationary. Thus the chamber acts as a velocity reduction means. Alternately, other devices that obstruct the air flow passage and thus act to decrease the velocity of the air carrying the medicament may be used. The user may then inhale via nozzle 122. As the user inhales, carrier air may be fed into the chamber via nozzles 120. Thus, mechanical means may be used to disperse the medicament and the inhalation by the user merely entrains the particles and is not required to disperse the particles. The high pressure which is used to deliver the medicament to the position from which it may be inhaled is sufficiently great to effectively disperse the particles. Alternately, it will be appreciated that the chamber may be configured so as to permit the inhalation to further assist in the dispersion of the particles.

In a further embodiment, it will be appreciated that instead of using a spring actuated mechanism, the medicament in the inhaler may be stored under pressure. Pursuant to this alternate

embodiment, the pressure which is maintained in the medicament storage container is used to deliver the medicament to chamber 124. Once again, as the medicament travels from the storage chamber to chamber 124, the high velocity imparted to medicament by the pressure from the storage chamber disperses, or assists in the dispersion of, the joined medicament particles. Further, by the time the medicament is delivered to chamber 124, its velocity is decreased to within the desired range of velocities.

Low velocity release inhalers may also use more sophisticated forms of mechanical assistance including aqueous atomization (the use of hydraulic amplification to generate high liquid pressures, eg. 400 bar, to atomize a medicament), ultrasound and the use of meshes driven by piezoelectric crystals to deaggragate the medicament. These inhalers deliver the medicament to a chamber from which the person may inhale the medicament or they may expel the medicament from the inhaler at a sufficiently low velocity to permit the medicament to be entrained with the air inhaled by the user (compared to the pressurized inhaler of Jacobs).

As a means of regulating dosage, or as a means of regulating the frequency with which a dosage may be administered, it may be desirable to include means to limit the frequency with which inhaler (10) may be utilized. For example, as shown in Figure 1, rotatable disc (20) may be mounted on plate (52) which is attached to axle (54). Axle (54) has one end (56) which is attached to electric motor (58) powered by a battery (not shown). Rotation of motor (58) causes axle (54) to rotate thus rotating rotatable disc (20). Motor (58) is calibrated so that each activation of motor (58) causes rotatable disc (20) to move a sufficient distance to place a new spaced container (22) adjacent piercing means (46). Actuator button (42) is connected to timing means (60). Accordingly, when a person utilizes inhaler (10), button (42) is moved to the position shown in dotted outline in Figure 1.

If the amount of nicotine contained in a single dose is designed to simulate an entire cigarette, then timer (60) may be preset so as to allow a further dose to be taken only after a reasonable period of time (e.g. 20 to 30 minutes) has elapsed. Timer (60) is conventional and is connected to and actuated when button (42) is pushed. Timer (60) cuts off power to motor (58), for example, two seconds after button (42) is pushed (to allow the motor enough time to advance disc (20) by one step) and keeps the power to motor (58) cut off until timer (60) has counted down the desired time (which can be made adjustable).

If each nicotine dose is made equivalent only to that obtained by one or two puffs from a cigarette, then timer (60) would normally not be needed. However, if desired, timer (60) may be preset to allow a plurality of doses to be taken over a relatively short period of time to simulate the nicotine levels which are achieved when an individual smokes a cigarette. For example, timer (60) could be provided and set to permit a desired number of doses (puffs) within a preset time (for example 5 to 10 doses within, for example, ten to fifteen minutes), and then to cut off power to motor (58) until a selected time interval (e.g 20 to 30 minutes) has elapsed. By adjusting the number of doses allowed in each period and the time intervals between the periods, the total nicotine dosage can be controlled and, if desired, gradually reduced to wean the person from his/her nicotine additions.

Alternatively, timer (60) can be set simply to count the time between doses even when one dose simply simulates one or two puffs on a cigarette.

In accordance with one embodiment of the invention a method of assisting a person to withdraw from cigarette induced nicotine dependency is provided. The method comprises delivering a medicament comprising one or more nicotine formulations suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, and preferably the alveoli and

small airways of the person's lungs, from an inhaler to the alveoli and lower airways of the person's lungs, and preferably the alveoli and small airways of the person's lungs, for use by the person as a cigarette substitute.

When smokers attempt to stop smoking the recidivism rate is high due to the negative symptoms of withdrawal from nicotine addiction. Replacement therapy with cigarette substitutes is designed to lessen the impact of nicotine withdrawal and to assist a person in withdrawing from cigarette induced nicotine dependency. Cigarette substitutes are suggested as a replacement for cigarettes during the withdrawal period. The optimal replacement therapy will involve reproducing the sharp increase in nicotine levels achieved by cigarette smoking in order to effectively suppress the withdrawal symptoms. Successful withdrawal from smoking may require the use of inhalers according to this invention over a period of time during which inhalers are used to deliver successively smaller nicotine doses until complete withdrawal may be effected.

In order to effect a controlled withdrawal from nicotine the present invention provides an inhaler to deliver a predetermined dose into the distal regions of the lung. The predetermined dose is introduced into the air conduit from where it is efficiently drawn deep into the lungs. The size of each individual dose may therefore be accurately controlled.

In a preferred embodiment the minimum time interval between doses is also controlled to prevent the person from receiving an overdose of nicotine. The timer may be set to enforce time periods of from 5 minutes to about 2 hours. If the dosage is set to represent a puff of a cigarette, then the timer may have a first setting to permit several dosages to be taken over a period of a few minutes and a second setting to prevent a second plurality of dosages being taken before the expiry of from 5 minutes to about 2 hours. Accordingly, the present invention provides a highly controlled yet flexible method of

assisting a person to withdraw from cigarette-induced nicotine dependency by providing controlled doses of nicotine having a pharmacologic effect similar to that of cigarette smoke without the adverse side effects. The act of inhaling from a device in the mouth may also provide persons with a short-term behaviour substitute for inhaling a cigarette. In some cases where a person is unable to stop smoking, then the inhaler may be used as a replacement for cigarettes or cigarette substitutes.

As stated above, the recidivism rate is high due to the addictivness of nicotine. The high recividism rate is due to dependance on nicotine which is contained in tobacco and not to dependance on tobacco. For some people, the use of the inhaler according to the instant invention in accordance with an appropriate schedule may not enable them to eliminate their nicotine dependance. However, the inhaler described herein provides a cleaner source of nicotine (eg. without nitrosamines and other carcinogens present in the tar of cigarette smoke) which may be delivered to the lower airways and alveoli of the user pursuant to the method of the instant invention. As such, the inhaler may be used as a long term replacement for tobacco.

According to another embodiment of this invention, the inhaler may be used to deliver predetermined doses of nicotine to a person for various other reasons. Nicotine is an effective stimulant. The health problems associated with cigarettes are due to the other chemicals and compounds which are present in tobacco. The method of this invention permits controlled doses of nicotine to be delivered to a person. Accordingly, the method may be used to provide nicotine to a person as a stimulant, to increase vigilance or overall performance (eg. accuracy, speed), to control weight or assist in weight loss, or to assist in the treatment of Alzheimer's Disease, Parkinson's Disease or inflammatory bowel disease.

An alternate inhaler for delivering a medicament to the lungs of a user is shown in Figure 3A. Inhaler (70) may comprises a longitudinally extending housing having a first end (72) and a second end (74). As will become more apparent below, inhaler (70) may also include filter (76). A stopper (78) is positioned in each of ends (72) and (74).

Inhaler (70) may be of any particular shape. As shown in Figure 3A, the inhaler may comprises a longitudinally extending cylinder so as to simulate the shape of a cigarette. One of ends (72) and (74) is adapted to deliver a medicament to the mouth of a person. The other of ends (72) and (74) may be of any particular shape.

Inhaler (70) is preferably manufactured from an air impervious or air impregnable material. Preferably, inhaler (70) is also made from a material which would be effectively electrostatically neutral to the medicament which is placed in inhaler (70). The material may be selected from those which will not develop an electrostatic charge which would attract the medicament particles. For example, inhaler (70) may be manufactured from nylon. Alternately, an electrostatically neutral liner or coating may be placed in inhaler (70). In addition, stoppers (78) are also preferably made of an air impervious or air impregnable material and form a airtight seal with ends (72) and (74). Accordingly, when manufactured, the inhaler has a stable internal environment which is not in air flow communication with the surrounding air.

A particulate medicament suitable for absorption into the bloodstream of a person through the lungs of the person and, preferably, through the alveoli and small airway of the person's lungs, is positioned within the inhaler (70). The medicament may be a nicotine formulation of the particle size discussed above. Preferably, the individual medicament particles may vary in size up to about 7 μm, more preferably, up to about 5 μm, and most preferably, up to about 3 μm.

Figures 3B and 3C show a method for the use of inhaler (70). As shown in Figure 3B, mouth end piece (80) may be inserted through stopper (78) at end (72) of inhaler (70). For example, stopper (78) may be a thin walled plastic or rubber member which may be punctured by mouth end piece (80). Accordingly, end (72) of inhaler (70) may itself be sized or adapted so as to be received in the mouth of a person or may be adapted to receive mouth end piece (80). Mouth end piece (80) may include one way valve (82).

Once mouth end piece (80) is inserted through stopper (78) at end (72) of inhaler (70), stopper (78) may be removed from end (74). Accordingly, end (74), inhaler (70) and mouth end piece (80) define an air conduit. When the person inhales, the medicament contained in housing (70) is transported through mouth end piece (80), through one way valve (82) and into the lungs of the person. Preferably, the air conduit is sized so as to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the person and, preferably, the airflow rate is up to about 0.5 L/s.

The inhaler may be manufactured by the steps shown in Figures 4A - 4D. As shown in Figure 4A, inhaler (70) commences as an longitudinally extending member. Filter (76) is positioned at one end of inhaler (70) and filter (84) is provided at the other end of inhaler (70). Preferably, the filters and in particular filter (76) is made from an electrostatically neutral material such as nylon. Filter (84) is sized so as to prevent large particles which may irritate the throat and upper airways from entering inhaler (70). Filter (76) is sized so as to allow minute particles which would be expelled from the lung of the person to exit therethrough while retraining in tube (70) those particles of a sufficient size which would be capable of being absorbed in the lungs of the person. Filter (84) may be sized so as to allow therethrough particles less than 7 μm, preferably less than about 5 μm, more preferably less than about 3 μm and, most preferably less than about 1 μm. Filter (76) may permit particles less than about 0.1 μm from

passing therethrough. Accordingly, when air containing a medicament travels in the direction of the arrow shown in Figure 4A from end (72) to end (74), the larger particles will not enter inhaler (70) and particles which are too small to be retained in the lungs of a person pass completely through inhaler (70). Thus, the particles which are retained in inhaler (70) may conform to the dimension of particles contained in ordinary cigarette smoke (for example 0.5 - 2 μm or more preferably 0.5 - 1 μm).

A sufficient amount of air is passed through filter (72) and (74) to insert a predetermined dosage of medicament in inhaler (70). The dosage inserted into inhaler (70) may be determined based upon the concentration of medicament in the air flow and the particle size range contained in the medicament. The medicament will tend to accumulate around filter (76). Once the predetermined dose of medicament is inserted into inhaler (70), filter (84) may be removed from inhaler (70) by cutting inhaler (70) at point (86) as shown in Figure 4B. As shown in Figure 4C, one way valve (88) may then be inserted at cut end (86) of inhaler (70). Stoppers (78) may then be inserted in ends (86) and (74).

In an alternate embodiment, the step shown in Figure 4C may be omitted and a stopper may be placed in end (86) without installing a one way valve (88). According to this embodiment, the inhaler shown in Figure 3A may be prepared. In another embodiment (not shown) Filter (84) may be part of the machine which injects medicament into inhaler (70). According to this embodiment, the machine would contain an injector (not shown) containing filter (84). The injector would be sized so as to prevent air flowing out end (72) of inhaler (70) thus forcing all of the air and entrained medicament to enter inhaler (70).

When stoppers (78) are removed, and the person inhales, inhalation will cause the medicament to exit the inhaler and enter the airways of the person. The medicament may have a tendency to stick

to the inner walls of inhaler (70) and to filter (76). Accordingly, a rapid inhalation may be required and this may cause an undesirable amount of medicament to impact upon the throat and upper airways of the person. According to a preferred embodiment of the instant invention, the medicament in inhaler (70) is agitated prior to inhalation so as to cause the medicament to draw away from the walls of inhaler (70) and filter (76). This may be achieved by the person shaking inhaler (70) prior to removing stopper (78) and inhaling. Alternately, the medicament in inhaler (70) may be at sub-atmospheric pressure. When one of stoppers (78) is removed, and preferably stopper (78) located at end (74), the in rush of air will cause the medicament to fill inhaler (70). Accordingly, when the other stopper (78) is removed, the person may inhale in a controlled, slow manner so as to draw all of the medicament into the lungs of the person.

Inhaler (70) may be used with any particular medicament, including a nicotine compound as discussed herein. Inhaler (70) provides a simple method of providing a controlled dose of a medicament into the alveoli and small airways of the person's lung without any significant deposition of same in the throat and upper airways which may result in irritation of the throat and upper airways and a reduction in the amount of medicament which is actually absorbed into the bloodstream of the person.

Due to the design of inhaler (70) a relatively large dose of medicament may be placed in inhaler (70). Due to the low momentum which is imparted to the medicament as it leaves inhaler (70) and enters the person's mouth, a large dose of medicament may be inhaled in a single breath. Depending upon the medicament and the dosage which may be required, it is appreciated that it may not be possible, even with the use of inhaler (70) for a person to inhale a full dosage without causing some irritation to the person's throat and upper airways. If the amount of the dosage is sufficiently high, then two or more inhalers (70) may be utilized by the person to achieve a full dose.

Alternately, inhaler (70) may be designed to contain a full dose of medicament but, due to the use of dilution air, several breaths may be required to inhale all of the medicament in inhaler (70). For example, inhaler (70) which is shown in Figure 5A is similar to the inhaler shown in Figure 4D. Accordingly, inhaler (70) has a filter (76) located adjacent end (74) in addition, one way valve (88), which opens at sub-atmospheric pressure, is positioned adjacent end (72). End (72) is sealed by stopper (78). Medicament (90) is generally represented as being located near or on filter (76). As discussed above, if inhaler (70) is manufactured according to the steps set out in Figures 4A - 4D, the medicament will tend to accumulate near or adjacent filter (76).

In order to restrict the amount of air which may be drawn through inhaler (70) with any inhalation, inhaler (70) is provided with end member (92) positioned at end (74) of inhaler (70) and one or more by-pass valve (98). End member (92) seals end (74) of inhaler (70). End member (92) may be formed as an integral part of inhaler (70). End member (92) has longitudinally extending member (94) which is sealed by releasable seal (96). Similarly, by-pass valve (98) is sealed by releasable seal (100).

As discussed above, the medicament in inhaler (70) is preferably agitated so as to disperse medicament (90) throughout inhaler (70) prior to inhalation. One way to achieve this is to manufacture inhaler (78) to be at sub-atmospheric pressure. If this method is utilized, one of the releasable seals may be removed thus allowing air to enter inhaler (70) as shown in Figure 5B. The in rush of air disperses medicament (90) throughout inhaler (70). Subsequently, as shown in Figure 5C, stopper (78) may be removed. Subsequently, as shown in Figure 5D, releasable seal (100) may be removed. Thus, when the person inhales, air is drawn through member (94), through inhaler (70) and through one way valve (88) into the airways of the person. Simultaneously, air enters by-pass valve (98) thus diluting the concentration of medicament (90) in the air inhaled by the person.

Thus, more than one inhalation is required to withdraw all of the medicament from inhaler (70).

By varying the number and size of by-pass valves (98), as well as the size of member (94), the amount of air which flows through inhaler (70) as opposed to by-pass valve (98) may be adjusted thereby controlling the number of inhalations which may be required to withdraw all of the medicament from inhaler (70). Alternately, other modifications may be utilized to control the amount of medicament which is withdrawn from inhaler (70). For example, end member (92) may be replaced by a variable aperture which controls the amount of air which may pass through inhaler (70).

If the medicament in inhaler (70) is nicotine, inhaler (70) may be designed to look like a cigarette. In addition, by appropriately dimensioning by-pass valves (98) and member (94), inhaler (70) may contain an amount of nicotine which is contained in a cigarette. Several inhalations (i.e. puffs) would be required to withdraw all of the medicament in stages from inhaler (70). Thus, not only would the person use inhaler (70) in the same manner as they would smoke a cigarette, but the transportation of nicotine into the person and the absorbtion thereof in the lungs of the person would more closely simulate smoking.

**WE CLAIM:**

1. A method of delivering a medicament including at least one nicotine formulation to a person comprising introducing a predetermined dose of a medicament including at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, from a portable inhaler into the alveoli and lower airways of the person's lungs.

2. A method as claimed in claim 1 wherein the formulation is suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs and the medicament is introduced into the alveoli and small airways of the person's lungs.

3. A method as claimed in claim 1 wherein the predetermined dose comprises from about 0.1 to about 10 mg of nicotine.

4. A method as claimed in claim 1 wherein the predetermined dose comprises from about 0.2 to about 2 mg of nicotine.

5. A method as claimed in claim 1 wherein the predetermined dose comprises from about 0.1 to about 0.5 mg of nicotine.

6. A method as claimed in claim 1 wherein said medicament, upon entry into the airways of the person, includes medicament particles which vary in size up to about 10 μm.

7. A method as claimed in claim 1 wherein said medicament, upon entry into the airways of the person, includes medicament particles which vary in size up to about 5 μm.

8. A method as claimed in claim 1 wherein said medicament, upon entry into the airways of the person, includes medicament particles which vary in size up to about 3 μm.

9. A method as claimed in claim 1 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

10. A method as claimed in claim 7 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 2 L/s upon inhalation by the person.

11. A method as claimed in claim 7 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the person.

12. A method as claimed in claim 7 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

13. A method as claimed in claim 1 and including the step, after introducing said medicament, of preventing said inhaler from introducing a further dosage of said medicament into the person's lung until a timed interval has elapsed.

14. A method as claimed in claim 1 wherein the introduction of said predetermined dose is used as a replacement for tobacco or tobacco substitutes.

15. A method as claimed in claim 1 wherein the introduction of said predetermined dose is used to assist the person to withdraw from nicotine dependency.

16. A method as claimed in claim 1 wherein said inhaler is a low velocity release inhaler.

17. A method as claimed in claim 1 wherein, upon activation of said inhaler, said medicament is released from a container and, upon inhalation by the person, said medicament is dispersed by the said person's breath.

18. A method as claimed in claim 17 wherein said inhaler includes means to mechanically assist the dispersion of said medicament and said method includes the step of mechanically assisting such dispersion.

19. A method as claimed in claim 18 wherein said means to mechanically assist the dispersion includes mixing means adapted to disperse said particles as the person inhales.

20. A method as claimed in claim 19 wherein said mixing means comprises a non-rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said impeller to assist in the dispersion of said medicament.

21. A method as claimed in claim 19 wherein said mixing means comprises a rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said rotating impeller to assist in the dispersion of said medicament.

22. A method as claimed in claim 21 wherein the rotation of said impeller is assisted by mechanical means.

23. A method as claimed in claim 21 wherein the rotation of said impeller is driven by battery operated motor means.

24. A method as claimed in claim 1 wherein, upon activation of said inhaler, said medicament is released from a pressurized container into the air at a

velocity sufficiently slow to be entrained in the air inhaled by the user.

25. A method as claimed in claim 1 wherein said medicament is a particulate medicament.

26. A method as claimed in claim 1 wherein said introduction of said nicotine formulation is used to assist the person to withdraw from cigarette dependency.

27. A method as claimed in claim 1 wherein said introduction of said nicotine formulation is used to provide nicotine to supply the person's tobacco smoking induced nicotine dependency.

28. A method of introducing a medicament comprising at least one nicotine formulation into the lungs of a patient using a portable inhaler having a housing having a first opening and a second opening, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the person and storage means for storing a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the patient's lungs, said method comprising the steps of:

(a) releasing said medicament from said storage means;

(b) dispersing said medicament for inhalation by the person; and,

(c) inhaling said medicament

said medicament being at a velocity sufficiently slow prior to said inhalation to be entrained in the air upon inhalation by the person.

29. A method as claimed in claim 28 wherein the formulation is suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs and the medicament is introduced into the alveoli and small airways of the person's lungs.

30. A method as claimed in claim 28 wherein said inhaler includes means to

mechanically assist the dispersion of said medicament and said method includes the step of mechanically assisting such dispersion.

31. A method as claimed in claim 30 wherein said means to mechanically assist the dispersion includes mixing means adapted to impart disperse said particles as the person inhales.

32. A method as claimed in claim 31 wherein said mixing means comprises a non-rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said impeller to assist in the dispersion of said medicament.

33. A method as claimed in claim 31 wherein said mixing means comprises a rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said rotating impeller to assist in the dispersion of said medicament.

34. A method as claimed in claim 33 wherein the rotation of said impeller is assisted by mechanical means.

35. A method as claimed in claim 28 wherein said medicament is under pressure in said storage means and said medicament is at least partially dispersed by releasing said medicament from said storage means.

36. A method of introducing a medicament into the lungs of a person using a portable inhaler having a housing having a first opening and a second opening, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the person and container means for receiving a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the patient's lungs, said method comprising the steps of:

(a) delivering said medicament to said container means

(b) dispersing said medicament for inhalation by the person; and,

(c) inhaling said medicament

said medicament being at a velocity sufficiently slow prior to said inhalation to be entrained in the air upon inhalation by the person.

37. A method as claimed in claim 36 wherein the formulation is suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs and the medicament is introduced into the alveoli and small airways of the person's lungs.

38. A method as claimed in claim 36 wherein said inhaler includes means to mechanically assist the dispersion of said medicament and said method includes the step of mechanically assisting such dispersion.

39. A method as claimed in claim 38 wherein said means to mechanically assist the dispersion includes mixing means adapted to disperse said particles as the person inhales.

40. A method as claimed in claim 38 wherein said mixing means comprises a non-rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said impeller to assist in the dispersion of said medicament.

41. A method as claimed in claim 38 wherein said mixing means comprises a rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said rotating impeller to assist in the dispersion of said medicament.

42. A method as claimed in claim 40 wherein the rotation of said impeller is assisted by mechanical means.

43. A method as claimed in claim 38 wherein said medicament is under pressure in said storage means and said medicament is at least partially dispersed by releasing said medicament from said storage means.

44. A method as claimed in claim 38 wherein said inhaler is a low velocity release inhaler.

45. A method of manufacturing a portable inhaler for use by a person to introduce a medicament into the patient's lungs, said inhaler having a housing with a first opening and a second opening, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the person comprising the steps of:

(a) placing said housing between first and second filter means;

(b) passing a fluid containing entrained medicament through said first filter means and said second filter means, to deposit said medicament in said housing; and

(c) sealing said first and said second openings, said first filter means being adapted to remove from said fluid particles of the medicament which are sufficiently large to irritate the throat and upper airways of the person, said second filter means being adapted to pass therethrough said fluid and particles which are sufficiently small that they would not be absorbed in the lungs of the person.

46. The method as claimed in claim 45 wherein said second filter means comprises part of said housing.

47. The method as claimed in claim 45 wherein step (b) is conducted at subatmospheric pressure.

48. The method as claimed in claim 45 wherein subsequent to step (b) fluid is

removed from said housing so that, when said housing is sealed, the fluid in said housing is at subatmospheric pressure.

49. A method of assisting a person to withdraw from cigarette dependency comprising introducing a predetermined dose of a non-pressurized, particulate medicament comprising at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, from a breath activated inhaler into the alveoli and small airways of the person's lungs.

50. A method as claimed in claim 49 wherein the predetermined dose is from about 0.1 to about 10 mg of nicotine.

51. A method as claimed in claim 49 wherein the predetermined dose is from about 0.2 to about 2 mg of nicotine.

52. A method as claimed in claim 49 wherein the predetermined dose is from about 0.1 to about 0.5 mg of nicotine.

53. A method as claimed in claim 49 wherein said individual medicament particles vary in size up to about 5 μm.

54. A method as claimed in claim 49 wherein the individual medicament particles vary in size up to about 2 μm.

55. A method as claimed in claim 49 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

56. A method as claimed in claim 53 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

57. A method as claimed in claim 53 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

58. A method as claimed in claim 53 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

59. A method as claimed in claim 49 and including the step, after introducing said medicament, of preventing said inhaler from introducing a further dosage of said medicament into said person's lung until a timed interval has elapsed.

60. A method as claimed in claim 49 wherein the introduction of said predetermined dose is used as a tobacco substitute.

61. A method as claimed in claim 49 wherein the introduction of said predetermined dose is used to assist the person to withdraw from nicotine dependency.

62. A method as claimed in claim 49 wherein said medicament is dispersed in said person's breath and including the step of mechanically affixing such dispersion.

63. A method of providing nicotine to supply a person's tobacco smoking induced nicotine dependency comprising introducing a predetermined dose of a non-pressurized, particulate medicament comprising at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, from a breath activated inhaler into the alveoli and small airways of the person's lungs.

64. A method as claimed in claim 63 wherein the predetermined dose is from

about 0.1 to about 10 mg of nicotine.

65. A method as claimed in claim 63 wherein the predetermined dose is from about 0.2 to about 2 mg of nicotine.

66. A method as claimed in claim 63 wherein the predetermined dose is from about 0.1 to about 0.5 mg of nicotine.

67. A method as claimed in claim 63 wherein said individual medicament particles vary in size up to about 5 μm.

68. A method as claimed in claim 63 wherein the individual medicament particles vary in size up to about 2 μm.

69. A method as claimed in claim 63 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

70. A method as claimed in claim 67 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

71. A method as claimed in claim 67 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

72. A method as claimed in claim 67 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

73. A method as claimed in claim 63 and including the step, after introducing said medicament, of prevent said inhaler from introducing a further dosage of said medicament into said person's lung until a timed interval has elapsed.

74. A method of assisting a person to withdraw from tobacco induced nicotine dependency, comprising introducing a predetermined dose of a non-pressurized, particulate medicament comprising at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs into a breath activated inhaler for use by said person as a cigarette substitute.

75. A method as claimed in claim 74 wherein the predetermined dose is from about 0.1 to about 10 mg of nicotine.

76. A method as claimed in claim 74 wherein the predetermined dose is from about 0.2 to about 2 mg of nicotine.

77. A method as claimed in claim 74 wherein the predetermined dose is from about 0.1 to about 0.5 mg of nicotine.

78. A method as claimed in claim 74 wherein said individual medicament particles vary in size up to about 5 μm.

79. A method as claimed in claim 74 wherein the individual medicament particles vary in size up to about 2 μm.

80. A method as claimed in claim 74 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

81. A method as claimed in claim 78 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

82. A method as claimed in claim 78 wherein said inhaler has an air conduit

which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

83. A method as claimed in claim 78 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

84. A method as claimed in claim 74 and including the step, after introducing said medicament, of prevent said inhaler from introducing a further dosage of said medicament into said person's lung until a timed interval has elapsed.

85. A method of introducing a medicament into the lungs of a patient using a breath activated inhaler having a housing having a first opening and a second opening, said first opening and said second opening being releasably sealed, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the patient; and, a non-pressurized, particulate medicament suitable for absorption into the bloodstream of the patient through the alveoli and small airways of the patient's lungs positioned in said housing, said method comprising the steps of:

(a) agitating said medicament in said housing to disperse said medicament throughout said housing;

(b) releasing said seals on said first and second openings; and

(c) inhaling said medicament

said medicament being under sub-atmospheric pressure in said sealed housing and said medicament being dispersed by releasing said seal on said other of said first and second openings.

86. The method as claimed in claim 85 wherein said individual medicament particles vary in size up to about 2 μm.

87. The method as claimed in claim 86 wherein said individual medicament particles vary in size up to about 1 μm.

88. The method as claimed in claim 85 wherein, when said seals are removed, said first and second openings and said housing define an air conduit and said air conduit is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

89. The method as claimed in claim 88 wherein, when said seals are removed, said first and second openings and said housing define an air conduit and said air conduit is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

90. The method as claimed in claim 85 wherein, the breath activated inhaler includes by-pass air feed means for supplying air to dilute the air passing through said housing so as to reduce the concentration of the medicament in the air which is inhaled by the patient.

91. The method as claimed in claim 90 wherein said by-pass air feed means is located near said one of said first opening and said second opening which is adapted to deliver the medicament to the mouth of the patient.

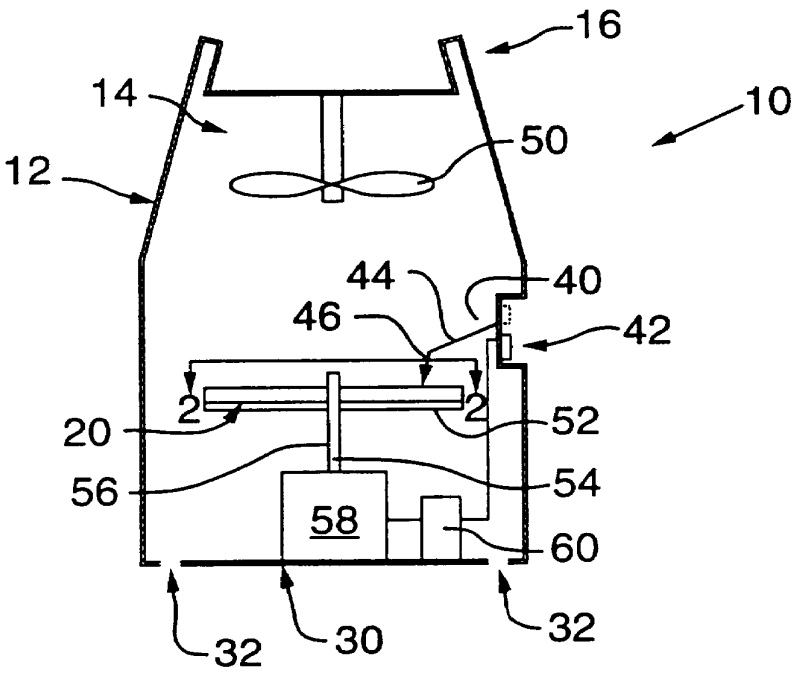



FIG.1

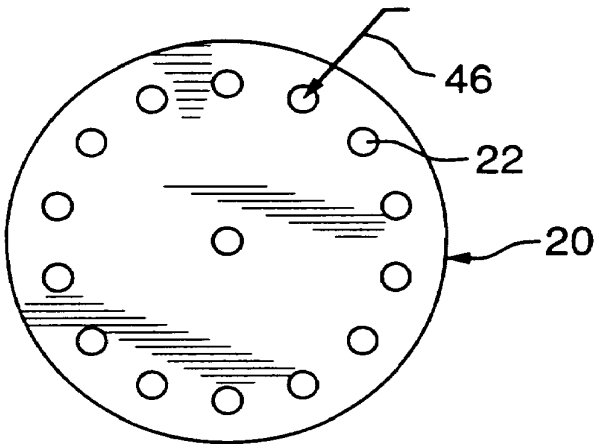



FIG.2

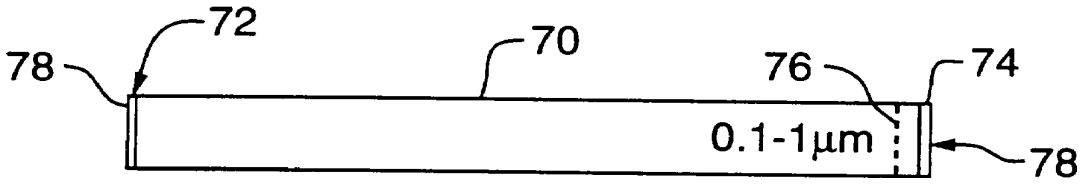



FIG.3A

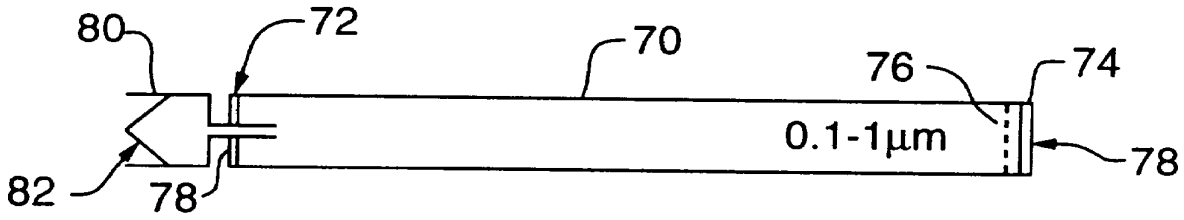



FIG.3B

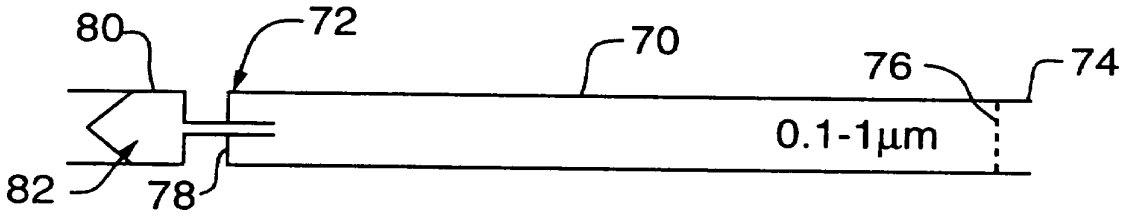



FIG.3C

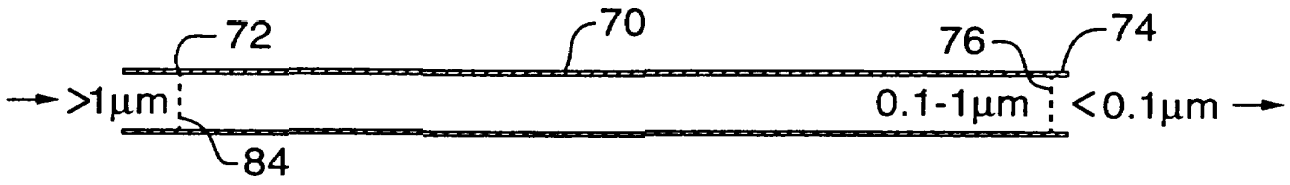



FIG.4A

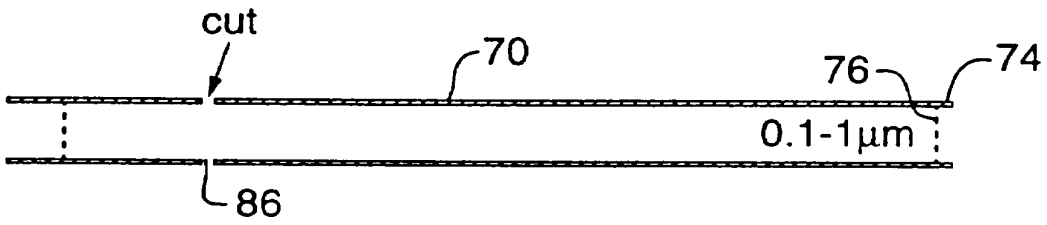



FIG.4B

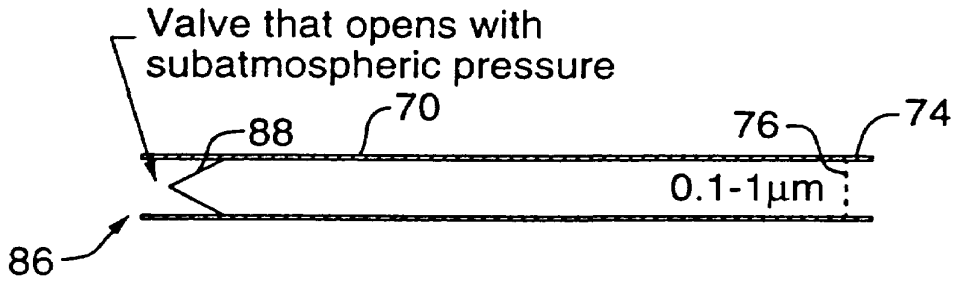



FIG.4C

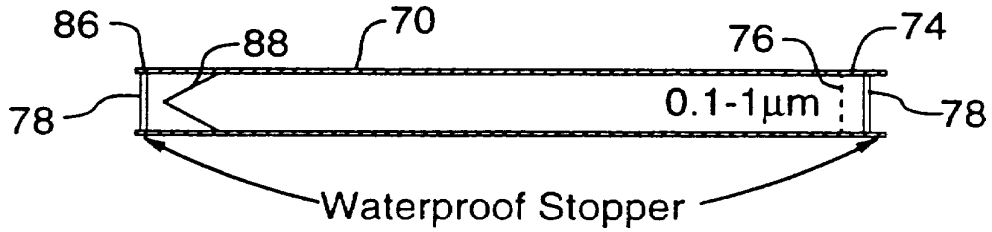



FIG.4D

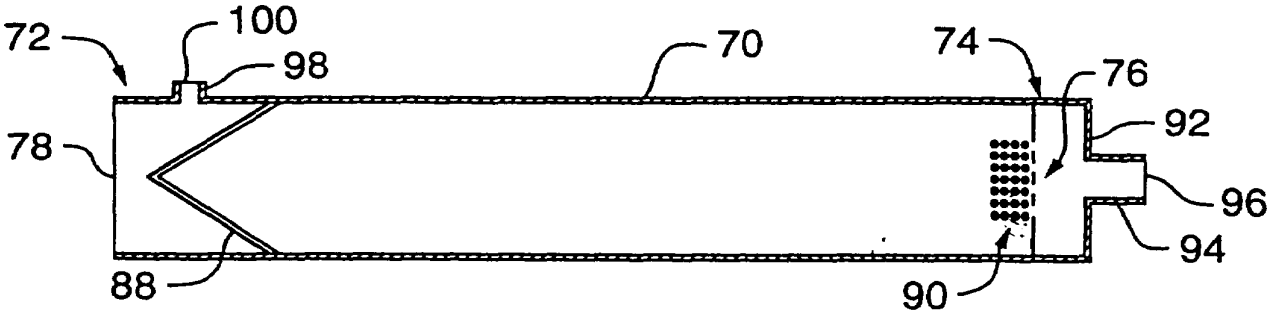



FIG.5A

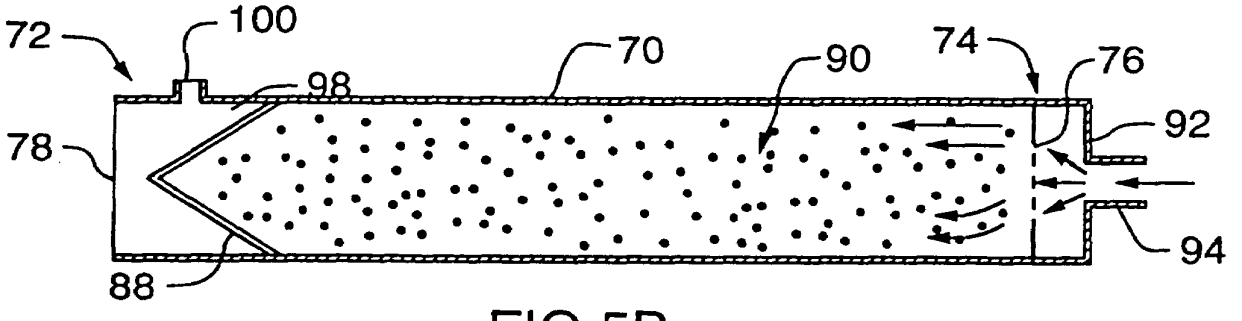



FIG.5B

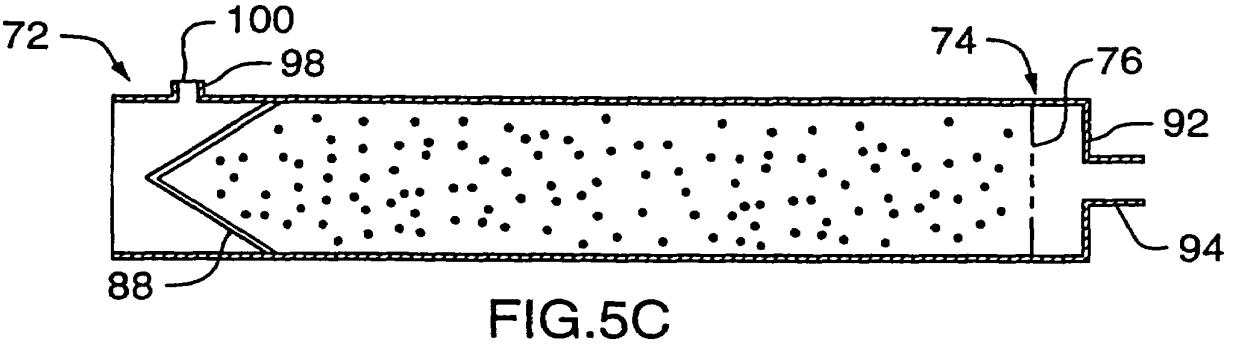



FIG.5C

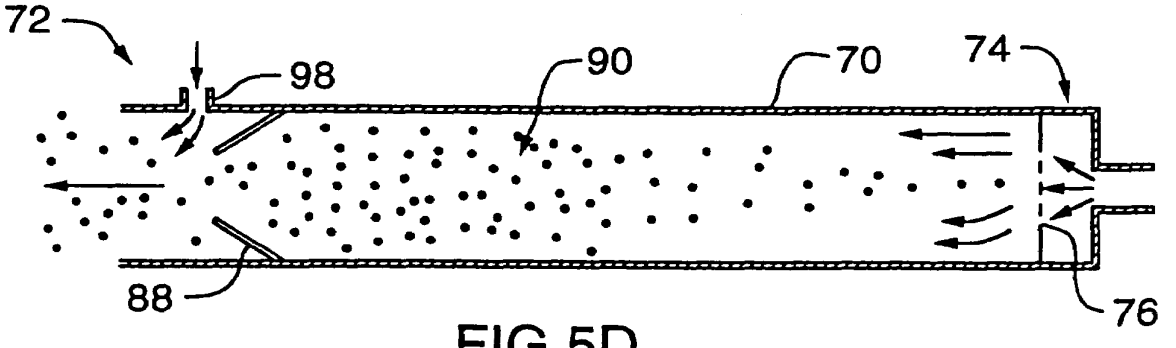



FIG.5D

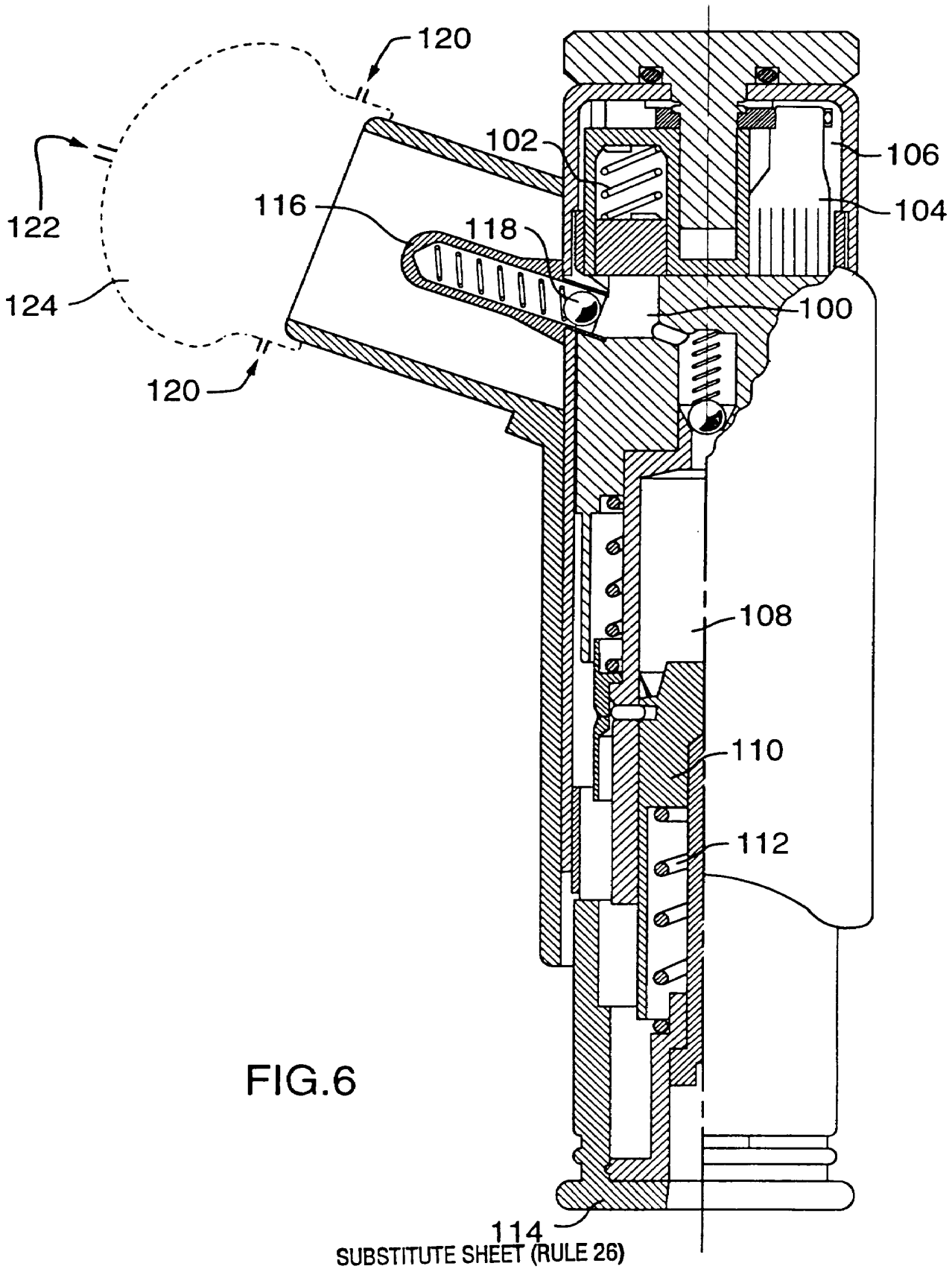



FIG.6

# INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/CA 95/00562

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M15/06 A61M15/00 A61K9/00 A24F47/00

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 A24F A61K

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. |
|---|---|---|
| A | US,A,5 441 060 (ROSE ET AL.) 15 August 1995<br>see abstract; figures | 45-48 |
| A | US,A,4 655 229 (SENSABAUGH ET AL.) 7 April 1987<br>see abstract; figures | 45-48 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

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2

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|---|---|
| 17 May 1996 | 06.06.96 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: ( + 31-70) 340-3016 | Villeneuve, J-M |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA95/00562

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-44,49-91
because they relate to subject matter not required to be searched by this Authority, namely:
PCT Rule 39.1 (iv)

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 95/00562

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| US-A-5441060 | 15-08-95 | AU-B- | 6171994 | 29-08-94 |
| | | EP-A- | 0683632 | 29-11-95 |
| | | WO-A- | 9417679 | 18-08-94 |
| US-A-4655229 | 07-04-87 | AU-B- | 3664184 | 08-08-85 |
| | | CA-A- | 1227713 | 06-10-87 |
| | | EP-A- | 0150810 | 07-08-85 |
| | | JP-A- | 60192581 | 01-10-85 |

Form PCT/ISA/210 (patent family annex) (July 1992)

**PCT** WELTORGANISATION FÜR GEISTIGES EIGENTUM
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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) -

| (51) Internationale Patentklassifikation 7 : | | (11) Internationale Veröffentlichungsnummer: **WO 00/28842** |
|---|---|---|
| **A24F 47/00** | **A1** | (43) Internationales Veröffentlichungsdatum: 25. Mai 2000 (25.05.00) |

(21) **Internationales Aktenzeichen:** PCT/EP99/08427

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(30) **Prioritätsdaten:**
198 54 009.4 12. November 1998 (12.11.98) DE

(71) **Anmelder** *(für alle Bestimmungsstaaten ausser US)*: H.F. & PH.F. REEMTSMA GMBH [DE/DE]; Parkstrasse 51, D–22605 Hamburg (DE).

(72) **Erfinder; und**
(75) **Erfinder/Anmelder** *(nur für US)*: WILDENAU, Wolfgang [DE/DE]; Hartwigsahl 17, D–23863 Bargfeld–Stegen (DE).

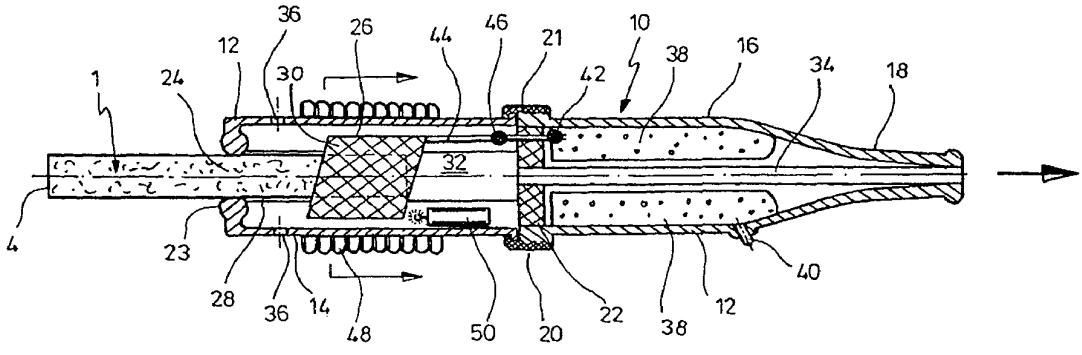
(74) **Anwälte:** BOTH, Georg usw.; Uexküll & Stolberg, Beselerstrasse 4, D–22607 Hamburg (DE).

(81) **Bestimmungsstaaten:** AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Veröffentlicht**
*Mit internationalem Recherchenbericht.*
*Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.*

(54) **Title:** SYSTEM FOR SUPPLYING AN INHALABLE AEROSOL

(54) **Bezeichnung:** SYSTEM ZUR BEREITSTELLUNG EINES INHALIERBAREN AEROSOLS




(57) **Abstract**

A system for supplying an inhalable aerosol contains an inhaling device (10) which has a rod–shaped housing (12) with a rear, mouth–end area (16) and a front area (14). A substrate holder (26), which can be heated by a heating device (30, 38, 44, 50), is situated in the front area (14) of the housing (12) and is accessible via a loading opening (24) that is preferably located at the front end (23) of the housing (12). A flow channel (34) leads from the substrate holder (26) to the rear end of the housing (12). The heating device (30, 38, 44, 50) is configured for generating heat by thermal or catalytic combustion. A substrate portion (1) that is configured for introducing into the substrate holder (26) through the loading opening (24) contains aerosol–forming material inside a casing which has an air inlet and an aerosol outlet.

(57) **Zusammenfassung**

Ein System zur Bereitstellung eines inhalierbaren Aerosols enthält eine Inhaliervorrichtung (10), die ein stabartiges Gehäuse (12) mit einem hinteren mundseitigen Bereich (16) und einem vorderen Bereich (14) aufweist. Im vorderen Bereich (14) des Gehäuses (12) ist eine von einer Heizeinrichtung (30, 38, 44, 50) beheizbare Substrathalterung (26) angeordnet, die über eine vorzugsweise an der Vorderseite (23) des Gehäuses (12) befindliche Beschickungsöffnung (24) zugänglich ist. Ein Strömungskanal (34) führt von der Substrathalterung (26) bis zum hinteren Ende des Gehäuses (12). Die Heizeinrichtung (30, 38, 44, 50) ist dazu eingerichtet, durch thermische oder katalytische Verbrennung Wärme zu erzeugen. Eine Substratportion (1), die zum Einsetzen in die Substrathalterung (26) durch die Beschickungsöffnung (24) eingerichtet ist, enthält innerhalb einer Umhüllung, die eine Lufteintrittsöffnung und eine Aerosolaustrittsöffnung aufweist, aerosolbildendes Materials.

*LEDIGLICH ZUR INFORMATION*

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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# System zur Bereitstellung eines inhalierbaren Aerosols

Die Erfindung betrifft ein System zur Bereitstellung eines inhalierbaren Aerosols sowie Komponenten eines derartigen Systems. Dieses System ist insbesondere als Rauchartikel zur Bereitstellung von Rauchaerosol für Raucher geeignet.

Beim Abrauchen konventioneller Cigaretten wird der größte Teil des Tabaks nicht während der Züge, sondern in den Zugpausen verbrannt. Dies führt zur Bildung des sogenannten Nebenstromrauches, der von Nichtrauchern oft als belästigend empfunden wird.

Zur Überwindung dieses Problems sind zahlreiche neue Rauchartikel vorgeschlagen worden. Ein gemeinsames Prinzip solcher Entwicklungen ist, daß nicht die Verbrennungswärme des Tabaks, sondern andere Energiequellen zur Freisetzung des Rauchaerosols genutzt werden. Hierdurch wird die Entstehung von Nebenstromrauch weitgehend vermieden. Häufig kommen in den vorgeschlagenen Rauchartikeln zur Aerosolbildung statt Tabak Ersatzmaterialien wie spezielle Folientabake oder mit Aromasubstanzen beaufschlagte Trägermaterialien zur Anwendung.

So werden in den US-Patenten 5 060 666, 5 067 499 und 5 099 861 cigarettenähnliche Rauchartikel beschrieben, bei denen die Wärme-

energie eines glimmenden Kohleelements auf aerosolbildendes Material übertragen wird, das neben Tabak oder Tabakextrakten Aromen und einen Aerosolbildner wie Glycerin enthält. Dabei werden die Verbrennungsgase des Heizelements mit dem Rauchaerosol inhaliert, was zu einer erhöhten Aufnahme von Kohlenmonoxid durch den Raucher führt. Weiterhin muß der gesamte Rauchartikel nach dem Abrauchen entsorgt werden, was einen erhöhten Anfall komplex zusammengesetzter Reststoffe und damit verbundene Entsorgungsprobleme zur Folge hat.

Es sind auch Vorrichtungen bekannt, bei denen mittels elektrischer Energie eine Substratportion erwärmt wird, um Rauchaerosol freizusetzen. Eine derartige Vorrichtung, die in der Hand gehalten werden muß und wegen ihrer Größe und ihres Gewichts nicht im Mund tragbar ist, ist in dem US-Patent 4 141 369 beschrieben. Weitere cigarettenähnliche Rauchartikel, in denen spezielle Tabakaromensubstrate mittels Batteriestrom elektrisch beheizt werden und dabei ein inhalierbares Aerosol ergeben, sind in den US-Patenten 5 095 921, 5 179 666 und 5 269 327 offenbart. Eine Cigarette für ein elektrisch beheiztes Rauchsystem zeigt das US-Patent 5 499 636. Alle diese Vorrichtungen sind jedoch relativ schwer und unhandlich.

Aus dem US-Patent 4 474 181 sind Rauchvorrichtungen bekannt, bei denen Nikotin und tabaksimulierende Substanzen indirekt, z.B. über brennbare Celluloseschäume, erwärmt und inhaliert werden.

Die WO 97/48294 zeigt ein weiteres System zur Bereitstellung eines inhalierbaren Aerosols. Dabei befinden sich in einem in der Hand zu haltenden Gehäuse ein Brenner und ein Heizmitteltank, der ein Heizmittel zum Betreiben des Brenners enthält. Die aufsteigenden, heißen Verbrennungsgase strömen durch einen Wärmetauscher, in dem Ventilationskanäle angeordnet sind. Die Ventilationskanäle stehen mit einem Ende mit der Außenluft in Verbindung und münden mit dem anderen Ende in einen vom oberen Bereich des Gehäuses ausgehenden rohrartigen Strömungskanal, der an seinem

freien Ende als Mundstück ausgestaltet ist. Der mittlere Abschnitt des Strömungskanals wird von einer Substratportion eingenommen, die durch die von dem Benutzer eingesogene und über den Wärmetauscher erwärmte Luft indirekt beheizt wird, um Aerosol freizusetzen. Auch dieses System ist relativ schwer und unhandlich und muß geöffnet werden, um eine neue Substratportion einzusetzen.

Es ist Aufgabe der Erfindung, ein leichtes, handliches und von einem Benutzer im Mund tragbares System zur Bereitstellung eines inhalierbaren Aerosols zu schaffen, das eine wiederverwendbare Inhaliervorrichtung enthält und insbesondere als Rauchartikel dienen kann, der einen ähnlichen Geschmackseindruck wie herkömmliche Cigaretten bietet, bei dessen Gebrauch jedoch zwischen den Zügen kein Nebenstromrauch erzeugt wird.

Diese Aufgabe wird gelöst durch ein System mit den Merkmalen des Anspruch 1, das eine Inhaliervorrichtung mit den Merkmalen des Anspruchs 26 und eine Substratportion mit den Merkmalen des Anspruchs 28 aufweist. Vorteilhafte Ausgestaltungen der Erfindung ergeben sich aus den abhängigen Ansprüchen.

Das erfindungsgemäße System zur Bereitstellung eines inhalierbaren Aerosols weist eine Inhaliervorrichtung auf, die ein stabartiges Gehäuse mit einem hinteren mundseitigen Bereich und einem vorderen Bereich hat. Im vorderen Bereich des Gehäuses ist eine von einer Heizeinrichtung beheizbare Substrathalterung angeordnet, die über eine vorzugsweise an der Vorderseite des Gehäuses befindliche Beschickungsöffnung zugänglich ist. Ein Strömungskanal führt von der Substrathalterung bis zum hinteren Ende des Gehäuses. Die Heizeinrichtung ist dazu eingerichtet, durch thermische oder katalytische Verbrennung Wärme zu erzeugen, wobei vorzugsweise ein Heizmitteltank im hinteren Bereich des Gehäuses angeordnet ist. Das System enthält ferner eine Substratportion, die zum Einsetzen in die Substrathalterung durch die Beschickungsöffnung eingerichtet ist und die innerhalb einer

Umhüllung, die eine Lufteintrittsöffnung und eine Aerosolaustrittsöffnung aufweist, aerosolbildendes Material enthält.

Da die zum Erhitzen des Aerosols benötigte Energie einem gasförmigen und/oder flüssigen Heizmittel entnommen wird, steht ein kostengünstiger und leicht zu beschaffender Energieträger hoher Energiedichte zur Verfügung. Die Inhaliervorrichtung kann daher selbst dann, wenn sie einen vollen Heizmitteltank enthält, so leicht und handlich konstruiert sein, daß sie von einem Benutzer problemlos im Mund getragen werden kann. Dabei liegt das stabartige Gehäuse gut in der Hand und vermittelt dem Benutzer in etwa das Gefühl, eine Cigarette mit einer Cigarettenspitze oder eine Cigarre zu rauchen. Die Substratportion ist im vorderen Bereich des stabartigen Gehäuses in die beheizbare Substrathalterung eingesetzt, und zwar über eine Beschickungsöffnung, die sich vorzugsweise an der Vorderseite des Gehäuses befindet. Dies verstärkt noch den Eindruck, eine Cigarre oder Cigarette mit Cigarettenspitze zu verwenden. Die Substratportion wird über die beheizbare Substrathalterung erwärmt, um inhalierbares Aerosol freizusetzen, das über den Strömungskanal bis zum hinteren Ende des Gehäuses geführt wird.

Im hinteren Bereich des Gehäuses kann die Inhaliervorrichtung ein Mundstück aufweisen, das mit dem Strömungskanal in Verbindung steht und vorzugsweise schlecht wärmeleitend ist, damit für den Benutzer keine unangenehmen hohen Temperaturen auftreten. Anstelle des Mundstücks ist es denkbar, einen als Filtermundstück gestalteten Filter im hinteren Bereich des Gehäuses in den Strömungskanal einzusetzen. Bei einer Variante ist ein Filter an einer anderen Stelle in den Strömungskanal einsetzbar; eine derartige Ausgestaltung kann auch im Zusammenhang mit einem festen Mundstück benutzt werden.

Bei einer bevorzugten Ausgestaltung weist die Substrathalterung der Inhaliervorrichtung mindestens eine Heizfläche auf, die vorzugsweise hohlzylindrisch oder rinnenartig ist. Die Sub-

strathalterung kann beispielsweise zwei parallel zueinander angeordnete Heizflächen haben, deren gegenseitiger Abstand vorzugsweise einstellbar ist. Dabei ist es denkbar, daß die Einstellung des Abstands in Abhängigkeit von der Temperatur automatisch erfolgt, z.B. mit Hilfe einer Bimetallschiene. Bei einer bevorzugten Ausgestaltung weist die Substrathalterung der Inhaliervorrichtung innerhalb der Heizflächen einen vorzugsweise mit Bohrungen versehenen gut wärmeleitenden Mantel auf, der dazu eingerichtet ist, an einer in die Substrathalterung eingesetzten Substratportion anzuliegen. Diese Ausführungsformen gewährleisten einen guten thermischen Kontakt (entweder direkt über die Heizflächen oder über den wärmeleitenden Mantel) zwischen den Heizflächen und der Zone der Substratportion, die sich im Bereich der Heizflächen befindet. Die Heizflächen oder der Mantel müssen die Substratportion aber nicht direkt berühren; Ausführungsformen, bei denen ein Abstand zur Substratportion vorgesehen ist und der Wärmetransport z.B. durch Strahlung erfolgt, sind ebenfalls denkbar.

Vorzugsweise weist die Substrathalterung der Inhaliervorrichtung hinter den Heizflächen einen hinteren Hohlraum auf, in den der hintere Bereich einer eingesetzten Substratportion einschiebbar ist. Diese Ausgestaltung erlaubt es dem Benutzer, eine Substratportion abschnittsweise zu erwärmen und das freigesetzte Aerosol zu inhalieren. Dabei schiebt er die Substratportion nach und nach, vorzugsweise nach jedem Zug, ein Stück weiter nach hinten, wobei der verbrauchte Teil der Substratportion von dem hinteren Hohlraum aufgenommen wird, bis die gesamte Substratportion verbraucht (abgeraucht) ist. Um zu verhindern, daß die Substratportion zu weit in das Gehäuse der Inhaliervorrichtung eingeschoben wird, kann am hinteren Ende des hinteren Hohlraums ein Anschlag für die Substratportion vorgesehen sein.

Bei einer bevorzugten Ausführungsform sind die Heizflächen der Inhaliervorrichtung dazu eingerichtet, durch katalytische Verbrennung eines gasförmigen und/oder flüssigen Heizmittels

beheizt zu werden. Eine katalytische Verbrennung vermeidet Schwierigkeiten bei der Flammenführung der Heizeinrichtung, was einer kompakten Bauweise zugutekommt.

Ein vorzugsweise von außen nachfüllbarer Heizmitteltank kann im hinteren Bereich des Gehäuses der Inhaliervorrichtung angeordnet sein. Alternativ ist eine Ausgestaltung denkbar, bei der eine austauschbare Nachfüllpatrone mit Heizmittel in das Gehäuse eingesetzt wird. Als Heizmittel kommen übliche brennbare Substanzen in Frage, die bei Zimmertemperatur flüssig oder gasförmig sein können, wie in den Ansprüchen im einzelnen angegeben.

Die Inhaliervorrichtung kann eine Schalteinrichtung aufweisen, die mit einer zum Zünden des Heizmittels eingerichteten, vorzugsweise piezoelektrisch arbeitenden Zündeinrichtung und einer zum Freigeben von Heizmittel aus dem Heizmitteltank eingerichteten Ventileinrichtung in Verbindung steht. Bei einer bevorzugten Ausführungsform ist die Schalteinrichtung rein mechanisch gestaltet und weist einen axial auf dem vorderen Bereich des Gehäuses der Inhaliervorrichtung verschiebbaren, vorzugsweise schlecht wärmeleitenden Ring auf, der vorzugsweise in zwei Stellungen fixierbar ist. So kann beispielsweise der piezoelektrisch bewirkte Zündvorgang durch Verschieben des Rings ausgelöst werden, wobei sich gleichzeitig die Ventileinrichtung öffnet, um Heizmittel für die katalytische Verbrennung freizugeben; danach wird der Ring zum Arretieren verdreht, wobei die Ventileinrichtung geöffnet bleibt und der Heizvorgang andauert. Wenn genügend Zeit verstrichen ist, z.B. nach Beenden eines Zuges, kann der Benutzer den Ring durch Zurückdrehen entarretieren und in seine Ausgangsposition zurückschieben, was vorzugsweise mit Unterstützung einer Feder erfolgt, so daß sich die Ventileinrichtung wieder schließt und der Heizvorgang beendet ist.

Vorzugsweise weist der vordere Bereich des Gehäuses der Inhaliervorrichtung Luftzutrittsöffnungen zum Zuführen von Verbrennungsluft zu der Heizeinrichtung auf. Die von der Heizeinrichtung ausgehenden Verbrennungsgase (im wesentlichen Kohlendioxid und Wasser) treten bei einer bevorzugten Ausführungsform der Erfindung zu dem inhalierbaren Aerosol hinzu, wobei durch die Züge des Benutzers eine günstige Luft-, Verbrennungsgas- und Aerosolführung erreichbar ist. Insbesondere bei einer katalytischen Verbrennung enthalten die Verbrennungsgase so geringe Mengen an schädlichen Substanzen wie z.B. Kohlenmonoxid, daß dies unbedenklich ist. In einer anderen bevorzugten Ausführungsform der Erfindung werden dagegen die Verbrennungsgase von dem inhalierbaren Aerosol ferngehalten.

Bei einer vorteilhaften Ausgestaltung hat das Gehäuse der Inhaliervorrichtung vor einer bei Betrieb der Heizeinrichtung leuchtenden Komponente, z.B. einer Heizfläche, ein Fenster. Der Benutzer kann dann auf einfache Weise den Betriebszustand der Inhaliervorrichtung kontrollieren.

Das Gehäuse der Inhaliervorrichtung kann einteilig oder mehrteilig ausgestaltet sein. Im letzteren Fall ist es vorzugsweise zweiteilig und weist eine lösbare Verbindung auf, z.B. im mittleren Bereich zwischen dem vorderen Bereich des Gehäuses, in dem die beheizbare Substrathalterung angeordnet ist, und dem hinteren Bereich des Gehäuses, in dem sich der Heizmitteltank befindet. An der lösbaren Verbindung kann das Gehäuse geöffnet werden, z.B. für Reinigungszwecke. Das Material für das Gehäuse der Inhaliervorrichtung sollte wärmebeständig sein. So kommen Duroplaste, mehrkomponentige Kunststoffe, Harthölzer, Edelhölzer, Wurzelholz und/oder Metall in Frage.

Die Substratportion hat vorzugsweise eine zylindrische Form, wobei die Umhüllung als Zylindermantel angeordnet ist und die Stirnseiten des Zylinders als Lufteintrittsöffnung und als Aerosolaustrittsöffnung eingerichtet sind. Dabei ist die

Umhüllung vorzugsweise niedrigporös bis luftundurchlässig, um einen Nebenstromrauch zu vermeiden. In ihrem vorderen Bereich kann die Substratportion eine Isolierumhüllung aufweisen, die vorzugsweise über das vordere Ende der Umhüllung vorsteht, damit der Benutzer beim Zurückschieben der Substratportion in das Gehäuse der Inhaliervorrichtung nicht mit heißen Flächen in Berührung kommt. Das aerosolbildende Material der Substratportion kann ein weitgehend inertes Trägermaterial oder Tabakmaterial und zusätzliche Zuschlagstoffe aufweisen. Vorzugsweise enthält das Material einen höheren Anteil an Polyolen, die als Aerosolbildner dienen. Denkbar ist es auch, daß die Substratportion eine dünne, filterlose an sich handelsübliche Cigarette ist, die Polyole mit einem Anteil von 5 Gew.-% bis 10 Gew.-% aufweist. Einzelheiten über mögliche Ausgestaltungen der Substratportion finden sich in den Ansprüchen.

Im folgenden wird die Erfindung anhand eines Ausführungsbeispiels näher erläutert. Die Zeichnungen zeigen in:

Figur 1 einen schematischen Längsschnitt durch ein als Rauchartikel gestaltetes erfindungsgemäßes System zur Bereitstellung eines inhalierbaren Aerosols, bei dem eine Substratportion in eine Inhaliervorrichtung eingesetzt ist, und

Figur 2 einen Längsschnitt durch eine Substratportion.

In Figur 1 ist dargestellt, wie eine Substratportion 1 in eine als Rauchgerät dienende Inhaliervorrichtung eingesetzt ist. Figur 2 zeigt die Substratportion 1 genauer. Bei dieser Ausführungsform der Substratportion 1 befindet sich aerosolbildendes Material 2 innerhalb einer zylindrischen Umhüllung 3. Die Umhüllung 3 läßt die Stirnseiten des Zylinders frei, so daß dort eine Lufteintrittsöffnung 4 und eine Aerosolaustrittsöffnung 5 ausgebildet sind.

Das aerosolbildende Material 2 kann z.B. geschnittenen Blattabak, geschnittene Tabakrippen, rekonstituierten Tabak oder ein mit Aromasubstanzen behandeltes Trägermaterial aufweisen. Der Einsatz von Blatt- und Rippenschnitt kann auch in expandierter Form erfolgen. Als Trägermaterialien für Aromastoffe können sowohl organische Materialien wie z.B. Papier oder Cellulosefasern, als auch anorganische Materialien wie z.B. Silicagel zur Anwendung kommen. Auch beliebige Mischungen der genannten Komponenten sind einsetzbar. In den Ansprüchen sind zahlreiche Komponenten und Bestandteile für das aerosolbildende Material genannt, so daß zahlreiche Varianten denkbar sind.

Um die Aerosolbildung zu verstärken, enthält das aerosolbildende Material 2 vorzugsweise einen hohen Anteil eines Polyols oder mehrerer Polyole, z.B. Glycerin und/oder Propylenglykol, z.B. beim Einsatz von weitgehend inerten Trägermaterialien wie Aluminiumoxid, Silicagel, Aktivkohle, Cellulosefasern, Ligningranulat, Zeolithen, Tonerden oder Meerschaum oder Kombinationen davon im Bereich von 10 Gew.-% bis 60 Gew.-%. Beim Einsatz von Tabakmaterialien beträgt der bevorzugte Anteil der Polyole 10 Gew.-% bis 40 Gew.-%. Eine andere Möglichkeit, die Aerosolbildung zu verstärken, ist der Einsatz der aerosolbildenden Materialien mit einer Feuchte, die deutlich über der Gleichgewichtsfeuchte liegt; so kann z.B. Tabak, dessen Gleichgewichtsfeuchte ca. 10% bis 12% beträgt, mit einer Feuchte von 20% verwendet werden. In diesem Fall ist durch eine geeignete Verpackung dafür zu sorgen, daß bis zum Gebrauch kein Feuchteverlust auftritt.

Die Umhüllung 3 kann aus Papier, Kunststoffolie oder Metallfolie bestehen. Auch eine mehrlagige Umhüllung aus den genannten Komponenten ist verwendbar. Bevorzugt wird jedoch eine einlagige Umhüllung aus Papier oder metallkaschiertem Papier. Besonders vorteilhaft ist niedrigporöses oder nahezu luftundurchlässiges Cigarettenpapier, das vorzugsweise einen hohen Anteil an mineralischen Zuschlagstoffen hat. Dies gewährleistet, daß beim

Erwärmen und Abrauchen der Substratportion praktisch kein Nebenstromrauch auftritt.

Bei einer bevorzugten Ausgestaltung ist die Substratportion 1 in ihrem vorderen Bereich, d.h. im Bereich der Lufteintrittsöffnung 4, von einer zusätzlichen Isolierumhüllung (in den Figuren 1 und 2 nicht eingezeichnet) umgeben, die vorzugsweise über das vordere Ende der Umhüllung 3 vorsteht. Diese Isolierumhüllung gewährleistet, daß der Benutzer nicht mit unangenehm heißen Flächen in Berührung kommt, wenn er die Substratportion 1 beim Abrauchen tiefer in die Inhaliervorrichtung einschiebt (siehe unten).

Es ist auch denkbar, als Substratportion eine dünne, filterlose, an sich handelsübliche Cigarette zu verwenden, die Polyole mit einem Anteil von 5 Gew.-% bis 10 Gew.-% aufweist.

Im folgenden sind zwei weitere Beispiele für Ausgestaltungen der Substratportion 1 beschrieben.

Beispiel 1

Eine American-Blend-Tabakmischung mit einem Gehalt von 30% Burley-Tabak, 40% expandiertem Virginia-Tabak, 20% nicht-expandiertem Virginia-Tabak und 10% Orient-Tabak wurde konditioniert und mit 12 Gew.-% eines wäßrigen Casings mit einem Glyceringehalt von 80 Gew.-% besprüht. Anschließend wurde der Tabak mit 0,8 mm Schnittbreite geschnitten und auf eine Feuchte von 12% abgetrocknet. 180 kg dieses Schnittabaks wurden mit 20 kg expandiertem Rippenschnitt vermischt. Aus dieser Mischung wurde auf einer Cigarettenstrangmaschine ein Endlosstrang mit einem Durchmesser von 5 mm und einer Stopfdichte von 200 mg/ml hergestellt. Als Umhüllungsmaterial kam ein auf der Außenseite aluminiumkaschiertes, luftundurchlässiges Papier zum Einsatz. Der Endlosstrang wurde in Einzelportionen von 40 mm Länge geschnitten.

Beispiel 2

Ein nach bekannten Verfahren hergestellter Papierfolientabak mit einem Gehalt an Propylenglykol von 12 Gew.-% wurde mit einer Schnittbreite von 0,8 mm geschnitten, wie in Beispiel 1 einer Cigarettenstrangmaschine zugeführt und in dieser mit einem Cigarettenpapier umhüllt, wobei das Cigarettenpapier eine Luftdurchlässigkeit von 5 CU aufwies. Durch Ablängen des Endlosstranges (6 mm Durchmesser) erhielt man Substratportionen mit einer jeweiligen Länge von 50 mm; die Stopfdichte betrug 240 mg/ml.

Im Prinzip ist auch die Verwendung einer Substratportion denkbar, die hinter der Aerosolaustrittsöffnung 5 mit einem handelsüblichen Filter versehen ist. Dabei muß allerdings gewährleistet sein, daß beim Einsetzen einer derartigen Substratportion in die Inhaliervorrichtung nicht der Filter, sondern das aerosolbildende Material 2 vor dem Filter erwärmt wird.

Figur 1 zeigt in einem schematischen Längsschnitt eine Ausführungsform einer Inhaliervorichtung 10. Die Inhaliervorichtung 10 hat ein stabartiges oder cigarrenformartiges Gehäuse 12 mit einem vorderen Bereich 14 und einem hinteren mundseitigen Bereich 16. Das hintere Endstück des hinteren Bereichs 16 ist als Mundstück 18 gestaltet, siehe Figur 1.

Das Gehäuse 12 besteht vorzugsweise aus einem wämebeständigen Material wie einem Duroplast, einem mehrkomponentigen Kunststoff, einem Hartholz, einem Edelholz, Wurzelholz oder Metall oder aus mehreren derartiger Materialien. Um zu vermeiden, daß der Benutzer mit heißen Flächen in Berührung kommt, sind kritische Stellen mit einer Wärmeisolierung versehen oder bestehen aus wärmeisolierenden Materialien.

Im Ausführungsbeispiel ist das Gehäuse 12 zweiteilig gestaltet, wobei der vordere Bereich 14 und der hintere Bereich 16 über eine Verbindung 20 zusammengefügt werden können. An der Verbindung 20

können der vordere Bereich 14 und der hintere Bereich 16 des Gehäuses 12 ineinander gesteckt werden, wobei eine in Figur 1 nicht eingezeichnete Führung, bei der ein Vorsprung in eine Nut eingreift, eine definierte Stellung des hinteren Bereichs 16 in bezug auf den vorderen Bereich 14 gewährleistet und ein Verdrehen verhindert. Zur Sicherung dient eine dünnwandige Überwurfmutter 21, die an einem Außengewinde an dem hinteren Bereich 16 angreift. Ein Isolierring 22 verhindert weitgehend eine Wärmeübertragung von dem im Betrieb erwärmten vorderen Bereich 14 des Gehäuses 12 auf den hinteren Bereich 16 mit dem Mundstück 18. Wenn das Gehäuse 12 an der Verbindung 20 geöffnet wird, läßt sich die Inhaliervorrichtung 10 reinigen.

An der Vorderseite 23 des Gehäuses 12 befindet sich eine Beschickungsöffnung 24, durch die eine Substratportion 1 in das Innere des Gehäuses 12 eingeschoben werden kann. Zum Halten der Substratportion 1 dient eine Substrathalterung 26, die eine auf den Außendurchmesser der Substratportion 1 abgestimmte Führungshülse 28 aufweist. Hinter der Führungshülse 28 ist eine im Ausführungsbeispiel hohlzylindrisch gestaltete Heizfläche 30 angeordnet. Hinter der Heizfläche 30 hat die Substrathalterung 26 einen hinteren Hohlraum 32, in den der hintere Bereich einer eingesetzten Substratportion 1 einschiebbar ist.

Ein axial angeordneter Strömungskanal 34 erstreckt sich über die volle Länge des hinteren Bereichs 16 des Gehäuses 12 und reicht von dem hinteren Hohlraum 32 bis zum hinteren Ende des Mundstücks 18.

Die Heizfläche 30 ist eine Komponente einer im Ausführungsbeispiel als flammenlos operierender Glühkatalysator arbeitenden Heizeinrichtung zum Beheizen der Substrathalterung 26. Dabei kann Verbrennungsluft zum Betrieb der Heizeinrichtung über Luftzutrittsöffnungen 36 im vorderen Bereich 14 in das Gehäuse 12 eintreten. Wenn sich die Heizfläche 30 auf hoher Temperatur befindet, erwärmt sie die Zone der Substratportion 1, die sich

in ihrem Bereich befindet. Wenn also im Ausführungsbeispiel die Heizfläche 30 als Hohlzylinder gestaltet ist, erwärmt sie den gerade in ihrem Innenraum angeordneten Bereich der Substratportion 1. Im Ausführungsbeispiel ist der Innendurchmesser der Heizfläche 30 größer als der Außendurchmesser der Substratportion 1. Dabei wird die Wärme von der Heizfläche 30 auf die Substratportion 1 vorwiegend durch Strahlung transportiert. Die Heizfläche 30 kann auch so angeordnet sein, daß ein Wärmetransport durch Wärmeleitung stattfindet. In diesem Fall ist es vorteilhaft, wenn die Heizfläche 30 die Substratportion 1 nicht unmittelbar berührt, sondern wenn innerhalb der Heizfläche 30 ein vorzugsweise mit Bohrungen versehener Mantel angeordnet ist, der aus einem gut wärmeleitenden Material wie z.B. Aluminium besteht und der in seinen Maßen auf die Substratportion 1 abgestimmt ist, so daß er vorzugsweise direkt an der Substratportion 1 anliegt (in Figur 1 nicht eingezeichnet). Für die Gestaltung der Heizfläche 30 sind zahlreiche Varianten denkbar. So können auch mehrere Heizflächen vorgesehen sein, z.B. zwei parallel zueinander angeordnete Heizflächen, oder es können andere Formen für die Heizfläche gewählt werden, z.B. eine Form mit rinnenartigem Profil. Wesentlich ist, daß die Heizfläche 30 eine Erwärmung der in ihrem Bereich befindlichen Zone der Substratportion 1 über die Außenseite der Substratportion 1 bewirkt, also eine direkte Erwärmung, im Gegensatz zu einer indirekten Erwärmung, bei der erhitztes Gas (vor allem Luft) durch die Substratportion gezogen wird.

Das zum Betrieb der Heizeinrichtung erforderliche Heizmittel, z.B. Butangas, Pentan oder Isopropanol, befindet sich in einem Heizmitteltank 38, der im hinteren Bereich 16 des Gehäuses 12 angeordnet ist. Der Heizmitteltank 38 kann über einen nach außen geführten Nachfüllstutzen 40, der mit einem Verschluß versehen ist, nachgefüllt werden. Im Ausführungsbeispiel ist der Heizmitteltank 38 ringartig gestaltet, wobei der Strömungskanal 34 durch seinen axialen Bereich führt. Anstelle eines nachfüllbaren Heizmitteltanks 38 kann auch ein als Nachfüllpatrone gestalteter

Heizmitteltank vorgesehen sein, der als Ganzes in den hinteren Bereich 16 des Gehäuses 12 eingesetzt wird. Alternativ ist es denkbar, den gesamten hinteren Bereich 16 des Gehäuses 12 als Einwegartikel auszubilden, der ausgetauscht wird, wenn der Heizmitteltank 38 leer ist.

Um Heizmittel aus dem Heizmitteltank 38 zu der Heizfläche 30 zu führen, muß ein Ventil 42 geöffnet werden, das in eine Heizmittelleitung 44 mündet, die mit der Heizfläche 30 verbunden ist. Da im Ausführungsbeispiel der vordere Bereich 14 von dem hinteren Bereich 16 des Gehäuses 12 getrennt werden kann, muß auch die Heizmittelleitung 44 eine Trennstelle aufweisen, die als abgedichtete Kupplung 46 ausgestaltet ist.

Zum Zünden des Heizmittels und zum Betätigen des Ventils 42 dient eine mechanische Schalteinrichtung, die einen auf dem vorderen Bereich 14 des Gehäuses 12 axial verschiebbaren, schlecht wärmeleitenden Ring 48 aufweist. An seiner Außenseite ist der Ring 48 mit einer Griffffläche versehen. Wenn der Ring 48 nach hinten verschoben wird, also in Richtung der in Figur 1 eingezeichneten Pfeile, wird das Ventil 42 geöffnet, so daß Heizmittel aus dem Heizmitteltank 38 zur Heizfläche 30 strömen kann, und gleichzeitig ein piezoelektrischer Zünder 50 betätigt, was die katalytische Verbrennung des Heizmittels einleitet. In der nach hinten verschobenen Stellung kann der Ring 48 durch Verdrehen arretiert werden. Das Ventil 42 bleibt in dieser Stellung des Rings 48 geöffnet, so daß die katalytische Verbrennung andauert und die Heizfläche 30 Wärme abgibt, auch wenn während dieser Zeitspanne der Zünder 50 nicht aktiv ist. Wenn der Heizvorgang beendet werden soll, wird der Ring 48 durch Drehen in der entgegengesetzten Richtung entarretiert und nach vorne geschoben. Dabei schließt sich das Ventil 42. Vorzugsweise drückt eine in Figur 1 nicht eingezeichnete Feder den Ring 48 nach vorne. Die mechanischen Komponenten zum Betätigen des Ventils 42 und des Zünders 50 sind der Übersichtlichkeit halber in Figur 1 nicht eingezeichnet.

Wenn ein Benutzer die Inhaliervorrichtung 10 gebrauchen will, schiebt er zunächst eine frische Substratportion 1, z.B. eine spezielle Slim-Cigarette mit einem Durchmesser von 5 mm und einer Länge von 40 mm, durch die Beschickungsöffnung 24, bis die hintere Zone der Substratportion 1 im Bereich der Heizfläche 30 zu liegen kommt. Wenn er den ersten Zug inhalieren will, zieht er den Ring 48 auf das Mundstück 18 zu und arretiert ihn durch Verdrehen. Wie bereits erläutert, strömt dadurch Heizmittel zu der Heizfläche 30 und wird entzündet. Durch die bei der katalytischen Verbrennung abgegebene Wärme wird die Zone der Substratportion 1 im Bereich der Heizfläche 30 erhitzt, so daß das aerosolbildende Material 2 Geschmacksaerosol freisetzt. Wenn der Benutzer am Mundstück 18 zieht, gelangt Luft durch die Lufteintrittsöffnung 4 in die Substratportion 1 und fördert das Geschmacksaerosol durch die Aerosolaustrittsöffnung 5 der Substratportion 1 über den Strömungskanal 34 zum Benutzer. Vorzugsweise tritt zusätzliche Luft, die zur Verdünnung dient, über die Luftzutrittsöffnungen 36 hinzu. Das inhalierte Aerosol enthält im Ausführungsbeispiel ferner Kohlendioxid und Wasserdampf aus der katalytischen Verbrennung des Heizmittels. Falls das Gehäuse 12 ein Fenster (in Figur 1 nicht eingezeichnet) aufweist, das dem Benutzer einen Blick auf die Heizfläche 30 gestattet, sieht er, daß die Heizfläche 30 beim Zünden rot leuchtet und dann, wenn er am Mundstück 18 zieht, ihre Farbe in hellrot ändert.

Bevor er den nächsten Zug einnimmt, schiebt der Benutzer die Substratportion 1 ein Stück auf das Mundstück 18 zu. Dabei tritt die hintere, abgerauchte Zone der Substratportion 1 in den hinteren Hohlraum 32 ein, während eine frische Zone in den Bereich der Heizfläche 30 gelangt. So strömt beim nächsten Zug frisches Geschmacksaerosol zum Benutzer. Um Heizmittel zu sparen und Nebenstromrauch zu vermeiden, kann der Benutzer den Ring 48 nach jedem Zug durch Gegendrehen entarretieren und nach vorne schieben, so daß sich das Ventil 42 schließt. Der letzte Zug wird entnommen, wenn die Substratportion 1 an dem Isolierring 22

anliegt. Anschließend kann der Benutzer die Substratportion 1 durch die Beschickungsöffnung 24 aus dem Gehäuse 12 herausziehen und entsorgen.

Bei der beschriebenen Ausführungsform der Inhaliervorrichtung 10 sorgt der Benutzer durch Ziehen am Mundstück 18 für die erforderliche Strömung der Umgebungsluft durch die Luftzutrittsöffnungen 36 zu der Heizfläche 30 (katalytische Verbrennung) sowie durch die Lufteintrittsöffnung 4 in die Substratportion 1 hinein und durch die Substratportion 1 hindurch. Die bei der katalytischen Verbrennung entstehenden Verbrennungsgase werden dabei in den Strömungskanal 34 eingesogen und treten, wie bereits erwähnt, zu dem inhalierten Aerosol hinzu. Da die katalytische Verbrennung ziemlich vollständig abläuft, ist der Gehalt an Kohlenmonoxid und anderen aus der Verbrennung stammenden, unerwünschten Substanzen in dem inhalierten Aerosol gering, so daß diese Art der Gas- und Aerosolführung akzeptabel ist.

Es ist jedoch auch möglich, die Verbrennungsgase von dem inhalierten Aerosol fernzuhalten. Dazu kann zum Beispiel innerhalb der Heizfläche 30 eine an beiden Enden offenstehende Hülse aus gut wärmeleitendem Metall vorgesehen sein, die die Führungshülse 28 mit dem hinteren Hohlraum 32 verbindet, so daß die Verbrennungsgase keinen Zutritt zu dem Strömungskanal 34 haben. Vorzugsweise liegt diese Hülse in wärmeleitendem Kontakt an einer eingesetzten Substratportion 1 an. Bei dieser Ausführungsform muß die Wandung des Gehäuses 12 mindestens eine Austrittsöffnung für die Verbrennungsgase aufweisen. Die gewünschte Strömung von den Luftzutrittsöffnungen 36 über die Heizfläche 30 zu dieser Austrittsöffnung läßt sich durch einen Temperaturgradienten erreichen (Thermik).

## Patentansprüche

1. System zur Bereitstellung eines inhalierbaren Aerosols, mit
   - einer Inhaliervorrichtung (10), die ein stabartiges Gehäuse (12) mit einem hinteren mundseitigen Bereich (16) und einem vorderen Bereich (14) aufweist, wobei im vorderen Bereich (14) des Gehäuses (12) eine von einer Heizeinrichtung (30, 38, 44, 50) beheizbare Substrathalterung (26) angeordnet ist, die über eine vorzugsweise an der Vorderseite (23) des Gehäuses (12) befindliche Beschickungsöffnung (24) zugänglich ist, wobei ein Strömungskanal (34) von der Substrathalterung (26) bis zum hinteren Ende des Gehäuses (12) führt und wobei die Heizeinrichtung (30, 38, 44, 50) dazu eingerichtet ist, durch thermische oder katalytische Verbrennung Wärme zu erzeugen, und
   - einer Substratportion (1), die zum Einsetzen in die Substrathalterung (26) durch die Beschickungsöffnung (24) eingerichtet ist und die innerhalb einer Umhüllung (3), die eine Lufteintrittsöffnung (4) und eine Aerosolaustrittsöffnung (5) aufweist, aerosolbildendes Material (2) enthält.

2. System nach Anspruch 1, dadurch gekennzeichnet, daß in den Strömungskanal (34) der Inhaliervorrichtung (10) ein Filter einsetzbar ist.

3. System nach Anspruch 2, dadurch gekennzeichnet, daß im hinteren Bereich (16) des Gehäuses (12) der Inhaliervorrichtung (10) ein als Filtermundstück gestalteter Filter in den Strömungskanal (34) einsetzbar ist.

4. System nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Inhaliervorrichtung (10) im hinteren Bereich (16) des Gehäuses (12) ein Mundstück (18) aufweist, das mit dem Strömungskanal (34) in Verbindung steht und vorzugsweise schlecht wärmeleitend ist.

5. System nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Substrathalterung (26) der Inhaliervorrichtung (10) mindestens eine Heizfläche (30) aufweist, die vorzugsweise hohlzylindrisch oder rinnenartig ist.

6. System nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die Substrathalterung (26) der Inhaliervorrichtung (10) zwei parallel zueinander angeordnete Heizflächen aufweist, deren gegenseitiger Abstand vorzugsweise einstellbar ist.

7. System nach Anspruch 5 oder 6, dadurch gekennzeichnet, daß die Substrathalterung (26) der Inhaliervorrichtung (10) innerhalb der Heizflächen (30) einen vorzugsweise mit Bohrungen versehenen gut wärmeleitenden Mantel aufweist, der dazu eingerichtet ist, an einer in die Substrathalterung (26) eingesetzten Substratportion (1) anzuliegen.

8. System nach einem der Ansprüche 5 bis 7, dadurch gekennzeichnet, daß die Substrathalterung (26) der Inhaliervorrichtung (10) hinter den Heizflächen (30) einen hinteren Hohlraum (32) aufweist, in den der hintere Bereich einer eingesetzten Substratportion (1) einschiebbar ist.

9. System nach einem der Ansprüche 5 bis 8, dadurch gekennzeichnet, daß die Heizflächen (30) der Inhaliervorrichtung (10) dazu eingerichtet sind, durch katalytische Verbrennung eines gasförmigen und/oder flüssigen Heizmittels beheizt zu werden.

10. System nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß im hinteren Bereich (16) des Gehäuses (12) der Inhaliervorrichtung (10) ein Heizmitteltank (38) angeordnet ist, der vorzugsweise von außen nachfüllbar ist.

11. System nach Anspruch 10, dadurch gekennzeichnet, daß das Heizmittel eine oder mehrere der aus der folgenden Gruppe ausgewählten Substanzen aufweist: n-Alkane mit eins bis vier Kohlenstoffatomen, n-Alkane mit fünf bis zwanzig Kohlenstoffatomen, verzweigte oder ringförmige Alkane mit vier bis zwanzig Kohlenstoffatomen, Alkohole, Ketone, Ester, Aldehyde.

12. System nach Anspruch 10 oder 11, dadurch gekennzeichnet, daß die Inhaliervorrichtung (10) eine Schalteinrichtung (48) aufweist, die mit einer zum Zünden des Heizmittels eingerichteten, vorzugsweise piezoelektrisch arbeitenden Zündeinrichtung (50) und einer zum Freigeben von Heizmittel aus dem Heizmitteltank (38) eingerichteten Ventileinrichtung (42) in Wirkverbindung steht.

13. System nach Anspruch 12, dadurch gekennzeichnet, daß die Schalteinrichtung (48) einen axial auf dem vorderen Bereich (14) des Gehäuses (12) der Inhaliervorrichtung (10) verschiebbaren, vorzugsweise schlecht wärmeleitenden Ring (48) aufweist, der vorzugsweise in zwei Stellungen fixierbar ist.

14. System nach einem der Ansprüche 1 bis 13, dadurch gekennzeichnet, daß der vordere Bereich (14) des Gehäuses (12) der Inhaliervorrichtung (10) Luftzutrittsöffnungen (36) aufweist.

15. System nach einem der Ansprüche 1 bis 14, dadurch gekennzeichnet, daß das Gehäuse (12) der Inhaliervorrichtung (10) vor einer bei Betrieb der Heizeinrichtung (30, 38, 44, 50) leuchtenden Komponente (30) ein Fenster aufweist.

16. System nach einem der Ansprüche 1 bis 15, dadurch gekennzeichnet, daß das Gehäuse (12) der Inhaliervorrichtung (10) einteilig ausgestaltet ist.

17. System nach einem der Ansprüche 1 bis 15, dadurch gekennzeichnet, daß das Gehäuse (12) der Inhaliervorrichtung (10) mehrteilig, vorzugsweise zweiteilig, ausgestaltet ist und eine lösbare Verbindung (20) aufweist.

18. System nach einem der Ansprüche 1 bis 17, dadurch gekennzeichnet, daß das Gehäuse (12) der Inhaliervorrichtung (10) eines oder mehrere der aus der folgenden Gruppe ausgewählten Materialien aufweist: Duroplaste, mehrkomponentige Kunststoffe, Harthölzer, Edelhölzer, Wurzelholz, Metall.

19. System nach einem der Ansprüche 1 bis 18, dadurch gekennzeichnet, daß die Substratportion (1) eine zylindrische Form mit einer Länge von 10 mm bis 100 mm, vorzugsweise von 15 mm bis 60 mm, und einem Durchmesser von 4 mm bis 12 mm, vorzugsweise von 5 mm bis 8 mm, hat, wobei die Umhüllung (3) als Zylindermantel angeordnet ist und die Stirnseiten des Zylinders als Lufteintrittsöffnung (4) und als Aerosolaustrittsöffnung (5) eingerichtet sind.

20. System nach einem der Ansprüche 1 bis 19, dadurch gekennzeichnet, daß die Umhüllung (3) der Substratportion (1) niedrigporöses oder nahezu luftundurchlässiges Cigarettenpapier aufweist, das vorzugsweise einen hohen Anteil an mineralischen Zuschlagstoffen hat.

21. System nach einem der Ansprüche 1 bis 20, dadurch gekennzeichnet, daß die Umhüllung (3) der Substratportion (1) eine metallische Folie, vorzugsweise eine Aluminiumfolie, aufweist.

22. System nach einem der Ansprüche 1 bis 21, dadurch gekennzeichnet, daß die Substratportion (1) in ihrem vorderen Bereich eine Isolierumhüllung aufweist, die vorzugsweise über das vordere Ende der Umhüllung (3) vorsteht.

23. System nach einem der Ansprüche 1 bis 22, dadurch gekennzeichnet, daß das aerosolbildende Material (2) der Substratportion (1) ein Trägermaterial, vorzugsweise Aluminiumoxid, Silicagel, Aktivkohle, Cellulosefasern, Ligningranulat, Zeolithe, Tonerden oder Meerschaum oder Kombinationen davon, sowie ein Polyol oder mehrere Polyole, vorzugsweise Glyzerin und/oder Propylenglycol, aufweist und vorzugsweise zusätzlich Bindemittel, Geliermittel, Zuschlagstoffe, Aromen und/oder Nikotin aufweist, wobei der Anteil der Polyole von 10 Gew.-% bis 60 Gew.-% beträgt.

24. System nach einem der Ansprüche 1 bis 22, dadurch gekennzeichnet, daß das aerosolbildende Material (2) der Substratportion (1) ein Tabakmaterial, vorzugsweise Schnittabak, Folientabakschnitt und/oder Tabakrippenschnitt, sowie ein Polyol oder mehrere Polyole, vorzugsweise Glycerin und/oder Propylenglycol, die vorzugsweise mit Tabakstaub angedickt sind, aufweist und vorzugsweise zusätzlich Bindemittel, Geliermittel, Zuschlagstoffe, Aromen und/oder Nikotin aufweist, wobei der Anteil der Polyole von 10 Gew.-% bis 40 Gew.-% beträgt.

25. System nach einem der Ansprüche 1 bis 22, dadurch gekennzeichnet, daß die Substratportion (1) eine dünne, filterlose, an sich handelsübliche Cigarette ist, die Polyole mit einem Anteil von 5 Gew.-% bis 10 Gew.-% aufweist.

26. Inhaliervorrichtung, die ein stabartiges Gehäuse (12) mit einem hinteren mundseitigen Bereich (16) und einem vorderen Bereich (14) aufweist, wobei im vorderen Bereich (14) des Gehäuses (12) eine von einer Heizeinrichtung (30, 38, 44, 50) beheizbare Substrathalterung (26) angeordnet ist, die über eine vorzugsweise an der Vorderseite (23) des Gehäuses (12) befindliche Beschickungsöffnung (24) zugänglich ist, wobei ein Strömungskanal (34) von der Substrathalterung (26) bis zum hinteren Ende des Gehäuses (12) führt und wobei die

Heizeinrichtung (30, 38, 44, 50) dazu eingerichtet ist, durch thermische oder katalytische Verbrennung Wärme zu erzeugen.

27. Inhaliervorrichtung nach Anspruch 26, gekennzeichnet durch Merkmale der Inhaliervorrichtung (10) aus einem der Ansprüche 2 bis 18.

28. Substratportion, die zum Einsetzen in die Substrathalterung (26) einer Inhaliervorrichtung (10) nach Anspruch 26 oder 27 durch die Beschickungsöffnung (24) eingerichtet ist und die innerhalb einer Umhüllung (3), die eine Lufteintrittsöffnung (4) und eine Aerosolaustrittsöffnung (5) aufweist, aerosolbildendes Material (2) enthält.

29. Substratportion nach Anspruch 28, gekennzeichnet durch Merkmale der Substratportion (1) aus einem der Ansprüche 19 bis 25.

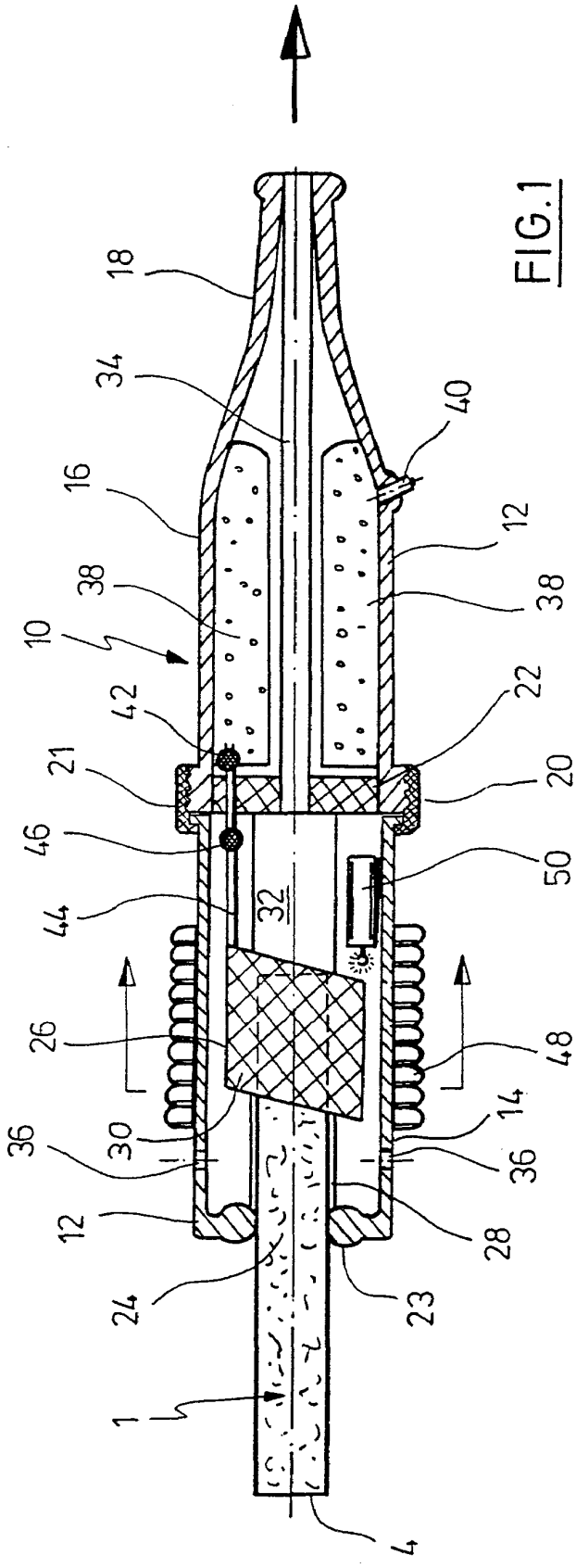

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FIG.1

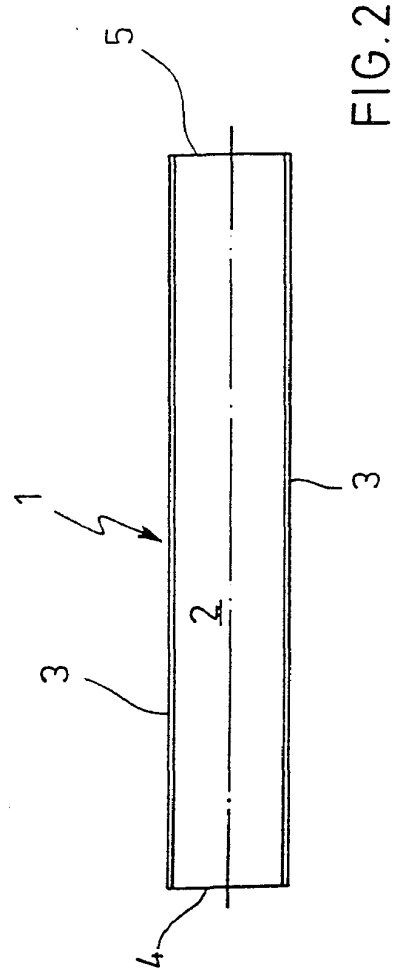

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FIG.2

# INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/EP 99/08427

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 A24F47/00

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 7 A24F

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**

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| A | EP 0 858 744 A (JAPAN TOBACCO INC.)<br>19 August 1998 (1998-08-19)<br>the whole document<br>& WO 97 48294 A<br>cited in the application | 1-4,26,<br>28 |
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☐ Further documents are listed in the continuation of box C.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 March 2000 | 15/03/2000 |

| Name and mailing address of the ISA | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Riegel, R |

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Inter. ...nales Aktenzeichen
PCT/EP 99/08427

**A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES**
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Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

**C. ALS WESENTLICH ANGESEHENE UNTERLAGEN**

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PCT/EP 99/08427

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(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
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(51) 国際特許分類[7]: A24F 13/16, 47/00

(21) 国際出願番号: PCT/JP02/13528

(22) 国際出願日: 2002 年12 月25 日 (25.12.2002)

(25) 国際出願の言語: 日本語

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(30) 優先権データ:
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(71) 出願人 (米国を除く全ての指定国について): 日本たばこ産業株式会社 (JAPAN TOBACCO INC.) [JP/JP]; 〒105-8422 東京都 港区 虎ノ門二丁目２番１号 Tokyo (JP).

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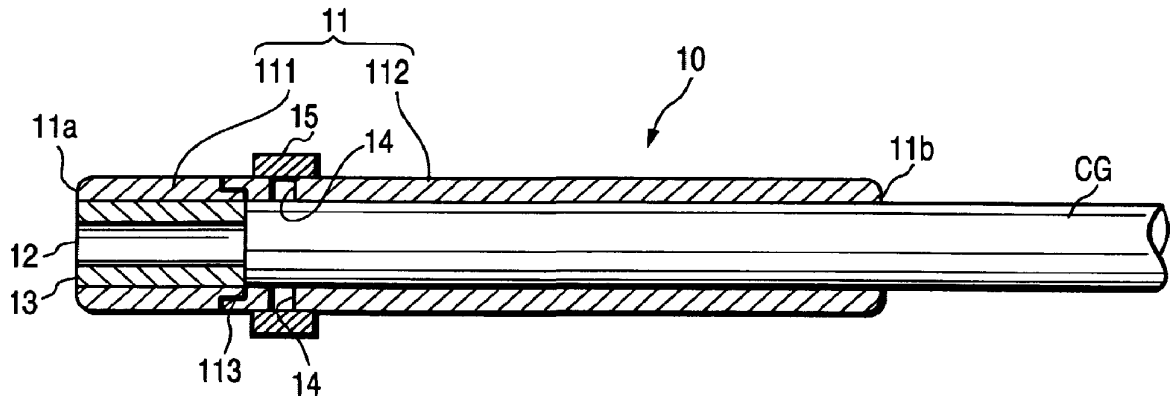
(74) 代理人: 鈴江 武彦, 外(SUZUYE,Takehiko et al.); 〒100-0013 東京都 千代田区 霞が関３丁目７番２号 鈴榮特許綜合法律事務所内 Tokyo (JP).

(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL,

[続葉有]

(54) Title: SMOKING IMPLEMENT

(54) 発明の名称: 喫煙用具




(57) Abstract: A smoking implement, comprising a tubular body having one end part opening for inserting a cigarette therein and the other end part opposed to one end part having a heating member for heating the cigarette.

(57) 要約:

一端がシガレットを挿入するために開放し、対向する他端部にシガレットを加熱するための発熱部材を備えた筒状体からなる喫煙用具。

WO 03/056948 A1

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

**(84) 指定国 (広域):** ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**添付公開書類:**
— 国際調査報告書

２文字コード及び他の略語については、定期発行される各*PCT*ガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

# 明　細　書

## 喫煙用具

### 技術分野

本発明は、喫煙用具に関する。

### 背景技術

シガレットにない利点を活かし、喫煙を楽しむ目的で、たばこに替る香味発生部材を燃料部材あるいは電気ヒーター等によって加熱するタイプの喫煙物が種々提案され、上市されてきている。しかし、たばこ由来の香味を再現することの困難性や、電気デバイス等の利便性が未だ克服されておらず、市場の拡大には相当な努力を要求されている。

本発明は上述のような問題点に鑑みてなされたものであり、簡単な構造で、シガレットにない利点を活かしながらたばこ由来の香味を楽しむことができる喫煙用具を提供することを目的とする。

### 発明の開示

本発明によれば、一端がシガレットを挿入するために開口し、対向する他端部にシガレットを加熱するための発熱部材とを備えた筒状体を包含する喫煙用具が提供される。

上記筒状体の内面には、絞り構造や螺旋状の凸構造を備えたことができる。

上記発熱部材は、着脱可能に設けることができる。

上記発熱部材は、炭素成形物であり得る。

本発明のさらなる展開は、以下の記述および請求の範囲に示されている。

図面の簡単な説明

図１は、本発明の一態様に係る喫煙用具の概略断面図であり；

図２は、本発明の他の態様に係る喫煙用具を部分的に示す概略断面図であり；

図３は、本発明のさらに他の態様に係る喫煙用具を部分的に示す概略断面図であり；

図４は、本発明のさらに他の態様に係る喫煙用具の概略断面図であり；

図５は、本発明のさらに他の態様に係る喫煙用具を部分的に示す概略断面図であり；

図６は、本発明のさらに他の態様に係る喫煙用具を部分的に示す概略断面図であり；

図７は、本発明のさらに他の態様に係る喫煙用具の概略断面図である。

発明を実施するための最良の形態

以下、本発明をより詳しく説明する。全図にわたり、同様の要素は、同様の符号で示されている。

図１は、本発明の一態様に係る喫煙用具の概略断面図である。図１に示す喫煙用具１０は、通常の市販のシガレットＣＧの外径とほぼ同じ内径を有する耐熱性の円筒状本体１１を備え、その後端１１ｂは、通常の市販のシガレットＣＧを挿入するために開放している。円筒状本体１１は、耐熱性の紙、金属コート紙、耐熱性プラスチック等の耐熱性材料で形成することができる。

円筒状本体１１の先端１１ａからは、シガレットＣＧを加熱するための発熱部材１２が、通常その外周を耐熱性の囲包部材１３で囲まれた状態で、円筒状本体１１内に挿入・固定されている。発熱部材１２としては、燃焼可能な炭素成形物（通常円柱状）を使用することができる。また、囲包部材１３は、耐熱性の成形物、耐熱紙、ガラス断熱材等で形成することができる。

炭素成形物等の発熱部材１２には、発熱効率を高めるための空気流路（図示せず）を配置することができる。そのような空気流通路は、円筒状本体１１の長手軸に沿って円柱状炭素成形物１２の外周面内に設けられた少なくとも１つの溝、または円筒状本体１１の長手軸に沿って円柱状炭素成形物１２を貫通する少なくとも１つの貫通孔により構成することができる。喫煙者による吸煙動作により、空気流路から外気が吸い込まれる。

喫煙に際し、図１に示すように、喫煙者はシガレットＣＧをその先端が発熱体１２に当接するまで筒状本体１１内に押し込み、発熱体１２を着火し、シガレットＣＧの吸い口部から吸引すると、通常の喫煙で立ち上る副流煙がほとんど出ない状態で、燃焼による生成物が低減したたばこの香味を楽しむことができる。

なお、図１に示すように、円筒状本体１１は、発熱体１２を収容する第１の部分１１１とシガレットＣＧを挿入させるための第２の部分１１２との２つの部分から構成することができる。第１の円筒状部分１１１は、第２の円筒状部分１１

２に対してそれ自体周知の方式で着脱自在に取り付けることができる。図１には、テーパ面スライド方式で両部分１１１，１１２が接続された構造１１３を示している。両部分１１１，１１２はねじ込み式により接続されていてもよい。このように発熱体１２を収容する第１の円筒状部材１１１を着脱自在に設けることによって、喫煙後、第１の円筒状部材１１１を第２の円筒状部材から取り外し、新たな第１の円筒状部材を接続し、喫煙に供することができる。

また、図１に示すように、発熱部材１２とシガレットＣＧの先端が接触する位置の近傍に、外気を導入するために円筒状本体１１の壁を貫通するいくつかの外気導入孔１４を設け、さらに外気導入量を調節するためのそれ自体周知の調節リング１５を取り付け、喫煙者が吸い込み量を調節できるようにしてもよい。外気導入孔１４から導入された外気は、シガレットの巻紙とこの巻紙により巻装されたタバコ刻みを通って喫煙者の口内に導入され得る。

さらに、図２に示すように、本発明においては、円筒状本体１１の内面はシガレットの挿入に支障がない程度に弾力を持った絞り構造を設けてもよい。この場合、円筒状本体１１は、シガレットの外径よりもやや大きな内径を有する。図２に示す絞り構造は、それ自体周知であるところの、一端のみにおいて円筒状本体１１の内面に接合された複数のストライプ状板体２１から構成され、シガレットは、絞り構造により挟持される。ストライプ状板体２１は、金属等の熱伝導性に優れた材料で構成することにより、これと接触するシガレッ

トに発熱体からの熱を良好に伝導することができる。

また、絞り構造の代わりに、図３に示すように、円筒状本体１１の内面に螺旋状の凸構造３１を設け、シガレットを軽く捩じりながら挿入するようにしてもよい。

図４は、図１に示す喫煙用具の変形例を示すものである。図４に示す喫煙用具は、円筒状本体１１の第２の部分１１２が全体的にシガレットＣＧの外径よりも大きな内径を有する。従って、この第２の部分１１２にシガレットを挿通したとき、第２の部分１１２の壁内表面とシガレットＣＧの外表面との間に隙間ＧＰが形成される。さらに、第２の部分１１２の後端１１ｂ近傍には、Ｏ－リング４０が設けられている。このＯ－リング４０は、第２の部分１１２の壁内表面内に一部埋め込まれるように形成することができる。Ｏ－リング４０は、第２の部分１１２内にシガレットＣＧが挿通されたとき、シガレットＣＧの外側表面と当接するように設けられる。喫煙者の吸引により外気導入孔１４から導入された外気は、隙間ＧＰ（外気流路）を通るが、その隙間ＧＰを通る外気の流れはＯ－リング４０により阻止される。したがって、外気は、シガレットの外表面（シガレット巻紙）全体からタバコ刻み内に導入され得る。

図５は、図２に示す喫煙具の変形例を示すものである。図５に示す喫煙具は、図４に示すＯ－リング４０と同様のＯ－リング５０を備える以外は、図２に示す喫煙具と同様の構成のものである。繰り返すと、Ｏ－リング５０も、円筒状本体１１の壁内表面内に一部埋め込まれるように形成することが

できまた円筒状本体１１内にシガレットＣＧ（図１参照）が挿通されたとき、シガレットＣＧの外側表面と当接するように設けられる。喫煙者の吸引により外気導入孔１４（図１参照）から導入された外気は、円筒状本体１１とシガレットＣＧとの間の隙間（外気流路）を通るが、その隙間を通る外気流はＯ－リング５０により阻止され、それにより、外気は、シガレットの外表面（シガレット巻紙）全体からタバコ刻み内に導入され得る。

図６は、図３に示す喫煙具の変形例を示すものである。図６に示す喫煙具は、図４または図５に示すＯ－リング４０または５０と同様のＯ－リング６０を備える以外は、図３に示す喫煙具と同様の構成のものである。

図７は、図１に示す喫煙用具の第２の変形例を示すものである。図７に示す喫煙用具は、円筒状本体１１の第２の部分１１２の壁内面内に、それぞれ外気導入孔１４と連通する軸方向の溝（図７では、溝７１，７２）が設けられており、かつ溝７１，７２の後端を閉じるようにＯ－リング８０が円筒状本体１１の下端１１ｂ近傍に設けられている以外は、図１に示す喫煙用具と同様の構成のものである。Ｏ－リング８０は、第２の部分１１２内にシガレットＣＧが挿通されたとき、シガレットＣＧの外側表面と当接するように設けられている。Ｏ－リング８０は、第２の部分１１２の壁内表面内に一部埋め込まれるように形成することができる。この第２の部分１１２にシガレットを挿通したとき、溝７１，７２とシガレットＣＧの外表面との間に外気流路が形成される。喫煙者の吸

引により外気導入孔１４から導入された外気は、上記外気流路を通るが、その外気流路を通る外気の流れはＯ－リング８０により阻止される。従って、外気は、溝全体に対応するシガレット表面部分からタバコ刻み内に導入され得る。

なお、図７を参照すると、シガレットＣＧは、いうまでもなく、タバコ巻紙ＣＷにより巻装されたタバコ刻み（図示せず）からなるタバコ部を備えるものであり、またその一端にフィルター部を有することができる。タバコ部とフィルター部は、チップペーパーＣＰにより接続される。チップペーパーには、いわゆるベンチレーション孔ＶＨをシガレットの円周方向に複数設けることができる。図７では、複数のベンチレーション孔ＶＨは１列で設けられているが、複数列に設けることができる。シガレットＣＧは、チップペーパーＣＰの先端がＯ－リング８０をやや超えるように筒状本体１１内に挿通することができる。ベンチレーション孔ＶＨの列は、筒状本体１１の外側に位置するようにされる。このようなシガレットの筒状本体１１内の挿入様態は、図１～図６の喫煙用具においても適用され得る。

以上述べたように、本発明によれば、簡単な構造で、シガレットにない利点を活かしながらたばこ由来の香味を楽しむことができる喫煙用具が提供される

# 請　求　の　範　囲

１．一端がシガレットを挿入するために開放し、対向する他端部にシガレットを加熱するための発熱部材を備えた筒状体を包含する喫煙用具。

２．筒状体の内面に絞り構造を備える請求項１に記載の喫煙用具。

３．筒状体の内面に螺旋状の凸構造を備える請求項１に記載の喫煙用具。

４．前記発熱部材が着脱可能に設けられている請求項１に記載の喫煙用具。

５．前記発熱部材が炭素成形物である請求項１に記載の喫煙用具。

６．前記筒状体が、その内部に外気を導入する外気導入孔を少なくとも１つ備える請求項１に記載の喫煙用具。

７．前記筒状体が、シガレットの外径よりも大きな内径を有し、該筒状体の前記他端近傍にＯ－リングが設けられている請求項６に記載の喫煙用具。

８．前記筒状体が、シガレットの外径と実質的に同じ大きさの内径を有し、該筒状体の壁内に前記外気導入孔と連通する軸方向の溝が設けられ、該溝の後端を閉じるようにＯ－リングが設けられている請求項６に記載の喫煙用具。

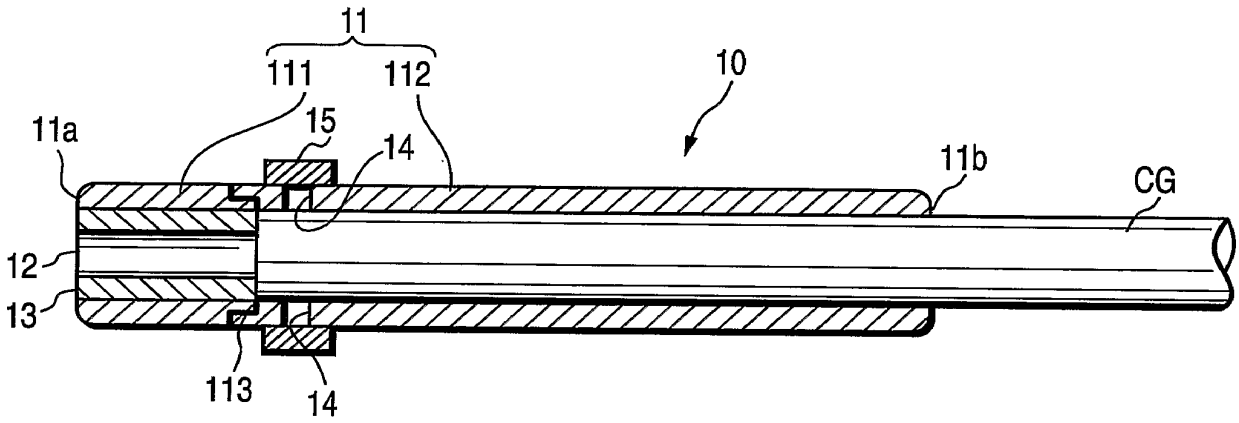



FIG. 1

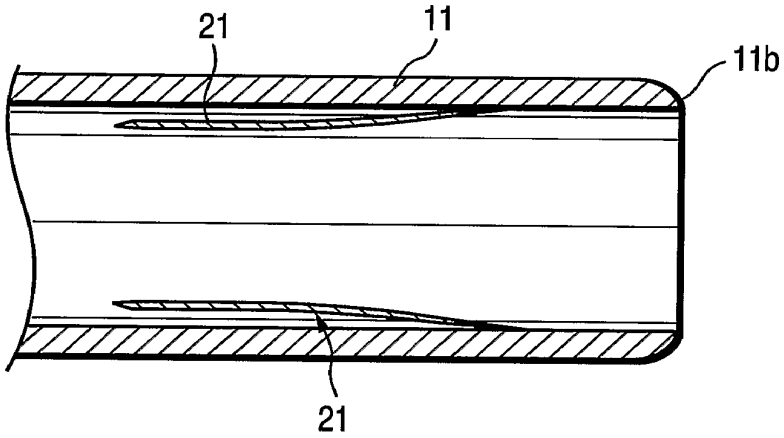



FIG. 2

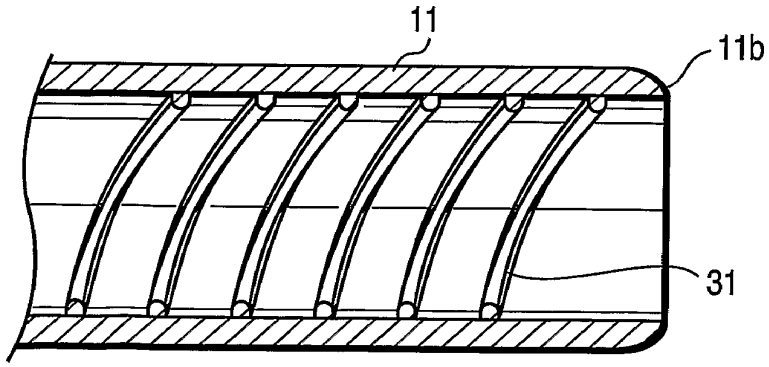



FIG. 3

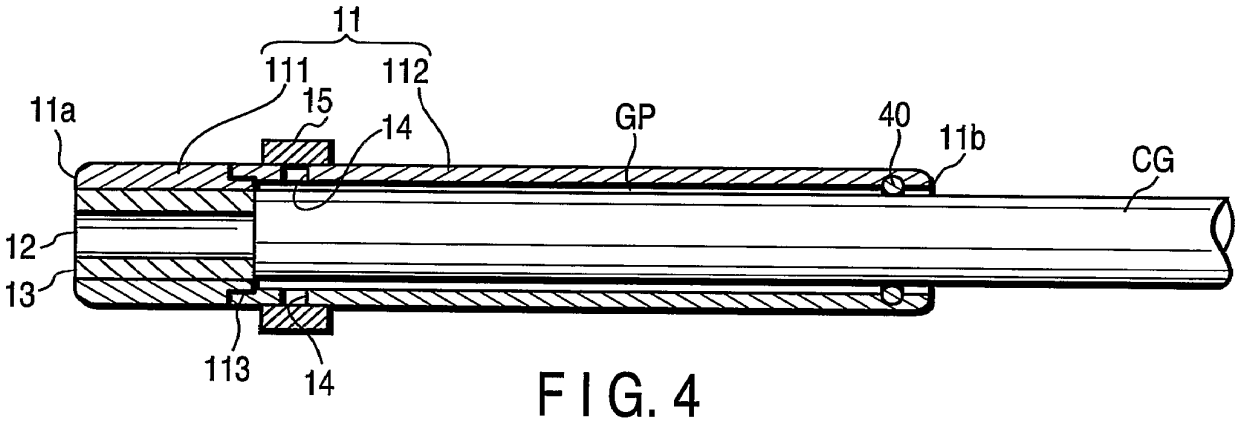



FIG. 4

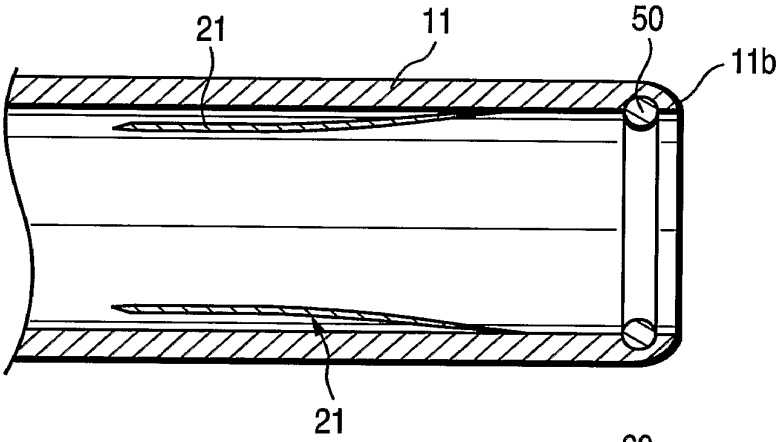



FIG. 5

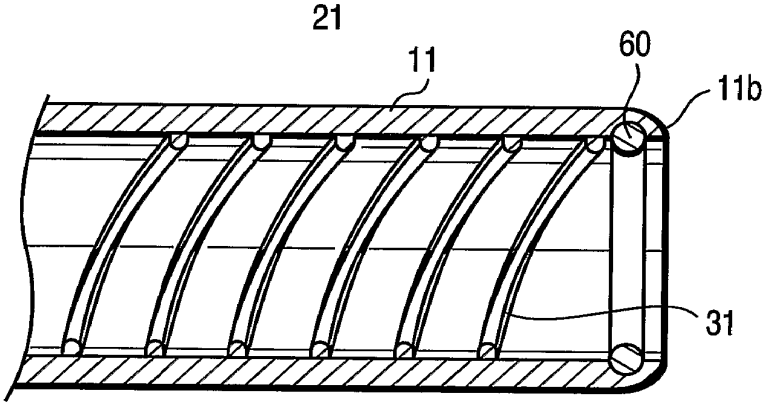



FIG. 6

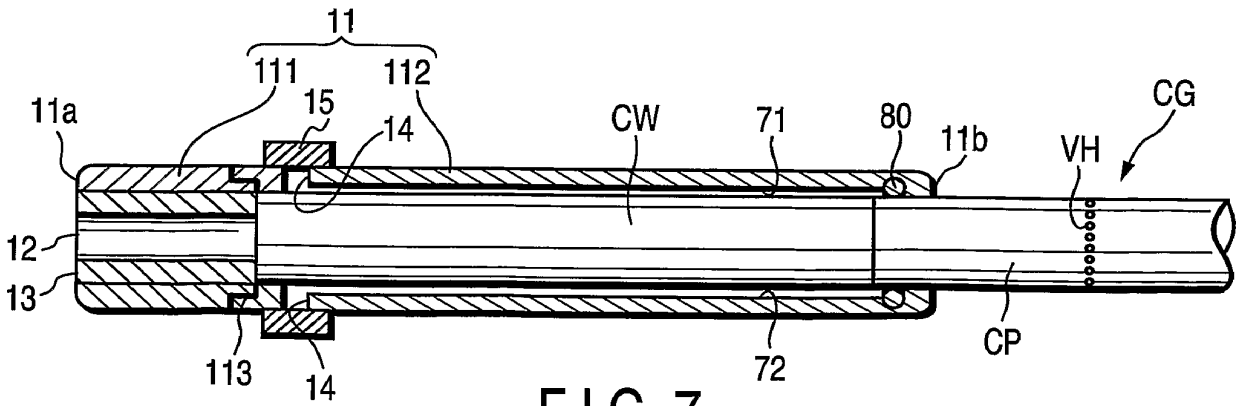



FIG. 7

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/13528

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A24F13/15, 47/00

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)
Int.Cl[7] A24F13/15, 47/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

| | | | |
|---|---|---|---|
| Jitsuyo Shinan Koho | 1926-1996 | Toroku Jitsuyo Shinan Koho | 1994-2003 |
| Kokai Jitsuyo Shinan Koho | 1971-2003 | Jitsuyo Shinan Toroku Koho | 1996-2003 |

Electronic data base consulted during the international search (name of data base and, where practicable, 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. |
|---|---|---|
| X<br>Y | JP 62-501050 A (Aktiebolaget Leo),<br>30 April, 1987 (30.04.87),<br>& WO 86/2528 A1 & NO 862617 A<br>& DK 313886 A & EP 230420 A<br>& CN 86102917 A & US 4776353 A1<br>& CA 1259181 A | 1,4,6-8<br>2,3,5 |
| Y | Microfilm of the specification and drawings annexed to the request of Japanese Utility Model Application No. 85734/1985(Laid-open No. 201594/1986)<br>(Hisashi SAKAMOTO),<br>17 December, 1986 (17.12.86),<br>(Family: none) | 2 |
| Y | JP 4-10527 Y1 (Yasube UMEBARA),<br>17 September, 1929 (17.09.29),<br>(Family: none) | 3 |

[x] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
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"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
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
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| Name and mailing address of the ISA/<br>Japanese Patent Office<br><br>Facsimile No. | Authorized officer<br><br>Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/13528

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | JP 62-48370 A (R.J. Reynolds Tobacco Co.), 03 March, 1987 (03.03.87), & EP 174645 A2 & US 4714082 A1 & CN 86105536 A | 5 |

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ０２／１３５２８

Ａ．　発明の属する分野の分類（国際特許分類（ＩＰＣ））
Ｉｎｔ．Ｃｌ⁷　Ａ２４Ｆ１３／１５，４７／００

Ｂ．　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））
Ｉｎｔ．Ｃｌ⁷　Ａ２４Ｆ１３／１５，４７／００

最小限資料以外の資料で調査を行った分野に含まれるもの
日本国実用新案公報　１９２６－１９９６年
日本国公開実用新案公報　１９７１－２００３年
日本国登録実用新案公報　１９９４－２００３年
日本国実用新案登録公報　１９９６－２００３年

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

Ｃ．　関連すると認められる文献

| 引用文献のカテゴリー＊ | 引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示 | 関連する請求の範囲の番号 |
|---|---|---|
| Ｘ | ＪＰ　６２－５０１０５０　Ａ（ｱｸﾁｰﾎﾞﾗｹﾞｯﾄﾞ　ﾚｵ），１９８７．０４．３０&WO　８６／２５２８　Ａ１&NO　８６２６１７　Ａ&DK　３１３８８６　Ａ&EP　２３０４２０　Ａ&CN　８６１０２９１７　Ａ&US　４７７６３５３　Ａ１&CA　１２５９１８１　Ａ | 1,4,6-8 |
| Ｙ | | 2,3,5 |
| Ｙ | 日本国実用新案登録出願第６０－８５７３４号（日本国実用新案出願公開第６１－２０１５９４号）の願書に添付した明細書及び図面の内容を撮影したマイクロフィルム（坂本　久），１９８６．１２．１７（ファミリーなし） | 2 |

☒ Ｃ欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

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国際調査報告の発送日　12.02.03

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特許庁審査官（権限のある職員）　３Ｂ　９２５４
水野　治彦

電話番号　０３－３５８１－１１０１　内線　３３２０

様式ＰＣＴ／ＩＳＡ／２１０（第2ページ）（１９９８年7月）

Ｃ（続き）．　関連すると認められる文献

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| Ｙ | ＪＰ　６２－４８３７０　Ａ（ｱｰﾙ･ｼﾞｪｲ･ﾚﾉﾙｽﾞ･ﾀﾊﾞｺ･ｶﾝﾊﾟﾆｰ），１９８７．０３．０３&ＥＰ　１７４６４５　Ａ２&ＵＳ　４７１４０８２　Ａ１&ＣＮ　８６１０５５３６　Ａ | 5 |

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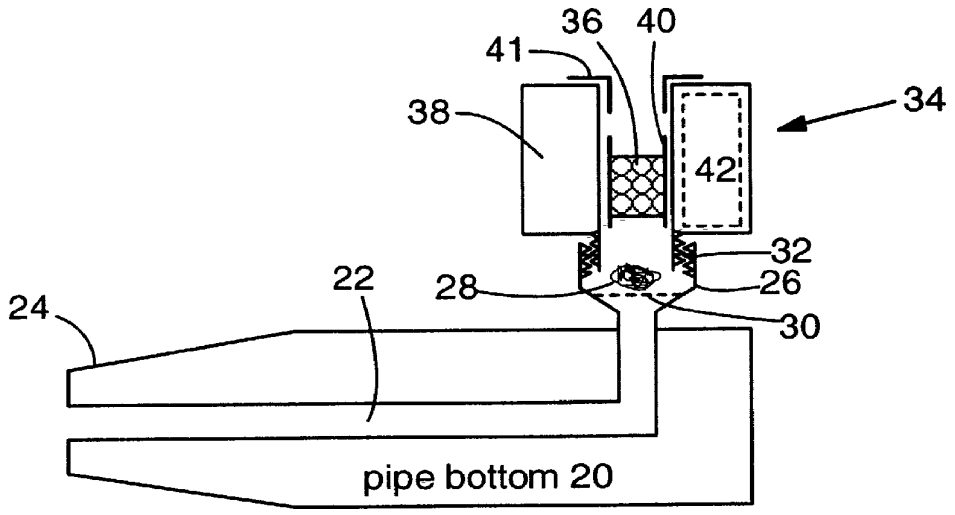
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(54) Title: VAPORIZATION PIPE WITH FLAME FILTER




(57) Abstract: A vaporizer device that uses a flame (46) for vaporizing flavor and psychoactive compounds from smoking materials such as tobacco (28). The present device has a filter unit (34) with a porous flame filter (36). The flame filter (36) can be made of open-cell ceramic or metal foam, sintered ceramic or metal granules or other porous, heat resistant materials. In use, flame (46) is supplied to the flame filter (36), and inhalation causes ambient air to enter the flame filter (36) as well. The flame exhaust and ambient air are mixed within the flame filter (36) and produce an air stream of intermediate temperature. The intermediate temperature air stream is hot enough to vaporize desirable components from the smoking material (28), but generally is not hot enough to burn the smoking material (28). The temperature of the air stream can be controlled by adjusting the amount of flame (46) supplied to the flame filter (36).

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# VAPORIZATION PIPE WITH FLAME FILTER

## FIELD OF THE INVENTION

The present invention relates generally to smoking devices and vaporization devices. More particularly, the present invention relates to a pipe designed to provide vaporization by using heat from a flame.

## BACKGROUND OF THE INVENTION

Tobacco or other herbs are typically smoked by burning and inhaling the combustion fumes and smoke. In recent years, interest has grown in the technique of vaporization in which the smoking material is carefully heated so that the desired flavor and psychoactive components are liberated, and combustion is minimized.

Vaporization provides many benefits over smoking. When performed properly, vaporization does not produce nearly as much toxic and carcinogenic pyrolytic products as smoking. Also, vaporization is smoother and more flavorful, and lacks a burned taste that many find disagreeable. Further, vaporization allows more efficient use of smoking materials, since desired flavor and psychoactive compounds are not destroyed by combustion.

However, vaporization is difficult to perform, since vaporization only occurs in a relatively narrow temperature range. If the temperature is too low, desired compounds are not volatilized and nothing is inhaled; if the temperature is too high, combustion will occur, with its attendant ill effects. For most smoking materials, vaporization is optimal in a temperature range of about 325-450 degrees Fahrenheit. The optimal temperature depends upon the compounds being vaporized.

Most vaporizers in use today are electrically powered. For vaporizing plant materials such as tobacco or marijuana, a temperature-controlled heat gun is often used. Electrical vaporization devices are inconvenient to use since they are not portable and require electrical line power. Typically, heat guns require several hundred watts of power. Also, electrical vaporization devices tend to be expensive.

Some vaporizer devices employ a burning carbonaceous fuel element as a heat source. These devices are most well suited for use in cigarettes since the carbonaceous fuel element

burns for several minutes. However, a continuously burning fuel element is not desired for vaporizing some materials. Exemplary vaporizer devices in the prior art are listed below:

US patent 4,219,032 describes a smoking device using a fuel element.

US patent 5,993,748 describes a vaporization device that is electrically powered.

US patent 4,141,369 describes a vaporization device that is electrically powered.

US patent 6,354,301 describes a vaporizer attachment for a pipe so that the pipe can be coupled to an electric heat gun.

US patent 4,303,083 describes a vaporizer that is electrically powered.

It would be an advance in the art of vaporization devices to provide a vaporizer that operates without electrical power, is inexpensive, is easily transportable, is small, and is simple to operate. Such a device could be widely used by tobacco smokers and by users of medicinal herbs such as marijuana or mullein. Such a device would also largely avoid the harmful effects of inhaling toxic pyrolytic compounds found in smoke and provide the other benefits of vaporization.

## SUMMARY

The present invention includes a vaporization device having a pipe with a bowl for holding smoking material (e.g. tobacco), and a heat resistant and porous flame filter for receiving a flame, wherein the flame filter has a thickness of at least 0.02 inches, and wherein the flame filter is removably attachable to the pipe upstream from the bowl. The flame filter can also have thickness of at least 0.1 inch, or in the range of 0.125-0.75 inches. In one embodiment, the flame filter is made of open cell ceramic foam, which can comprise, silicon carbide, silicon, cordierite or other ceramics. The flame filter causes mixing between flame exhaust and ambient air.

The flame filter can also be made of bonded granules (e.g. sintered metal or ceramic granules), stacked discs (with each disc having at least one hole), a tangled lump of metal wire, or stacked screens, for example. Generally, the flame filter material should have a thermal conductivity of at least 30 W/mK. The pipe can also have an airflow shutter to automatically regulate the amount of airflow into the flame filter, and thereby regulate the temperature. The device can also have a means for indicating temperature, such as an electronic temperature sensor with a display, or a bimetallic strip that moves in response to temperature.

In one useful embodiment, the flame filter comprises open cell silicon carbide foam made by chemical vapor deposition. The foam can have about 60-110 pores-per-inch, for example.

The present invention also may have a filter housing for holding the flame filter. The filter housing can be made of thermally insulating material so that a user is protected from touching the hot flame filter. The filter housing can also be hollow to provide thermal insulation.

The present invention also includes a filter unit having a filter housing, a flame filter disposed in the housing, and a means for attaching the filter housing to a pipe. The filter unit of the present invention can be used with many different kinds and styles of smoking pipes and will transform conventional smoking pipe into a vaporization pipe. The means for attaching the pipe can be a threaded connection, magnet, clamp, hinge and the like.

## DESCRIPTION OF THE FIGURES

Fig. 1 shows a cross-sectional side view of a vaporization pipe according to the present invention.

Fig. 2 illustrates the present vaporization pipe in operation.

Fig. 3 shows a close-up of a filter unit according to the present invention.

Figs. 4a and 4b show an alternative embodiment of the invention having a hinged filter unit, and a straight pipe.

Fig. 5 shows an alternative embodiment of the invention having a friction-fit filter unit.

Fig. 6 shows an embodiment wherein the flame filter is a stack of screens (metal or ceramic).

Fig. 7 shows an embodiment wherein the flame filter is a tangled web of wire.

Fig. 8 shows a close-up of the filter unit where the flame filter comprises a stack of 5 discs with holes.

Figs. 9 and 10 show top view of exemplary discs possible in the embodiment of Fig. 9.

Fig. 11 shows a close-up of the filter unit where the flame filter is combined with a disc having holes that directs heat to the periphery of the flame filter.

Fig. 12 is a top view of an exemplary disc that can be used in the embodiment of Fig. 11.

Fig. 13 shows an embodiment having an electronic temperature sensor and temperature display.

Fig. 14 shows an embodiment having a mechanical airflow shutter responsive to temperature for regulating temperature.

Figs. 15a and 15b show top views of an exemplary airflow shutter usable in the embodiment of Fig. 14.

Fig. 16 shows an embodiment having a theromechanical element for indicating temperature inside the device.

## DETAILED DESCRIPTION

The present invention provides a vaporizing pipe that vaporizes flavor compounds and psychoactive compounds from smoking material such as tobacco, marijuana or other substances. The present vaporizer pipe can be used with a flame such as from a conventional butane lighter or a match. The vaporization pipe of the present invention has a heat resistant, porous flame filter disposed upstream from the smoking material. In operation, flame exhaust and ambient air are drawn into the flame filter. The flame filter causes mixing between the flame exhaust and ambient air, and also conducts heat between the flame exhaust and ambient air. The flame filter thereby creates an intermediate temperature air stream capable of vaporizing without burning. The smoking material is in the path of the intermediate temperature air stream, and so volatile flavor and psychoactive compounds are vaporized from the smoking material. The intermediate temperature air stream and vaporized compounds are then inhaled. The flame filter can be made of many heat-resistant materials such as metals (e.g. refractory metals), ceramics and the like. The material of the flame filter should be resistant to oxidation at high temperature, resistant to extreme thermal shock, and have a high thermal conductivity. In preferred embodiments of the invention, the flame filter comprises reticulated ceramic foam.

**Definitions:**

Heat resistant: Capable of not melting and maintaining its physical structure when exposed to heat from a small flame. Materials that oxidize slightly when exposed to flame (e.g. bronze, stainless steel) are considered heat resistant in the invention. However, combustible materials (e.g. carbon) are not heat resistant.

Porous: Having a plurality of flow paths or pores that create mixing of fluids.

Fig. 1 is a cross sectional side view of the present vaporization pipe. The pipe has a pipe bottom 20 having a hole 22 through which vapor is inhaled. The pipe has an inhalation end 24 for contact with a users mouth during use. The pipe also has a bowl 26 for holding smoking material 28, such as tobacco, marijuana or the like. The bowl 26 preferably has a mesh screen 30 for supporting the smoking material. A filter unit 34 is removably attached to the bowl 26 by threaded connection 32. The filter unit 34 has a heat-resistant and porous flame filter 36 and a filter housing 38 surrounding the flame filter 36. The filter unit 34 may optionally have a heat shield 40 disposed between the filter housing 38 and the flame filter 36. The heat shield 40 can be a thin sheet (0.002") of stainless steel foil, for example. A corner

heat shield 41 can also be provided at an opening in the filter housing 38. The corner heat shield 41 and heat shield can comprise a single component. The corner heat shield 41 helps protect the filter housing 38 from flame. The filter unit 34 may make an airtight seal with the bowl 26, but an airtight seal is not absolutely required in the invention; a small amount of air leakage is permissible.

The pipe bottom 20 can be made of many different materials such as wood, glass, ceramic, metal or the like. Materials with low thermal conductivity such as wood or closed cell ceramic foam are generally preferred, but not required in the invention. The filter housing 38 should also be made of a material with low thermal conductivity so that heat from the flame filter 36 does not escape to the exterior surfaces. The filter housing 38 can be made of wood, closed-cell ceramic foam, or the like. Alternatively, the filter housing has a hollow space 42 to provide low thermal conductivity. If the filter housing has a hollow space 42, it can be made of metal or glass, for example. The pipe bottom 20 can also have a hollow space (not shown) for thermal insulation. The bowl 26 can be made of metal, in which case it may be plated with a relatively chemically nonreactive metal such as silver, gold, platinum or chromium.

The present invention necessarily includes the porous flame filter 36. The flame filter is made of heat resistant material such as ceramic or metal (e.g. refractory metal). The flame filter is made of porous material. The flame filter can be made of many structures, such as open cell foam (ceramic or metal), sintered or bonded ceramic or metal granules, stacked ceramic or metal screens or porous plates, or stacked discs with holes. If plates are used, the plates can each have many holes or a single hole. A stack of plates with holes is considered to be porous in the invention, even if the plates are made of nonporous material.

Fig. 2 shows the pipe of the present invention in operation. In operation, smoking material 28 is disposed in the bowl, and a user (not shown) inhales air and vaporization products from the inhalation end 24, as indicated by arrow 44. Flame 46 is provided to the flame filter 36 by a lighter 48 or other flame source, such as a match. The flame may or may not touch the flame filter, but it is best for the flame to be held slightly above the flame filter 36. Hot exhaust from the flame 46 is drawn into the flame filter 36. Cold, ambient air 50 is also drawn into the flame filter. The flame filter 36 causes mixing between the flame exhaust and ambient air. The flame exhaust and ambient air, after mixing in the filter 36, form an intermediate-temperature air stream 52 that flows over the smoking material. The intermediate-temperature air stream 52 can have a temperature of about 250-500 degrees Fahrenheit, depending on a number of factors such as the speed of inhalation, the size and temperature of the flame 46, and the temperature of the ambient air. By controlling the application of flame to the flame filter 36 (e.g. lifting or lowering the lighter), and the size of

the flame, a user can modulate the temperature of the air stream 52. With experience, a user can determine the temperature by taste and mouth sensations, and adjust the amount of flame accordingly to obtain a perfect temperature for vaporization.

Fig. 3 shows a close-up view of the filter unit 34 of the present invention. The flame filter 36 has a thickness 54, which is measured in the direction of airflow through the filter 36. In the present invention, the flame filter 36 must have a thickness 54 of at least 0.02 inches. A thickness of 0.02 inches is the absolute minimum required for at least partially adequate mixing between the flame exhaust and ambient air. If the filter is thinner than 0.02 inches, then the flame will tend to burn the smoking material. More preferably, the flame filter has a thickness of at least 0.05 inches, 0.1 inches, 0.125 inches or 0.2 inches. A thicker flame filter provides more even heating of the smoking material. The flame filter will typically have a thickness in the range of about 0.25-0.75 inches, but the thickness of the filter can also be as great as 1 or 2 inches or greater in the invention. The thickness of the filter will depend somewhat on the amount of mixing provided by the filter structure (e.g. pore sizes), and the thermal conductivity of the filter material. High mixing capability (e.g. small pore size) and high thermal conductivity will allow for a thinner filter. Thicker filters are required if the pore size is large (e.g. 0.1 inch), and the filter has a low thermal conductivity (e.g. below 10 W/mK)

The flame filter 36 may be cylindrically shaped (although is not necessarily cylindrical), with a diameter 56. The diameter may be selected to be within the range of about 0.125-0.75 inches. The diameter of the flame filter 36 influences how much ambient air is admitted while inhaling. If the flame filter is very wide (e.g. a couple inches), then a large flame is required for adequately high temperature for vaporization. For flame sizes typical of conventional butane lighters (e.g., about 0.75-1 inch tall), it has been found that the best diameter is in the range of about 0.125 to 0.75 inches (i.e. cross sectional area of about 0.015 square inch to about 1 square inch). The present invention includes embodiments where the flame filter is larger or smaller than this range, but in operating such devices, care must be taken to properly select the flame size. The present invention also includes embodiments where the flame filter is square, rectangular or any other shape in cross-section.

The porous flame filter 36 is essential in the invention. The flame filter 36 can be made of many different materials and structures, all of which are understood to be included in the invention and within the scope of the appended claims. Materials and structures suitable for the flame filter include:

**Bonded granules**--In this embodiment, the flame filter is made of granules of heat resistant materials bonded or sintered together. Examples include sintered bronze, brass, stainless steel, or other metals. Also included are sintered ceramics such as alumina,

cordierite, or porcelain. Bonded silicon carbide granules can be used as well. The granules can have sizes in the range of about 100-2000 microns, for example. If metals are used, a chemically stable coating can be applied such as a gold or platinum to prevent oxidation. The porosity (volume % of open space) should be relatively high, for example at least 20 or 30%. The pore size should be relatively large so that one can inhale easily; for example, the pore size can be about 100-1000 microns.

**Stack of plates or screens**--The flame filter can comprise a stack of at least two, preferably at least three or four metal screens. For example, conventional metal screens can be used. In this case, the metal should have a relatively high thermal conductivity above about 30 W/mK (e.g. brass or silver). Also, the metal may be resistant to oxidation, or have a protective coating (e.g. platinum). Alternatively, the flame filter can comprise a stack of at least two, preferably at least three or four ceramic or metal plates with holes. A series of plates with holes is considered to be 'porous' in the present invention and appended claims.

**Metal wire**--The flame filter can also comprise a web of metal wire (e.g. 20-30 gauge). The metal may be resistant to oxidation or have a protective coating (e.g. platinum or gold), and have a high thermal conductivity (e.g. copper, brass or silver). The metal wire can be tangled, coiled, folded of in any other configuration that creates mixing of air and flame exhaust.

**Reticulated open-cell foam**--The flame filter can also comprise open cell metal or ceramic foam. In this case, the foam can have a pores-per-inch (PPI) rating of about 30-120, more preferably in the range of 50-100 PPI, inclusive. If metal is used, it should be heat resistant, and possibly coated with a protective coating (e.g. gold, platinum or other platinum-family metals). If ceramic is used, the foam can be made by applying a ceramic slurry to a polymer (e.g. urethane) foam substrate, and then kiln-firing, as known in the art. Also, the ceramic foam can be made by chemical vapor deposition (CVD) onto a foam substrate, also as known in the art. If CVD ceramic foam is used, it can be made of silicon carbide, which has very high oxidation resistance and thermal shock capability, is relatively inert, and has high thermal conductivity, which are all desirable properties. CVD ceramic foam can also be made of silicon, which also has high thermal conductivity and heat resistance. Other possible materials for the ceramic foam include cordierite, zirconium-containing ceramics, or silica-containing ceramics, or combinations of these materials. Some ceramic materials may break apart or crack due to the thermal shock of the applied flame, which is undesirable. Hence, a ceramic material should be selected that can withstand the thermal shock. A particularly useful material for the flame filter is 80 PPI CVD silicon carbide open-cell foam about 0.25-0.5 inches thick. The foam may have a relative density (volume occupied by solid material) of

about 5-25%. It is also noted that not all of the cells need to be open; some cells can be closed, as often occurs in ceramic foam made from slurry applied to polymer foam.

Most generally, the flame filter can comprise any heat-resistant, porous material that causes mixing of the flame exhaust and air, and has a thickness of at least 0.02 inches, or at least 1 millimeter or 0.1 inches. Reticulated structures such as open cell foams are preferred, but the invention includes all the materials listed above. The flame filter should resist melting up to at least the temperature of the flame of course, and preferably resists oxidation up to about 1000 degrees Fahrenheit. Some oxidation is acceptable if it forms a protective coating. Also, the material of the flame filter (i.e. not including pore spaces), may have a thermal conductivity of at least 30 W/mK. Silicon carbide can have thermal conductivity of about 120 W/mK, and so provides good heat transfer. A high thermal conductivity facilitates heat transfer between the flame exhaust and ambient air, thereby ensuring that the intermediate temperature air stream has a uniform temperature.

The flame filter can have a protective coating (e.g. platinum) to protect it from oxidation and chemical reactions. A protective coating can be particularly useful in embodiments employing metals, such as metal wire or sintered metal granules.

It is also noted that the flame filter 36 can have a combustion catalytic coating (e.g. platinum) for causing more complete combustion of the flame exhaust. This will tend to reduce the amount of harmful combustion products inhaled from the flame.

Also, it is noted that the filter can include means (e.g. threads, friction fit) for direct attachment to the pipe. Preferably, the flame filter is disposed in a filter housing, because the flame filter typically gets too hot to safely handle. If a filter housing is used, the flame filter can be attached to the pipe indirectly through the filter housing. It is understood that the flame filter is considered attached to the pipe even in embodiments where the flame filter is directly attached only to the filter housing.

It is noted that the filter unit 34 can attach to the pipe with many different mechanisms. Examples include magnetized components that attach by magnetic attraction, screw threads as shown in Figs 1 and 2, friction fit, with or without O-rings, hinges, spring clamps and the like.

Figs. 4a and 4b illustrate an alternative embodiment of the invention where the filter unit 34 is attached to a straight pipe 55 with a hinge 56. The hinge allows the smoking material 28 to be inserted, and removed when it is spent. It is understood that a hinge attachment is considered to be an example of a 'removable' attachment in the present invention and appended claims.

Fig. 5 shows an alternative embodiment where the filter unit 34 is attached to the straight pipe by sliding over the straight pipe 55 with a friction fit. An O-ring (not shown) can be disposed between the filter housing 38 and the straight pipe 55.

Fig. 6 shows an embodiment of the invention having a stack of 6 screens 58 as the flame filter. The screens can be made of metal mesh, for example, or ceramic. The filter unit 34 fits onto a pipe 57 with a friction fit, for example. The screens 58 may be spaced apart as shown, or may be in contact. A series of screens is considered to be 'porous' in the invention.

Fig. 7 shows an embodiment where the flame filter comprises a web of metal wire 60. The wire can be 20-30 gauge, for example. The wire can be tangled, as shown, or can be coiled or folded in an organized fashion.

Fig. 8 shows a close-up of the filter unit 34 in an embodiment where the porous flame filter comprises a series of 5 discs 61a-61e, with each disc having holes 64. The discs can be made of metal or ceramic or any other heat-resistant material, for example. The discs have holes in different locations, so that ambient air and flame exhaust follow a tortured path 62. The tortured path creates mixing between the flame exhaust and the ambient air, as required in the present invention. The disc material may or may not be porous, but the combination of stacked discs is considered porous in the invention. The number is discs can be in the range of about 3-20, for example.

Fig. 9a shows a group of 5 discs that can be used in the embodiment of Fig. 8. Each disc has the same hole pattern, but each disc is rotated so that the holes in adjacent discs are not overlapping. This assures that the flame exhaust and ambient air follow a tortured path and are mixed as they pass between the discs. Fig. 10 shows an alternative group of discs 61 having elongated holes 64 arranged in a striped pattern. The discs can be round (as shown), or square, rectangular or any other shape.

Fig. 11 shows yet another embodiment of the filter unit 34 wherein the flame filter 36 is combined with a disc 70 over the flame filter 36. The disc 70 has holes 72 around the periphery. The holes 72 are located at the periphery, and so tend to direct heat toward the periphery of the filter, and thereby create a more uniform heat distribution in the smoking material. Without the disc 70, sometimes the temperature can be too hot in the center, and too low at the edges. Fig. 12 shows a top view of the disc. The disc can have any number of holes (e.g. 3-10), and the holes can be any shape. The disc 70 can also be located under (on the downstream side of) the flame filter 36. The embodiment of Figs. 11 and 12 is most useful where the flame filter 36 comprises a reticulated structure such as a foam or bonded granules. In an alternative embodiment, the disc 70 has no holes, and has a smaller diameter than the flame filter 36, so that it directs airflow to the periphery. The disc 70 can be bonded to the flame filter 36.

Fig. 13 shows another embodiment having an electronic temperature indicator 80 coupled to a temperature sensor 82 such as a thermistor or thermocouple. The temperature sensor 82 should be located close to the smoking material 28. The temperature sensor can be

located behind (downstream from) the smoking material, as shown, or can be located between the flame filter 36 and the smoking material 28. In operation, the display 80 provide the user with an indication of the temperature at the smoking material. This is useful for some users who have difficultly adjusting the flame application to achieve the best vaporization temperature. The display may have an LED, or liquid crystal element to indicate an approximate temperature to the user, for example with a bar display. By using the display, the user can more accurately adjust the temperature inside the smoking material 28.

Fig. 14 shows another aspect of the invention wherein the pipe includes a thermo-mechanical airflow shutter 84 for controlling airflow in response to temperature. In the present vaporization pipe, the amount of airflow influences the temperature at the smoking material. Specifically, for a constant flame size, higher airflow (stronger inhalation) results in cooler temperature, since higher airflow requires more ambient air. Hence, the thermomechanical shutter 84 can maintain a somewhat constant temperature by restricting airflow when temperature is too low. More specifically, the shutter 84 opens when is it exposed to excessive temperature (e.g. temperatures that can cause burning), thereby allowing more ambient air, and reducing the temperature. The shutter can be made of a bimetallic strip partially blocking the air passage. When exposed to high temperature, the shutter 84 bends to open the airway. Many different shapes and structures can be used for the shutter 84. Figs. 15a and 15b, for example, show top views of a shutter made of bimetallic sheet at low and high temperature, respectively. Leaves 86 of the shutter curl in a direction out of the page when exposed to excessive temperature, and thereby allow more airflow when exposed to excessive temperature. The shutter 84 can be located between the flame filter 36 as shown, or can be placed below the smoking material 28 (i.e., within the pipe bottom). In an alternative embodiment, the shutter allows air directly from ambient (not through the flame filter), when the temperature is excessive.

Fig. 16 shows yet another embodiment of the invention having a temperature indicator. Specifically, the device has a thermomechanical element (e.g. bimetallic strip) 86 that responds to temperature by raising or lowering a rod 88 through a hole 90. The height of the rod 88 indicates the approximate temperature experienced by the smoking material 28.

The present invention is also directed toward only the filter unit, which has a flame filter inside the filter housing, and a means for attaching the filter housing to a pipe. The present filter unit can be used with many different kinds of pipes and devices ordinarily intended for use as conventional smoking devices. In fact, the present filter unit can effectively transform a conventional smoking device into a vaporization device. For example, the filter unit can be combined with a water pipe ("bong") or any other pipe known in the art, and the pipe will act as a vaporizer.

It is also noted that the present invention can be used to produce smoke, if desired. If smoke is desired, a large flame is provided to the flame filter. Smoke produced in the present device will tend to be smoother and more pleasant than smoke produced in a conventional pipe, but will contain the harmful substances known to occur in smoke.

It is noted in the present invention that ceramic materials are generally preferred over metals for use in the flame filter 36. This is because ceramics tend to be much more resistant to oxidation and corrosion at high temperatures. Metals such as brass, copper or bronze tend to oxidize, which produces unhealthful metal oxide particles, which are inhaled. Also, metal flame filters tend to create a metallic taste. Inert metals such as platinum or gold can be used (e.g. as a coating), but such materials are very expensive. Hence, inert ceramics such as silicon carbide, silicon, cordierite, and zirconia are preferred. It is also noted that semiconductor materials such as silicon can be used for the flame filter (e.g. silicon foam), and such materials are understood to fall under the rubric of ceramic materials in the present disclosure. Nevertheless, it is understood that even oxidizable metals (e.g. brass, bronze, steel) will function to provide flame filtering and air mixing, and are therefore included in the present invention and scope of the appended claims.

It will be clear to one skilled in the art that the above embodiments may be altered in many ways without departing from the scope of the invention. Accordingly, the scope of the invention should be determined by the following claims and their legal equivalents.

## CLAIMS

What is claimed is:

**1. A vaporization device, comprising:**

**a) a pipe having a bowl for holding smoking material;**

**b) a heat resistant and porous flame filter for receiving a flame, wherein the flame filter has a thickness of at least 0.02 inches, and wherein the flame filter is removably attachable to the pipe upstream from the bowl.**

2. The vaporization device of claim 1, wherein the flame filter has a thickness of at least 0.05 inches.

3. The vaporization device of claim 1, wherein the flame filter has a thickness in the range of 0.125-1 inches.

4. The vaporization device of claim 1, wherein the flame filter comprises open-cell foam.

5. The vaporization device of claim 4, wherein the open-cell foam comprises a material selected from the group consisting of silicon, cordierite, oxide-bonded silicon carbide, CVD silicon carbide, silica-containing ceramics and zirconium-containing ceramics.

6. The vaporization device of claim 1 wherein the flame filter comprises bonded granules.

7. The vaporization device of claim 1 wherein the flame filter has a cross sectional area in the range of 0.015-1 square inches.

8. The vaporization device of claim 1 wherein the flame filter comprises at least two discs with each disc having a least one hole, and holes in adjacent discs are non-overlapping.

9. The vaporization device of claim 1 wherein the flame filter comprises a web of wire.

10. The vaporization device of claim 1 wherein the flame filter comprises a stack of at least 3 mesh screens.

11. The vaporization device of claim 1 further comprising a filter housing surrounding the flame filter and wherein the flame filter is indirectly attachable to the pipe through the filter housing.

12. The vaporization pipe of claim 1 wherein the flame filter is made of metal, and the flame filter has a protective coating.

13. The vaporization device of claim 1 wherein the material of the flame filter has a thermal conductivity of at least 30 W/mK.

14. The vaporization device of claim 1 further comprising an airflow shutter that opens in response to excessive temperature, wherein the shutter is disposed in a path downstream of the flame filter.

15. The vaporization device of claim 1 further comprising a means for indicating temperature near the smoking material.

**16. A vaporization device, comprising:**

**a) a pipe having a bowl for holding smoking material;**

**b) a heat resistant flame filter for receiving a flame, wherein the flame filter is made of open-cell ceramic foam, and wherein the flame filter is removably attachable to the pipe upstream from the bowl.**

17. The vaporization pipe of claim 16 wherein the flame filter is made of CVD silicon carbide ceramic foam.

18. The vaporization pipe of claim 16 wherein the flame filter has a thickness of at least 0.05 inches.

19. The vaporization pipe of claim 16 wherein the ceramic foam has PPI rating in the range of 50-110, inclusive.

20. The vaporization pipe of claim 16 further comprising an airflow shutter that opens in response to excessive temperature, wherein the shutter is disposed in an airflow path downstream of the flame filter.

21. The vaporization pipe of claim 16 further comprising a disc on top of the flame filter for directing airflow to the periphery.

22. The vaporization device of claim 16 further comprising a filter housing surrounding the flame filter and wherein the flame filter is indirectly attachable to the pipe through the filter housing.

**23. A vaporization device, comprising:**
**a) a pipe having a bowl for holding smoking material;**
**b) a filter housing removably attachable to the pipe upstream from the bowl;**
**b) a heat resistant and porous flame filter disposed in the filter housing, wherein the flame filter has a thickness of at least 0.05 inches.**

24. The vaporization pipe of claim 23 wherein the filter housing is made of wood.

25. The vaporization pipe of claim 23 wherein the flame filter is made of open-cell ceramic foam.

**26. A filter unit for attachment to a pipe, comprising:**
**a) a filter housing;**
**b) a heat resistant and porous flame filter disposed in the filter housing;**
**c) a means for attaching the filter housing to the pipe.**

27. The filter unit of claim 26 wherein the flame filter comprises open-cell ceramic foam.

28. The filter unit of claim 26 wherein the flame filter comprises bonded granules.

29. The filter unit of claim 26 wherein the flame filter has a thickness of at least 0.05 inches

30. The filter unit of claim 26 wherein the flame filter has a thickness in the range of 0.125 to 0.75 inches.

31. The filter unit of claim 26 further comprising a heat shield disposed between the flame filter and the filter housing.

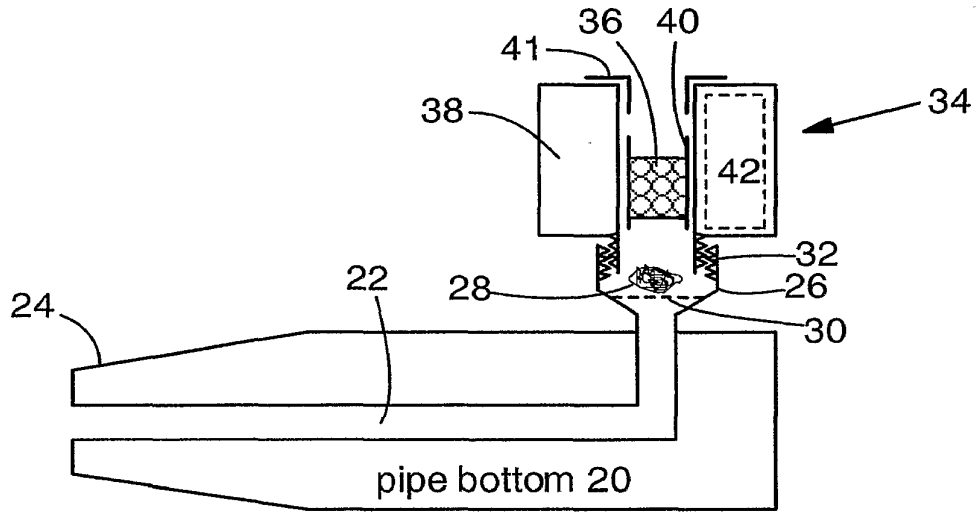

36
40
41
38
34
42
32
22
28
26
24
30
pipe bottom 20

Fig. 1

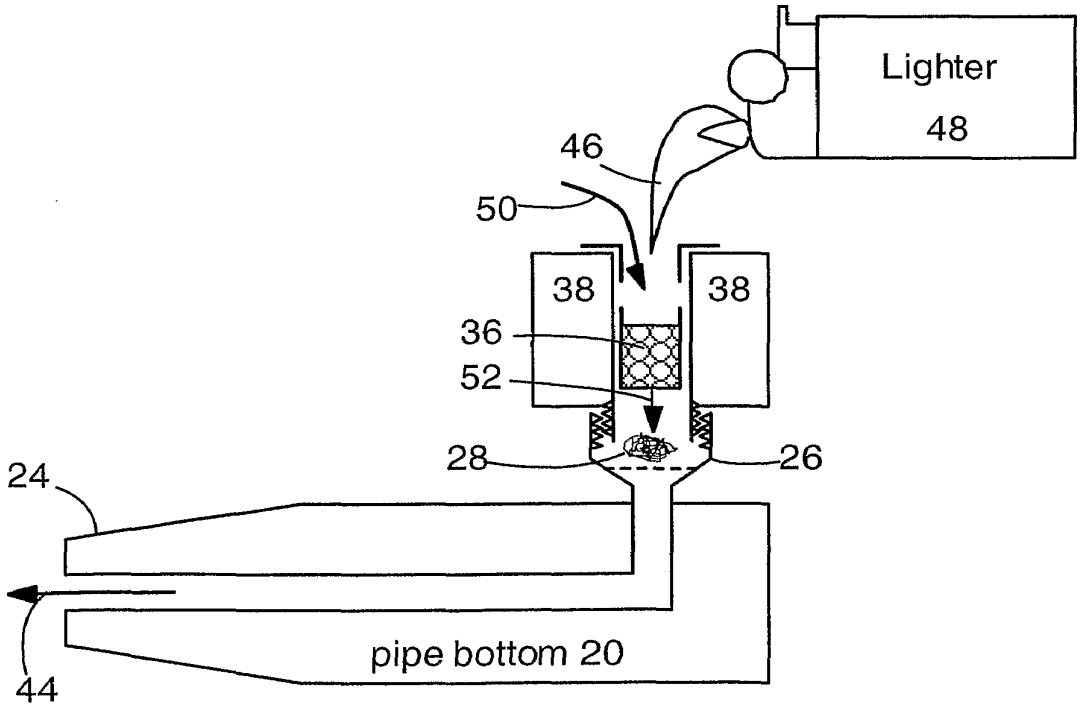

Lighter
48
46
50
38
38
36
52
28
26
24
pipe bottom 20
44

Fig. 2

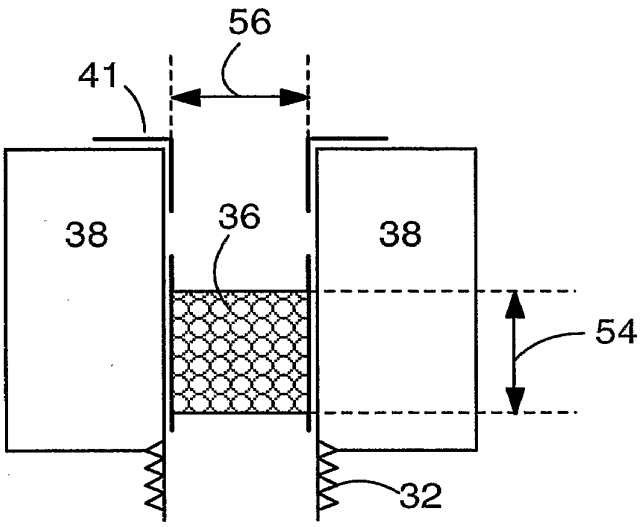



Fig. 3

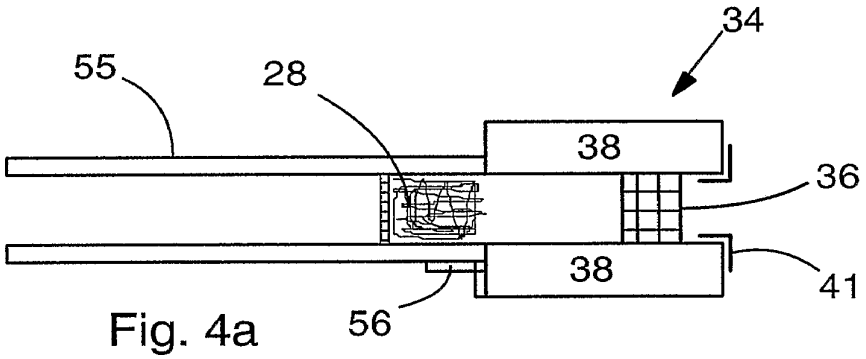



Fig. 4a

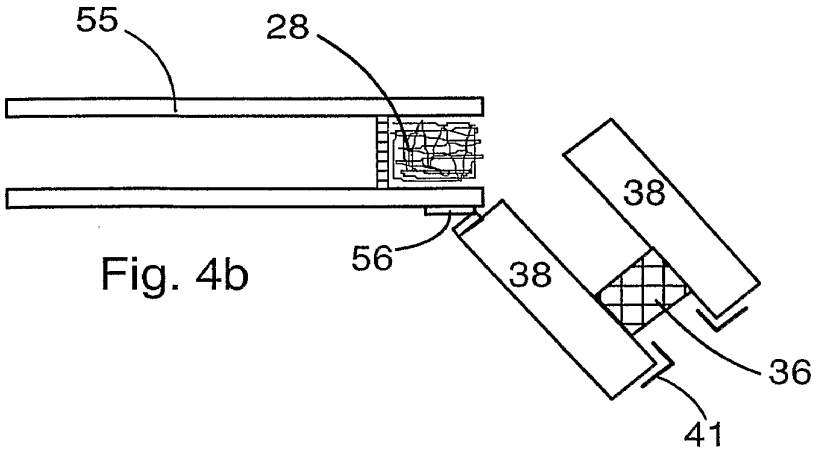



Fig. 4b

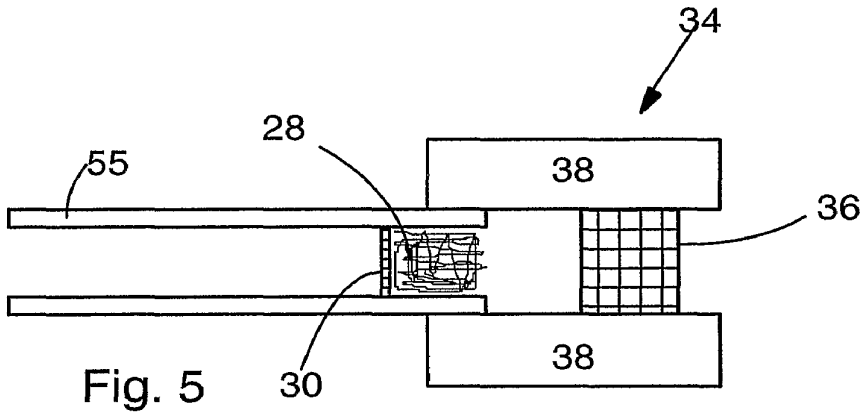



Fig. 5

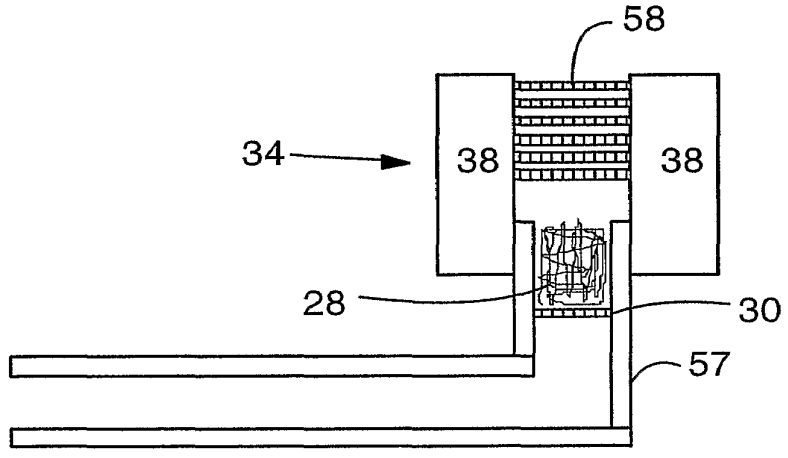



Fig. 6

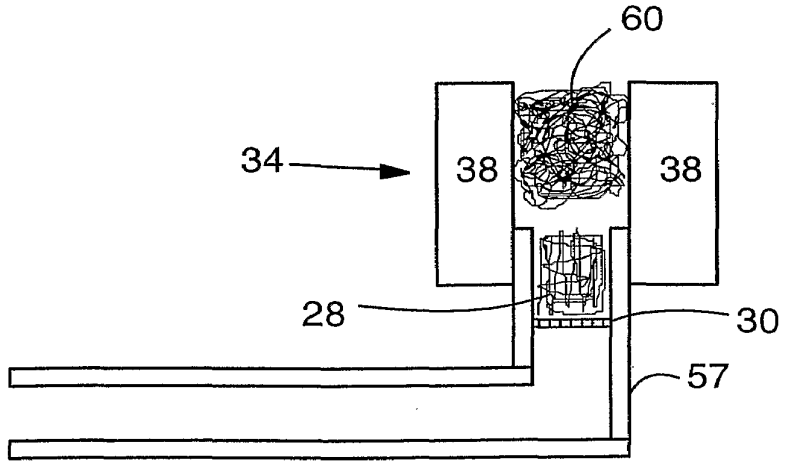



Fig. 7

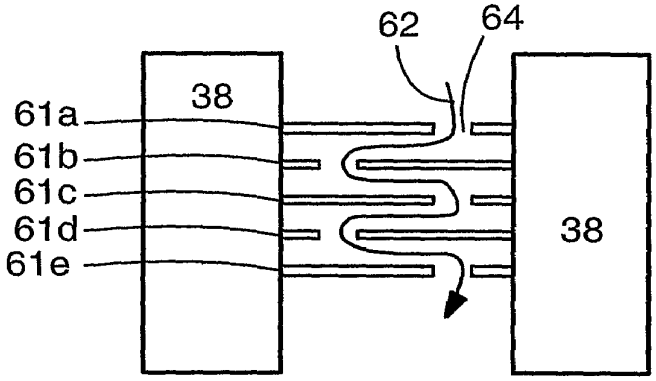



Fig. 8

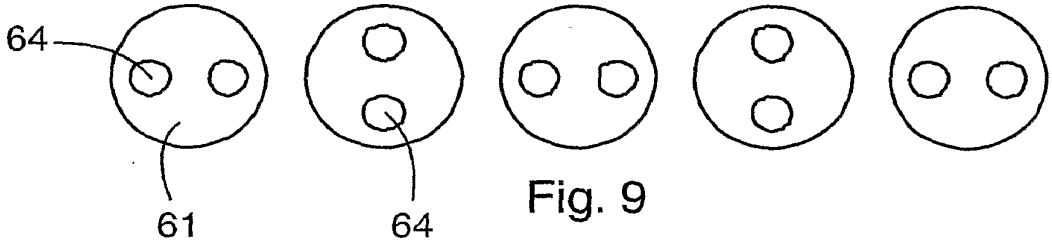



Fig. 9

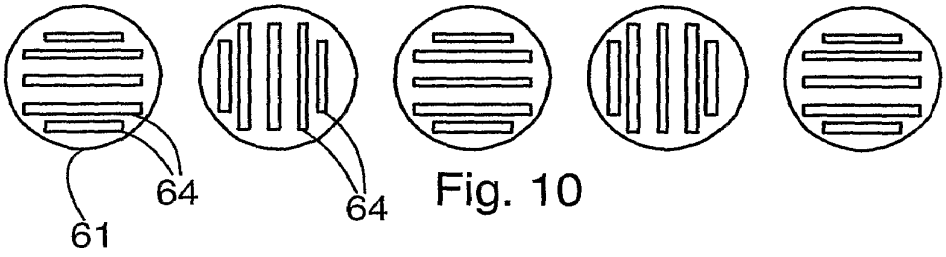



Fig. 10

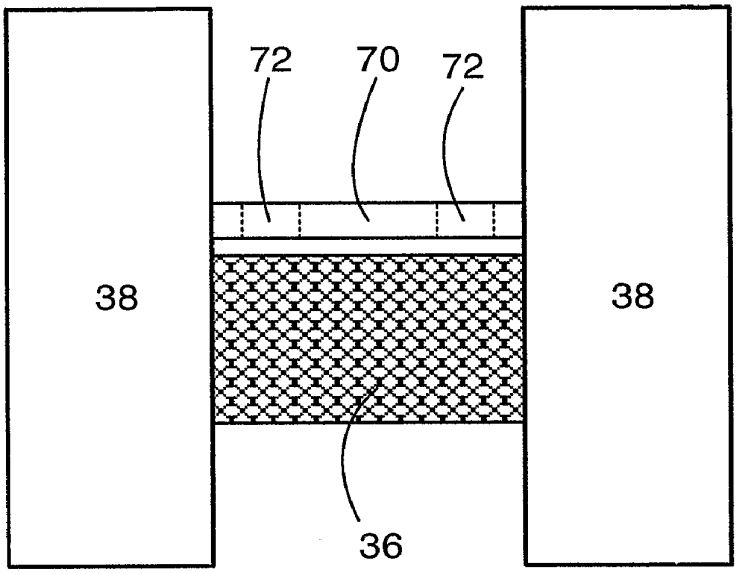



Fig. 11

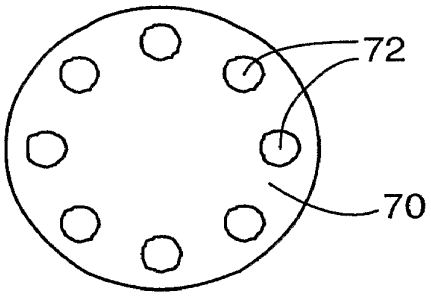



Fig. 12

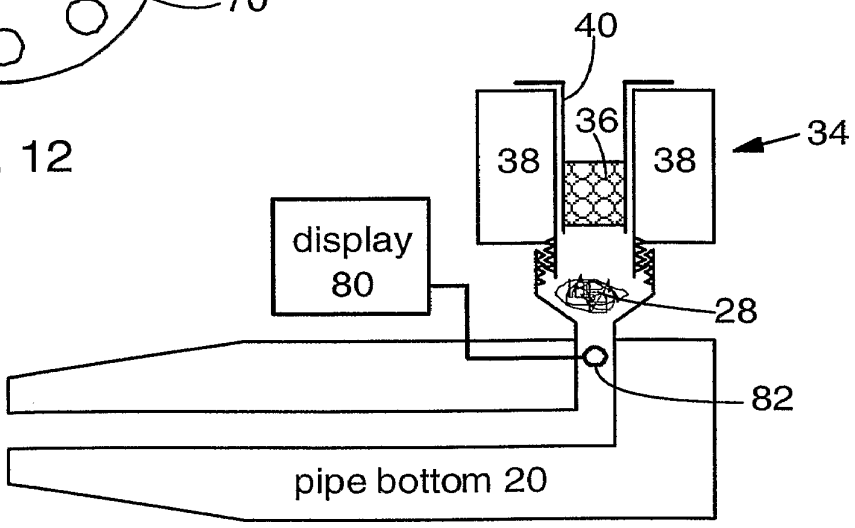



Fig. 13

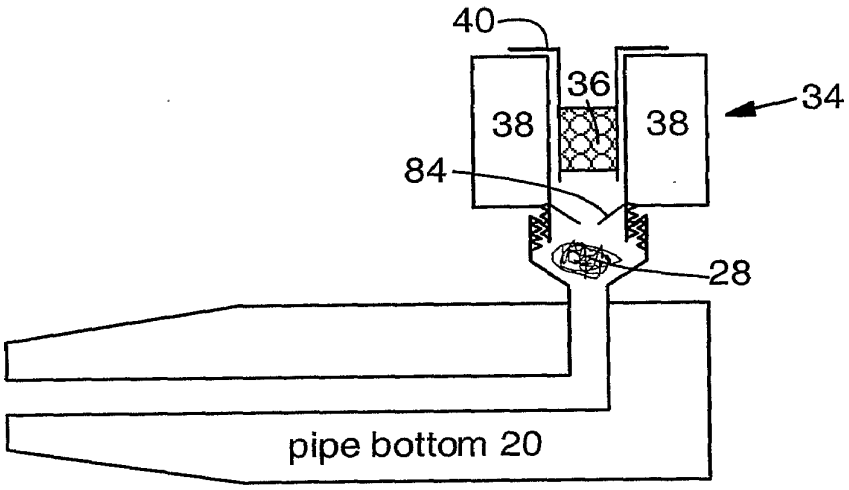
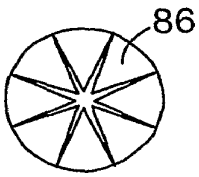
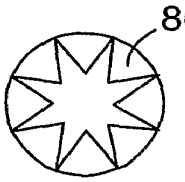



Fig. 14




low temp

Fig. 15a




high temp

Fig. 15b

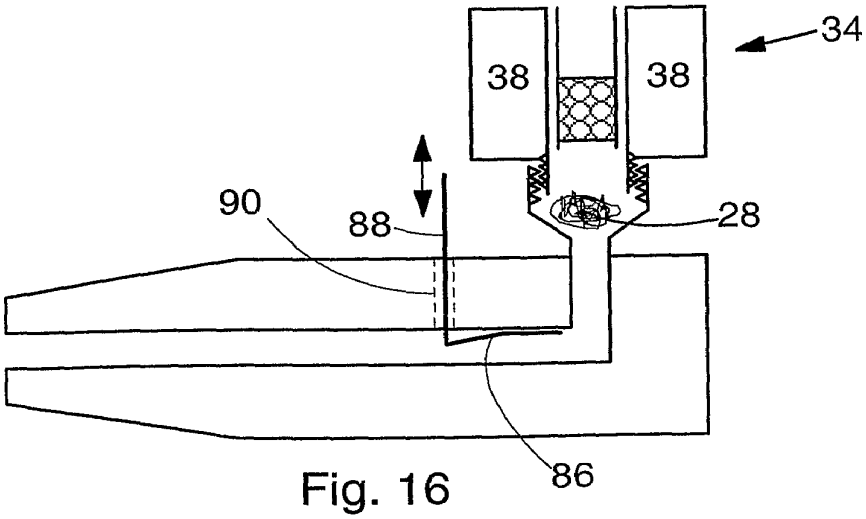



Fig. 16

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/41771

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A24F 1/22
US CL : 131/194, 226, 229, 220, 330
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)
U.S. : 131/194, 226, 229, 220, 330

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 6,354,301 B2 (MCCOY) 12 March 2002, see entire document. | 1-31 |
| A | US 4,219,032 A (TABATZNIK et al) 26 August 1980, see entire document. | 1-31 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| Date of the actual completion of the international search<br>24 MARCH 2003 | Date of mailing of the international search report<br>01 APR 2003 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>DIONNE A. WALLS<br>Telephone No. (703) 308-0661 |

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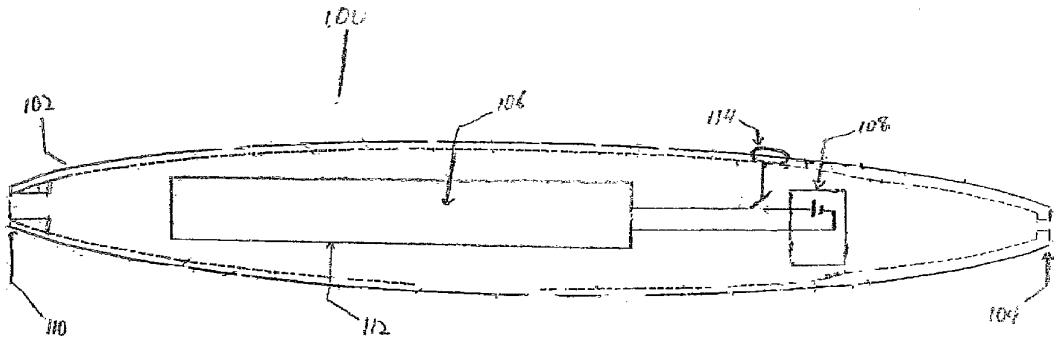
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(54) Title: DELIVERY OF DRUG AMINES THROUGH AN INHALATION ROUTE




(57) Abstract: The present invention relates to the delivery of drug amines through an inhalation route. Specifically, it relates to aerosols containing drug amines that are used in inhalation therapy. In one aspect of the present invention, a method of delivering an amine drug in an aerosol form is provided. The method comprises: a) heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating, b) by said heating, forming an amine drug vapor, and c) during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.

WO 03/094900 A1

# DELIVERY OF DRUG AMINES THROUGH AN INHALATION ROUTE

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional application Ser. No. 60/380,819 entitled "Delivery of Drug Amines Through an Inhalation Route," filed May 13, 2002, Rabinowitz and Zaffaroni, the entire disclosure of which is hereby incorporated by reference.

## FIELD OF THE INVENTION

The present invention relates to the delivery of drug amines through an inhalation route. Specifically, it relates to aerosols containing drug amines that are used in inhalation therapy.

## BACKGROUND OF THE INVENTION

There are a number of compounds containing amines that are currently marketed as drugs. In certain circumstances, the presence of such functionality, however, can prevent effective drug delivery. This phenomenon could be due to a range of effects, including poor solubility and instability.

Inhaled drugs, however, have the potential to enter the systemic circulation and thereby circumvent a number of the problems associated with oral and other drug delivery methods. Moreover, by manipulation of particle size and/or density, delivery of drugs into the alveoli may be facilitated. Alveoli have a large surface area for drug absorption and are surrounded by an extensive capillary network which facilitates rapid passage of drugs into the pulmonary circulation. Furthermore, because blood returning from the lungs is pumped directly to the systemic arterial circulation, drugs inhaled into the alveoli have the potential to reach target organs very rapidly. Of particular importance is that drugs delivered in this manner reach their target site without being exposed to potentially degrading conditions in the gastrointestinal tract and without undergoing modification by first pass metabolism in the liver. Thus, it is desirable to provide a new route of administration for drug amines that rapidly produces peak plasma concentrations of the compounds. This invention provides a route of administration to accomplish this goal.

One type of inhalation aerosol is a condensation aerosol formed from vaporization of compounds. The use of vaporized drugs, thus, provides a method of maximizing alveolar delivery and rapidly delivering drugs to target organs. However, the heat required to vaporize a drug often also generates degradation products, which may decrease the efficacy of the thermal vapor and are undesirable to be delivered to the patient.

Particularly, the salt form of a drug is expected to lower a compound's vapor pressure, and consequently raise its vaporization temperature and potentially increase the amount of degradation product that is likely generated. Thus, a method that enhances drug volatilization without the formation of a substantial amount of degradation products with amine drug salts and a method for selected amine drug salts suitable for use in condensation aerosol is needed. Therefore, one object of the invention is to provide a thermal vapor of amine drug salts for inhalation therapy that does not contain a significant amount of thermal degradation products.

Furthermore, while many drugs may be delivered in their free base form using vaporization, such as those, for example, disclosed in U.S. Application No's: 10/150,591, 10/150,267, 10/155,705 and 10/152,640, some amine drugs are liquid in their free base form and thus, are not optimal in a vaporization method that uses films or coatings to generate the aerosol. In such cases, the physical or chemical stability of the coating may be enhanced through formation of the drug amine salt. Thus, another object of the present invention is to provide amine drugs with desirable properties for thermal vapor delivery.

While dry powder formulations and new liquid aerosol devices are being developed or are available for inhalation therapy. See for example, U.S. Pat. No. 5,993,805 to Sutton et al.; WO 0000176 to Robinson et al.; WO 9916419 to Tarara et al.; WO 0000215 to Bot et al.; U.S. Pat. No. 5,855,913 to Hanes et al.; and U.S. Pat. Nos. 6,136,295 and 5,874,064 to Edwards et al.; U.S. Pat. No. 6,131,570 to Schuster et al.; U.S. Pat. No. 5,724,957 to Rubsamen et al.; and U.S. Pat. No. 6,098,620 to Lloyd et al.; U.S. Pat. Nos. 5,586,550; 5,758,637; and 6,085,740 to Ivri et al.; and U.S. Pat. No. 5,938,117.

These technologies are limited, however. Dry powders require excipients to formulate the dry powders for appropriate delivery. Whereas with liquid aerosols, because the solubility of many drug compounds in water or other solvents suitable for liquid aerosol delivery is low, the total quantity of drug that can be delivered in a single breath is quite small. Thus, there is a need for condensation aerosol of amine drug salts that overcome these limitations. This invention provides such a means.

These and other features of the invention will be described in detail below. All publications, patents, and patent applications referred to herein are incorporated herein by reference in their entirety.

## SUMMARY OF THE INVENTION

The present invention provides methods and reagents for selecting and generating novel amine drug condensation aerosols and vapors, as well as methods of delivering

amine drug aerosols, novel thermal vapor compositions, and methods for generating therapeutically effective inhalation doses of condensation aerosols.

In one aspect, the invention provides a method for selecting amine drugs salts for use in forming a condensation aerosol comprising:

a. dissolving or suspending a salt form of an amine drug in a solvent,

b. coating the suspended or dissolved salt form of the amine drug on a substrate,

c. heating the coated substrate to form a compound vapor,

d. cooling the vapor to form aerosol particles,

e. collecting the aerosol particles,

f. analyzing the collected particles to determine the purity of the aerosol particles; and

g, selecting the amine drug based on a decomposition index less than 0 .15.

Other preferred embodiments are those wherein the amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, drugs for erectile dysfunction, drugs for migraine headache, drugs for the treatment of addiction, muscle relaxants, non-steroidal anti-inflammatory, opioid, or analgesics.

Amine drug salts selected by the above method can be used to form novel amine drug condensations aerosols having preferably a mass median aerodynamic diameter between the range of 1 and 5, and less than 10% amine drug decomposition products. More preferable embodiments have a mass median aerodynamic diameter between the range of 1 and 3.

In another aspect of the invention, a method of delivering an amine drug in an aerosol form is provided, comprising:

a. heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating,

b. by said heating, forming a amine drug vapor, and

c. during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.

In more preferred embodiments of the method, the coating of the amine drug salt used has a thickness between about 0.5 and 20 μm and the aerosol particles generated have a mass median aerodynamic diameter between about 1 and 5 micrometers. More preferably, the

aerosol particles generated have a mass median aerodynamic diameter of about 1 to 3 micrometers with a geometric standard deviation of about 2.5 or less.

In a third aspect of the invention, novel thermal vapors are provided. These thermal vapors comprise gas and amine drug aerosol particles,

a. wherein said gas comprises an acid halide vapor, organic acid vapor, or organic acid decomposition product vapor, and

b. wherein said amine drug aerosol particles

i. comprise at least 10 micrograms of an amine drug and less than 10% amine drug decomposition products relative to said total mass of amine drug in the particles, and

ii. have a mass median aerodynamic diameter in the range 1 to 5 micrometers.

These thermal vapors typically further contain a supersaturated amine drug vapor. Preferably such vapor is warmer than ambient temperature, and more preferably such vapor is warmer than 100°C, 200°C, 250°C, or 300°C.

In yet another aspect of the invention, a method is provided for forming a therapeutically effective inhalation does of drug amine aerosol particles with less than 10% degradation products, comprising:

a) providing a drug delivery article comprising a body defining an interior flow-through chamber having upstream and down stream chamber ends and a drug supply unit contained within such chamber, wherein said drug supply unit comprises a heat-conductive substrate coated with a composition comprising at least a therapeutic amount of amine drug salt having a decomposition index less than 0.10;

b) heating said heat-conductive substrate to a temperature of greater than 200°C over a period of less than 5 seconds, thereby producing a vapor of a therapeutic dose of said amine drug salt; and

c) flowing a gas through said chamber thereby cooling said vapor to form drug amine aerosol particles.

In the preferred embodiments, the thickness of the coating of amine drug salt on the substrate is between about 0.2 and 20 μm. The typical amine drug particle mass median aerodynamic diameter of these embodiments is between about 1 and 5 micrometers. More preferably, the amine drug particle mass median aerodynamic diameter of these embodiments is between about 1 and 3 micrometers. In a more preferred embodiment the thermal vapor consists essential of gas and amine drug aerosol particles.

## BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a side view showing internal details of a device for vaporizing a drug including an external chamber in accordance with the present invention for delivery of a drug to a mammal.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for screening amine drug salts for suitability in condensation aerosols; methods to deliver aerosols, novel vapor compositions, and methods to generate therapeutically effective amounts of amine aerosols. To facilitate understanding and the practice of the invention in its many and diverse applications, this description is organized as shown below.

I. DEFINITIONS
II. CHARACTERISTICS OF THE AMINE DRUG SALTS
III. CHARACTERISTICS OF THE THERMAL VAPOR, AEROSOL AND/OR PARTICLES
IV. METHODS
V. EXAMPLES

### I. DEFINITIONS

"Acid halide" refers to HF, HCl, HBr, HI, HAt.

"Aerodynamic diameter" of a given particle refers to the diameter of a spherical droplet with a density of 1 g/mL (the density of water) that has the same settling velocity as the given particle.

"Aerosol" refers to a suspension of solid or liquid particles in a gas.

"Aerosol drug amine mass density" refers to the mass of drug amine per unit volume of aerosol.

"Aerosol mass density" refers to the mass of particulate matter per unit volume of aerosol.

"Aerosol particle density" refers to the number of particles per unit volume of aerosol.

"Condensation aerosol" refers to an aerosol formed by vaporization of a substance followed by condensation of the substance into an aerosol.

"Decomposition index" refers to a number derived from an assay and described in Example 3 and 4. The number is determined by substracting the fractional purity of the generated aerosol from 1.

"Drug" refers to any chemical compound that is used in the prevention, diagnosis, treatment, or cure of disease, for the relief of pain, or to control or improve any physiological or pathological disorder in humans or animals. Such compounds are oftentimes listed in the Physician's Desk Reference (Medical Economics Company, Inc. at Montvale, NJ, 56th edition, 2002), which is herein incorporated by reference. The drugs are preferably other than recreational drugs. More specifically, the drugs are preferably other than recreational drugs used for non-medicinal recreational purposes, e.g., habitual use to solely alter one's mood, affect, state of consciousness, or to affect a body function unnecessarily, for recreational purposes. Cocaine, amphetamine, methamphetamine, and their derivatives are recreational drugs specifically excluded from the term "drug". The terms "drug" and "medication" are herein used interchangeably.

"Drug amine" refers to a drug containing a primary, secondary, or tertiary amine moiety and not a quaternary amine moiety.

"Drug amine" refers to a drug containing an amine moiety. Drug amine and "amine drug" are terms that mean the same and herein are used interchangeably.

"Drug amine salt" refers to a drug amine, where the amine group is protonated by an acid to form an ammonium salt with a corresponding counterion derived from the acid. The counterion is a pharmaceutically acceptable anion (e.g., Cl- or $CH_3CO_2$-). The drug amines from which the salts are formed come from a variety of drug classes, including, without limitation, antibiotics, anticonvulsants, antidepressants, antiemetics, antihistamines, antiparkisonian drugs, antipsychotics, anxiolytics, drugs for erectile dysfunction, drugs for migraine headaches, drugs for the treatment of alcoholism, drugs for the treatment of addiction, muscle relaxants, nonsteroidal anti-inflammatories, opioids, and other analgesics. Drug amine salt and "amine drug salt" are terms that mean the same and herein are used interchangeably.

Examples of antibiotics from which drug amine salts are formed include cephalexin; cephaloglycin; cephalosporins, such as cephalosporin C; cephradine; amoxicillin; hetacillin; cyclacillin; and penicillins, such as penicillin N.

An example of anticonvulsants from which a drug amine salt is formed is tiagabine.

Examples of antidepressants from which drug amine salts are formed include amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, lofepramine, medifoxamine, mianserin, mirtazapine, nortriptyline, protriptyline, trimipramine, viloxazine, citalopram, cotinine, duloxetine, fluoxetine, fluvoxamine, milnacipran, paroxetine, reboxetine, sertraline, tianeptine, iproniazid, isocarboxazid, moclobemide, phenyhydrazine, phenelzine, selegiline, sibutramine,

tranylcypromine, ademetionine, amisulpride, amperozide, benactyzine, bupropion, idazoxan, metralindole, milnacipran, minaprine, nefazodone, nomifensine, ritanserin, roxindole, tofenacin, trazodone, tryptophan, and venlafaxine.

Examples of antiemetics from which drug amine salts are formed include alizapride, azasetron, benzquinamide, bromopride, buclizine, chlorpromazine, cinnarizine, clebopride, cyclizine, diphenhydramine, diphenidol, dolasetron, droperidol, granisetron, hyoscine, metoclopramide, metopimazine, ondansetron, perphenazine, promethazine, prochlorperazine, scopolamine, triethylperazine, trifluoperazine, triflupromazine, trimethobenzamide, and tropisetron.

Examples of antihistamines from which drug amine salts are formed include azatadine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexmedetomidine, diphenhydramine, doxylamine, hydroxyzine, cetrizine, fexofenadine, and promethazine.

Examples of antiparkisonian drugs from which drug amine salts are formed include amantadine, baclofen, biperiden, benztropine, orphenadrine, procyclidine, trihexyphenidyl, levodopa, carbidopa, selegiline, deprenyl, apomorphine, benserazide, bromocriptine, budipine, cabergoline, dihydroergokryptine, pramipexole, galanthamine, lazabemide, lisuride, memantine, mofegiline, pergolide, remacemide, and terguride.

Examples of antipsychotics from which drug amine salts are formed include acetophenazine, alizapride, amperozide, benperidol, benzquinamide, bromperidol, butaperazine, carphenazine, carpipramine, chlorpromazine, chlorprothixene, clocapramine, clomacran, clopenthixol, clospirazine, clothiapine, cyamemazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, mesoridazine, metofenazate, molindone, penfluridol, pericyazine, perphenazine, pimozide, pipamerone, piperacetazine, pipotiazine, prochlorperazine, promazine, remoxipride, sertindole, spiperone, sulpiride, thioridazine, thiothixene, trifluperidol, triflupromazine, trifluoperazine, ziprasidone, zotepine, zuclopenthixol, amisulpride, clozapine, melperone, olanzapine, quetiapine, and risperidone.

Examples of anxiolytics from which drug amine salts are formed include diazepam, alprazolam, triazolam, indiplon, zaleplon, mecloqualone, medetomidine, metomidate, adinazolam, chlordiazepoxide, clobenzepam, flurazepam, loprazolam, midazolam, azacyclonol, buspirone, captodiamine, enciprazine, flesinoxan, ipsapirone, lesopitron, loxapine, methaqualone, propanolol, tandospirone, trazadone, zopiclone, and zolpidem.

Examples of drugs for erectile dysfunction from which amine salts are formed include cialis (IC351), sildenafil, vardenafil, apomorphine, apomorphine diacetate, phentolamine, and yohimbine.

Examples of drugs for migraine headache from which drug amine salts are formed include almotriptan, eletriptan, alpiropride, codeine, dihydroergotamine, ergotamine, eletriptan, frovatriptan, isometheptene, lidocaine, lisuride, metoclopramide, naratriptan, oxycodone, propoxyphene, rizatriptan, sumatriptan, tolfenamic acid, zolmitriptan, amitriptyline, atenolol, clonidine, cyproheptadine, diltiazem, doxepin, fluoxetine, lisinopril, methysergide, metoprolol, nadolol, nortriptyline, paroxetine, pizotifen, pizotyline, propanolol, protriptyline, sertraline, timolol, and verapamil.

Examples of drugs for the treatment of alcoholism from which drug amine salts are formed include naloxone and naltrexone.

An example of a drug for the treatment of addiction from which drug amine salts are formed is buprenorphine.

Examples of muscle relaxants from which drug amine salts are formed include baclofen, cyclobenzaprine, orphenadrine, quinine, and tizanidine.

Examples of nonsteroidal anti-inflammatories from which drug amine salts are formed include aceclofenac, alminoprofen, amfenac, bromfenac, carprofen, cinchophen, diclofenac, etodolac, mazipredone, meclofenamate, pirprofen, and tolfenamate.

Examples of opioids from which drug amine salts are formed include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, cipramadol, clonitazene, codeine, dextromoramide, dextropropoxyphene, diamorphine, dihydrocodeine, diphenoxylate, dipipanone, fentanyl, hydromorphone, lofentanil, levorphanol, meperidine, methadone, meptazinol, metopon, morphine, nalbuphine, nalorphine, oxycodone, papaveretum, pethidine, pentazocine, phenazocine, remifentanil, sufentanil, and tramadol.

Examples of other analgesics from which drug amine salts are formed include apazone, benzpiperylon, benzydramine, caffeine, clonixin, ethoheptazine, flupirtine, nefopam, orphenadrine, propacetamol, and propoxyphene.

Examples of acids used to form the drug amine salt include, without limitation, the following: hydrochloric acid; hydrobromic acid; formic acid; acetic acid; maleic acid; fumaric acid, benzoic acid, and trifluoroacetic acid.

"Drug amine degradation product" refers to a compound resulting from a chemical modification of the amine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

"Inhalable aerosol drug amine mass density" refers to the aerosol drug amine mass density produced by an inhalation device and delivered into a typical patient tidal volume.

"Inhalable aerosol mass density" refers to the aerosol mass density produced by an inhalation device and delivered into a typical patient tidal volume.

"Inhalable aerosol particle density" refers to the aerosol particle density of particles of size between 100 nm and 5 microns produced by an inhalation device and delivered into a typical patient tidal volume.

"Mass median aerodynamic diameter" or "MMAD" of an aerosol refers to the aerodynamic diameter for which half the particulate mass of the aerosol is contributed by particles with an aerodynamic diameter larger than the MMAD and half by particles with an aerodynamic diameter smaller than the MMAD.

"Organic acid" refers to a compound, generally of less than 300 grams/mole of molecular weight, containing one or more carboxylic acid functional groups.

"Organic acid decomposition product" refers to products resulting from a chemical modification of the organic acid. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation or decarboxylation.

"Rate of aerosol formation" refers to the mass of aerosolized particulate matter produced by an inhalation device per unit time.

"Rate of inhalable aerosol particle formation" refers to the number of particles of size between 100 nm and 5 microns produced by an inhalation device per unit time.

"Rate of drug amine aerosol formation" refers to the mass of aerosolized, drug amine produced by an inhalation device per unit time.

"Settling velocity" refers to the terminal velocity of an aerosol particle undergoing gravitational settling in air.

"Suitable drug amine salt" refers to a drug amine salt that, when subjected to the assay described in Example 2, provides a drug amine aerosol in greater than 85% purity.

"Thermal vapor" refers to a vapor phase, aerosol phase or mixture of aerosol-vapor phases, formed preferably by heating. The thermal vapor may comprise a drug and optionally a carrier, and may be formed by heating the drug and optionally a carrier.

"Treatment" refers to an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviation of symptoms, diminishment of extent of a disease, stabilization (i.e., not worsening) of a state of disease, preventing spread (i.e., metastasis) of disease, preventing occurrence or recurrence of disease, delay or slowing of disease progression, amelioration of the disease state, and remission (whether partial or total).

"Typical patient tidal volume" refers to 1 L for an adult patient and 15 mL/kg for a pediatric patient.

"Vapor" refers to a gas, and "vapor phase" refers to a gas phase.

## II. CHARACTERISTICS OF THE AMINE DRUG SALTS

Preferably, the drug amine salt is a salt of a drug amine freebase, wherein the salt of the freebase has a molecular weight of greater than 200 grams/mole. More preferably, the drug amine salt has a molecular weight greater than 250 grams/mole, 300 grams/mole, or 350 grams/mole.

Preferably, the drug amine salt has a decomposition index less than 0.15. More preferably, the drug amine salt has a decomposition index less than 0.10. Most preferably, the drug amine salt has a decomposition index less than 0.05. Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

Typically, the drug amine salt is a salt of a drug amine from one of the following classes: antibiotics, anticonvulsants, antidepressants, antiemetics, antihistamines, antiparkisonian drugs, antipsychotics, anxiolytics, drugs for erectile dysfunction, drugs for migraine headaches, drugs for the treatment of alcoholism, drugs for the treatment of addiction, muscle relaxants, nonsteroidal anti-inflammatories, opioids, and other analgesics.

Typically, where the drug amine salt is a salt of an antibiotic, it is selected from a salt of one of the following compounds: cephalexin; cephaloglycin; cephalosporins, such as cephalosporin C; cephradine; amoxicillin; hetacillin; cyclacillin; and penicillins, such as penicillin N.

Typically, where the drug amine salt is a salt of an anticonvulsant, it is selected from a salt of one of the following compounds: gabapentin, tiagabine, and vigabatrin.

Typically, where the drug amine salt is a salt of an anticonvulsant, it is selected from a salt of tiagabine.

Typically, where the drug amine salt is a salt of an antidepressant, it is selected from a salt of one of the following compounds: amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, lofepramine, medifoxamine, mianserin, mirtazapine, nortriptyline, protriptyline, trimipramine, viloxazine, citalopram, cotinine, duloxetine, fluoxetine, fluvoxamine, milnacipran, paroxetine, reboxetine, sertraline, tianeptine, iproniazid, isocarboxazid, moclobemide, phenyhydrazine,

phenelzine, selegiline, sibutramine, tranylcypromine, ademetionine, amisulpride, amperozide, benactyzine, bupropion, idazoxan, metralindole, milnacipran, minaprine, nefazodone, nomifensine, ritanserin, roxindole, tofenacin, trazodone, tryptophan, and venlafaxine.

Typically, where the drug amine salt is a salt of an antiemetic, it is selected from a salt of one of the following compounds: alizapride, azasetron, benzquinamide, bromopride, buclizine, chlorpromazine, cinnarizine, clebopride, cyclizine, diphenhydramine, diphenidol, dolasetron, droperidol, granisetron, hyoscine, metoclopramide, metopimazine, ondansetron, perphenazine, promethazine, prochlorperazine, scopolamine, triethylperazine, trifluoperazine, triflupromazine, trimethobenzamide, and tropisetron.

Typically, where the drug amine salt is a salt of an antihistamine, it is selected from a salt of one of the following compounds: azatadine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexmedetomidine, diphenhydramine, doxylamine, hydroxyzine, cetrizine, fexofenadine, and promethazine.

Typically, where the drug amine salt is a salt of an antiparkisonian drug, it is selected from a salt of one of the following compounds: amantadine, baclofen, biperiden, benztropine, orphenadrine, procyclidine, trihexyphenidyl, levodopa, carbidopa, selegiline, deprenyl, apomorphine, benserazide, bromocriptine, budipine, cabergoline, dihydroergokryptine, pramipexole, galanthamine, lazabemide, lisuride, memantine, mofegiline, pergolide, remacemide, and terguride.

Typically, where the drug amine salt is a salt of an antipsychotic, it is selected from a salt of one of the following compounds: acetophenazine, alizapride, amperozide, benperidol, benzquinamide, bromperidol, butaperazine, carphenazine, carpipramine, chlorpromazine, chlorprothixene, clocapramine, clomacran, clopenthixol, clospirazine, clothiapine, cyamemazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, mesoridazine, metofenazate, molindone, penfluridol, pericyazine, perphenazine, pimozide, pipamerone, piperacetazine, pipotiazine, prochlorperazine, promazine, remoxipride, sertindole, spiperone, sulpiride, thioridazine, thiothixene, trifluperidol, triflupromazine, trifluoperazine, ziprasidone, zotepine, zuclopenthixol, amisulpride, clozapine, melperone, olanzapine, quetiapine, and risperidone.

Typically, where the drug amine salt is a salt of an anxiolytic, it is selected from a salt of one of the following compounds: diazepam, alprazolam, triazolam, indiplon, zaleplon, mecloqualone, medetomidine, metomidate, adinazolam, chlordiazepoxide, clobenzepam, flurazepam, loprazolam, midazolam, azacyclonol, buspirone, captodiamine,

enciprazine, flesinoxan, ipsapirone, lesopitron, loxapine, methaqualone, propanolol, tandospirone, trazadone, zopiclone, and zolpidem.

Typically, where the drug amine salt is a salt of a drug for erectile dysfunction, it is selected from a salt of one of the following compounds: cialis (IC351), sildenafil, vardenafil, apomorphine, apomorphine diacetate, phentolamine, and yohimbine.

Typically, where the drug amine salt is a salt of a drug for migraine headache, it is selected from a salt of one of the following compounds: almotriptan, alpiropride, eletriptan, codeine, dihydroergotamine, ergotamine, eletriptan, frovatriptan, isometheptene, lidocaine, lisuride, metoclopramide, naratriptan, oxycodone, propoxyphene, rizatriptan, sumatriptan, tolfenamic acid, zolmitriptan, amitriptyline, atenolol, clonidine, cyproheptadine, diltiazem, doxepin, fluoxetine, lisinopril, methysergide, metoprolol, nadolol, nortriptyline, paroxetine, pizotyline, propanolol, protriptyline, sertraline, timolol, and verapamil.

Typically, where the drug amine salt is a salt of a drug amine for the treatment of alcoholism, it is selected from a salt of one of the following compounds: naloxone, and naltrexone.

Typically, where the drug amine salt is a salt of a drug amine for the treatment of addiction it is buprenorphine.

Typically, where the drug amine salt is a salt of a muscle relaxant, it is selected from a salt of one of the following compounds: baclofen, cyclobenzaprine, orphenadrine, quinine, and tizanidine.

Typically, where the drug amine salt is a salt of a nonsteroidal anti-inflammatory, it is selected from a salt of one of the following compounds: aceclofenac, alminoprofen, amfenac, bromfenac, carprofen, cinchophen, diclofenac, etodolac, mazipredone, meclofenamate, pirprofen, and tolfenamate.

Typically, where the drug amine salt is a salt of an opioid, it is selected from a salt of one of the following compounds: alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, cipramadol, clonitazene, codeine, dextromoramide, dextropropoxyphene, diamorphine, dihydrocodeine, diphenoxylate, dipipanone, fentanyl, hydromorphone, lofentanil, levorphanol, meperidine, methadone, meptazinol, metopon, morphine, nalbuphine, nalorphine, oxycodone, papaveretum, pethidine, pentazocine, phenazocine, remifentanil, sufentanil, and tramadol.

Typically, where the drug amine salt is a salt of an other analgesic it is selected from a salt of one of the following compounds: apazone, benzpiperylon, benzydramine,

caffeine, clonixin, ethoheptazine, flupirtine, nefopam, orphenadrine, propacetamol, and propoxyphene.

Typically, where the drug amine salt is a salt of a stimulant, it is selected from a salt of one of the following compounds: amphetamine, brucine, caffeine, dexfenfluramine, dextroamphetamine, ephedrine, fenfluramine, mazindol, methyphenidate, pemoline, phentermine, and sibutramine.

Typically, the drug amine salt is a hydrochloric acid salt, hydrobromic acid salt, formic acid salt, acetic acid salt, maleic acid salt, fumaric acid salt, benzoic acid salt or trifluoroacetic acid salt.

Typically, the drug amine salt is selected from a group of salts consisting of brompheniramine maleate, carbinoxamine maleate, chlorpheniramine maleate, cyproheptadine hydrochloride, pyrilamine maleate, buproprion hydrochloride, trimipramine maleate, tranylcypromine hydrochloride, protriptyline hydrochloride, apomorphine diacetate hydrochloride, buprenorphine hydrochloride, nicotine dihydrochloride, nicotine sulfate, apomorphine hydrochloride, diphenhydramine hydrochloride, mexiletine hydrochloride, and nicotine hydrochloride..

Typically, the drug amine salt is a mono- or di-salt (e.g., monohydrochloride or dihydrochloride).

## III. CHARACTERISTICS OF THE THERMAL VAPOR, AEROSOL AND/OR PARTICLES

Typically, the particles comprise at least 5 percent by weight of drug amine. Preferably, the particles comprise at least 10 percent by weight of drug amine. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine.

Typically, the condensation aerosol particles have a mass of at least 0.01 mg. Preferably, the aerosol particles have a mass of at least 0.05 mg. More preferably, the aerosol particles have a mass of at least 0.10 mg, 0.15 mg, 0.2 g or 0.25 mg.

Typically, the particles comprise less than 10 percent by weight of drug amine degradation products relative to drug amine. Preferably, the particles comprise less than 5 percent by weight of drug amine degradation products relative to drug amine. More preferably, the particles comprise 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of drug amine degradation products relative to drug amine.

Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 micrometers. More preferably, the particles have a mass median aerodynamic diameter between the range of 1-3 micrometers.

Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of greater than 0.01 micrometers. Preferably, the particles have a mass median aerodynamic diameter of greater than 1 micrometers.

Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.3, 2.0, 2.0 or 1.8.

Typically, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 100 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 75 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 50 mg/L.

Typically, the delivered aerosol has an inhalable aerosol particle density greater than $10^6$ particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than $10^7$ particles/mL or $10^8$ particles/mL.

Typically, the rate of inhalable aerosol particle formation of the delivered condensation aerosol is greater than $10^8$ particles per second. Preferably, the aerosol is formed at a rate greater than $10^9$ inhalable particles per second. More preferably, the aerosol is formed at a rate greater than $10^{10}$ inhalable particles per second.

Typically, the delivered condensation aerosol is formed at a rate greater than 0.5 mg/second. Preferably, the aerosol is formed at a rate greater than 0.75 mg/second. More preferably, the aerosol is formed at a rate greater than 1 mg/second, 1.5 mg/second or 2 mg/second.

Typically, the thermal vapor comprises a gas and amine drug aerosol particles,

a. wherein said gas comprises an acid halide vapor, organic acid vapor, or organic acid decomposition product vapor, and

b. wherein said amine drug aerosol particles

i. comprise at least 10 micrograms of an amine drug and

less than 10% amine drug decomposition products relative to said total mass of amine drug in the particles, and

ii. have a mass median aerodynamic diameter in the range 1 to 5 micrometers.

Typically, the thermal vapor also includes supersaturated amine drug vapor. Generally, the supersaturated amine drug vapor is at a temperature greater than 200°C. More preferably, the temperature of the supersaturated amine drug vapor is greater than 300 °C.

Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

A number of gases can be used in the invention, including but not limited to air, nitrogen, argon, and carbon dioxide. The preferred embodiment includes air as a gas.

Typically, between 0.1 mg and 100 mg of drug amine are delivered to the mammal in a single inspiration. Preferably, between 0.1 mg and 75 mg of drug amine are delivered to the mammal in a single inspiration. More preferably, between 0.1 mg and 50 mg of drug amine are delivered in a single inspiration.

Typically, the delivered condensation aerosol results in a peak plasma concentration of drug amine in the mammal in less than 1 h. Preferably, the peak plasma concentration is reached in less than 0.5 h. More preferably, the peak plasma concentration is reached in less than 0.2, 0.1, 0.05, 0.02 or 0.01 h.

## IV. METHODS

**Selection of Drug Amine Salts for Condensation Aerosols**

In one aspect the present invention provides a method of selecting an amine drug salt suitable for use in forming a condensation aerosol, comprising

a. dissolving or suspending an amine drug salt in a solvent,

b. coating the suspended or dissolved amine drug salt on a substrate,

c. heating the coated substrate to form a compound vapor,

d. cooling the vapor to form aerosol particles,

e. collecting the aerosol particles,

f. analyzing the collected particles to determine the purity of the aerosol particles; and

g, selecting the amine drug based on a decomposition index less than 0 .15.

Substrates on which the composition is heated are of a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (*e.g.*, less than 1.0 mm-sized) pores. Preferably, substrates provide a large surface to volume ratio (*e.g.*, greater than 100 per meter) and a large surface to mass ratio (*e.g.*, greater than 1 $cm^2$ per gram).

A substrate of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

A number of different materials are used to construct the substrates. Classes of such materials include, without limitation, metals, inorganic materials, and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amphorous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 $m^2/g$ from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Chromatography resins such as octadecyl silane chemically bonded to porous silica are exemplary coated variants of silica.

In a preferred embodiment of the invention, the substrate is metallic. In more preferred embodiments, the substrate is aluminum foil or stainless steel.

The heating of the drug amine salt compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following: passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as exothermic solvation, hydration of pyrophoric materials, oxidation of combustible materials and heating on a hot plate.

The substrate is typically heated to a temperature of at least 200 °C to vaporize the amine drug salt. In more preferred embodiments, the substrate is heated to at least 300 °C, 350 °C, or 400 °C.

The particles are collected by means known to those of skill in the art; preferred means include collection in a vial or on a filter.

The resultant particles are analyzed by any technique known by those of skill in the art., including those disclosed below under Analysis of Drug Amine Aerosols. Preferred methods of analyses include reverse-phase HPLC by absorption of UV light, typically at 225 nm and LC/MS.

A drug amine salt was preferred for aerosolization where the purity of the drug isolated by this method was greater than 85%. Such a drug amine salt has a decomposition index less than 0.15. The decomposition index was arrived at by substracting the fractional purity (*i.e.*, 0.85) from 1.

**Formation and Delivery of Drug Amine Containing Aerosols**

Any suitable vaporization method is used to form the aerosols of the present invention. A preferred method, however, involves heating a thin coating or film of a composition comprising a drug amine salt to form a vapor, followed by cooling of the vapor such that it condenses to provide a drug amine comprising aerosol (condensation aerosol). The composition is heated in one of two forms: as pure active compound (*i.e.*, pure drug amine salt); or, as a mixture of active compound and a pharmaceutically acceptable excipient.

Typically, upon heating of the composition, in addition to vaporizing the drug amine, the acidic component of the salt or a decomposition product thereof is also vaporized. For example, upon heating of a salt of a drug amine and an acid, wherein there is an equilibrium between the cationic drug amine plus the anionic acid and the neutral form of the drug amine plus the neutral acid, the acid may vaporize leaving behind the freebase (neutral form) of the drug amine which subsequently vaporizes. Such vaporization may occur at a greater rate if the equilibrium results in a comparatively larger amount of the neutral form of the drug amine and acid, and if the neutral form of the acid has a high vapor pressure (e.g,, HCl). As such, in a preferred embodiment of the invention, the acid component of the drug salt is selected to favor such an equilibrium, or is selected for its high vapor pressure. In cases where the acid component of the drug amine salt is an organic acid, an alternative series of events may occur, which involves decarboxylation of the organic acid to form carbon dioxide plus organic acid decomposition products. Such decarboxylation may leave behind the drug amine in its freebase (neutral) form which may subsequently vaporize. In the case where the organic acid is, for example, lactic or tartaric acid or pyruvic acid, the acid may decompose to generate acetaldehyde in addition to

carbon dioxide. In preferred embodiments of the invention the counterion degrades to form carbon dioxide. In other preferred embodiments, the counterion boils at less than 50°C, less than 100 °C , or less than 200 °C.

In a particularly preferred embodiment, an amine drug aerosol is formed and delivered by a method, comprising:

a. heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating,

b. by said heating, forming a amine drug vapor, and

c. during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.

To deliver a compound through the thermal aerosol route without significant thermal decomposition prior to vaporizing, a key component of the invention involves the use of a coating of the drug as a thin film prior to vaporizing it. Such thin film coatings generally result in vaporization of drug salt amines without substantial decomposition, with thinner coatings generally resulting in less decomposition than thicker coatings. In general, coatings in the range of thickness from 0.05 to 50 micrometers are preferred, with coatings in the range of thickness of 0.1 to 30 micrometers more preferred, and 0.2 to 20 micrometers most preferred. Coatings at the thinner end of the ranges are preferred for drug amines with a substantial tendency to decompose upon heating, whereas the thicker coatings can be employed for drug amines with less tendency to decompose upon heating.

In addition, certain drug amines may undergo decomposition reactions that occur substantially more rapidly in the liquid phase than in the solid phase. For such drug amines, it is particularly preferred to form amine drug salts that sublime upon heating. In a preferred embodiment of the invention, the drug salt amine sublimes at greater than 0.001 atm, 0.01 atm, 0.1 atm, or 1 atm of pressure.

Preferably, the drug amine salt used in the methods of the invention has a decomposition index less than 0.10. More preferably, the drug amine salt has a decomposition index less than 0.05. Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

Pharmaceutically acceptable excipients that are volatile or nonvolatile may be included in compositions of the methods. Volatile excipients, when heated, are concurrently volatilized, aerosolized and inhaled with drug amine. Classes of such excipients are known in the art and include, without limitation, gaseous, liquid and solid solvents. The following is a list of exemplary carriers within the classes: water; terpenes, such as menthol; alcohols, such as ethanol, propylene glycol, glycerol and other similar alcohols; dimethylformamide; dimethylacetamide; wax;; and mixtures thereof.

Substrates on which the composition is heated are of a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (*e.g.*, less than 1.0 mm-sized) pores. Preferably, substrates provide a large surface to volume ratio (*e.g.*, greater than 100 per meter) and a large surface to mass ratio (*e.g.*, greater than 1 $cm^2$ per gram).

A substrate of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

A number of different materials are used to construct the substrates. Classes of such materials include, without limitation, metals, inorganic materials, carbonaceous materials and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amphorous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 $m^2/g$ from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Chromatography resins such as octadecyl silane chemically bonded to porous silica are exemplary coated variants of silica.

The heating of the drug amine salt compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following: passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as

exothermic solvation, hydration of pyrophoric materials and oxidation of combustible materials.

Drug amine containing aerosols of the present invention are delivered using an inhalation device. Where the aerosol is a condensation aerosol, the device has at least three elements: an element for heating a drug amine salt containing composition to form a vapor; an element allowing the vapor to cool, thereby providing a condensation aerosol; and, an element permitting inhalation of the aerosol. Various suitable heating methods are described above. The element that allows cooling is, in it simplest form, an inert passageway linking the heating means to the inhalation means. The element permitting inhalation is an aerosol exit portal that forms a connection between the cooling element and the mammal's respiratory system.

One device used to deliver the drug amine containing aerosol is described in reference to Fig. 1. Delivery device 100 has a down stream chamber end 102 and a upstream chamber end 104, a drug supply unit 106, a power source 108, and a mouthpiece 110.

A drug amine salt composition is deposited on a surface 112 of the drug supply unit 106. Upon activation of a user activated switch 114, power source 108 initiates heating of the drug supply unit 106 (*e.g.*, through ignition of combustible fuel or passage of current through a resistive heating element). The drug amine composition volatilizes due to the heating of the drug supply unit 106 and condenses to form a condensation aerosol prior to reaching the mouthpiece 110 at the downstream chamber end of the device 102. Air flow traveling from the device upstream chamber end 104 to the mouthpiece 110 carries the condensation aerosol to the mouthpiece 110, where it is inhaled.

Devices, if desired, contain a variety of components to facilitate the delivery of drug amine containing aerosols. For instance, the device may include any component known in the art to control the timing of drug aerosolization relative to inhalation (*e.g.*, breath-actuation), to provide feedback to patients on the rate and/or volume of inhalation, to prevent excessive use (*i.e.*, "lock-out" feature), to prevent use by unauthorized individuals, and/or to record dosing histories.

**Dosage of Drug Amine Containing Aerosols**

A typical dosage of a drug amine aerosol is either administered as a single inhalation or as a series of inhalations taken within an hour or less (dosage equals sum of inhaled amounts). Where the drug amine is administered as a series of inhalations, a different amount may be delivered in each inhalation. The dosage amount of drug amine in

aerosol form is generally no greater than twice the standard dose of the drug amine given orally.

One can determine the appropriate dose of drug amine containing aerosols to treat a particular condition using methods such as animal experiments and a dose-finding (Phase I/II) clinical trial. One animal experiment involves measuring plasma concentrations of drug amine in an animal after its exposure to the aerosol. Mammals such as dogs or primates are typically used in such studies, since their respiratory systems are similar to that of a human. Initial dose levels for testing in humans is generally less than or equal to the dose in the mammal model that resulted in plasma drug levels associated with a therapeutic effect in humans. Dose escalation in humans is then performed, until either an optimal therapeutic response is obtained or a dose-limiting toxicity is encountered.

In another aspect of the invention, a method is provided for forming an effective human therapeutic inhalation dose of drug amine aerosol particles having less than 10% degradation products and a drug amine particle mass median aerodynamic diameter between about 1 and 5 micrometers, comprising:

a) providing a drug delivery article comprising a body defining an interior flow-through chamber having upstream and down stream chamber ends and a drug supply unit contained within such chamber, wherein said drug supply unit comprises a heat-conductive substrate coated with a composition comprising at least a therapeutic amount of amine drug salt having a decomposition index less than 0.10;

b) heating said heat-conductive substrate to a temperature of greater than 200°C over a period of less than 5 seconds, thereby producing a vapor of a therapeutic dose of said amine drug salt; and

c) flowing a gas through said chamber thereby cooling said vapor to form drug amine aerosol particles

A number of drug delivery devices can be used including the one describe in Fig. 1 and above.

Preferably, the drug amine salt used in the method of the invention has a decomposition index less than 0.10. More preferably, the drug amine salt has a decomposition index less than 0.05. Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

The preferred coatings are those that result in vaporization of drug salt amines without substantial decomposition and are in the range of thickness from 0.05 to 50 micrometers. More preferred coatings are in the range of thickness of 0.1 to 30 micrometers, and the most preferred thickness is in the range 0.2 to 20 micrometers.

**Analysis of Drug Amine Containing Aerosols**

Purity of a drug amine containing aerosol is determined using a number of methods, examples of which are described in Sekine *et al.*, *Journal of Forensic Science* 32:1271-1280 (1987) and *Martin et al.*, *Journal of Analytic Toxicology* 13:158-162 (1989). One method involves forming the aerosol in a device through which a gas flow (*e.g.*, air flow) is maintained, generally at a rate between 0.4 and 60 L/min. The gas flow carries the aerosol into one or more traps. After isolation from the trap, the aerosol is subjected to an analytical technique, such as gas or liquid chromatography, that permits a determination of composition purity.

A variety of different traps are used for aerosol collection. The following list contains examples of such traps: filters; glass wool; impingers; solvent traps, such as dry ice-cooled ethanol, methanol, acetone and dichloromethane traps at various pH values; syringes that sample the aerosol; empty, low-pressure (*e.g.*, vacuum) containers into which the aerosol is drawn; and, empty containers that fully surround and enclose the aerosol generating device. Where a solid such as glass wool is used, it is typically extracted with a solvent such as ethanol. The solvent extract is subjected to analysis rather than the solid (*i.e.*, glass wool) itself. Where a syringe or container is used, the container is similarly extracted with a solvent.

The gas or liquid chromatograph discussed above contains a detection system (*i.e.*, detector). Such detection systems are well known in the art and include, for example, flame ionization, photon absorption and mass spectrometry detectors. An advantage of a mass spectrometry detector is that it can be used to determine the structure of drug amine degradation products.

Particle size distribution of a drug amine containing aerosol is determined using any suitable method in the art (*e.g.*, cascade impaction). An Andersen Eight Stage Non-viable Cascade Impactor (Andersen Instruments, Smyrna, GA) linked to a furnace tube by a mock throat (USP throat, Andersen Instruments, Smyrna, GA) is one system used for cascade impaction studies.

Inhalable aerosol mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring the

mass collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient.

Inhalable aerosol drug amine mass density is determined, for example, by delivering a drug amine-containing aerosol into a confined chamber via an inhalation device and measuring the amount of non-degraded drug collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient. The amount of non-degraded drug amine collected in the chamber is determined by extracting the chamber, conducting chromatographic analysis of the extract and comparing the results of the chromatographic analysis to those of a standard containing known amounts of drug amine.

Inhalable aerosol particle density is determined, for example, by delivering aerosol phase drug amine into a confined chamber via an inhalation device and measuring the number of particles of given size collected in the chamber. The number of particles of a given size may be directly measured based on the light-scattering properties of the particles. Alternatively, the number of particles of a given size is determined by measuring the mass of particles within the given size range and calculating the number of particles based on the mass as follows: Total number of particles = Sum (from size range 1 to size range N) of number of particles in each size range. Number of particles in a given size range = Mass in the size range/Mass of a typical particle in the size range. Mass of a typical particle in a given size range = $\pi*D^3*\varphi/6$, where D is a typical particle diameter in the size range (generally, the mean boundary MMADs defining the size range) in microns, $\varphi$ is the particle density (in g/mL) and mass is given in units of picograms ($g^{-12}$).

Rate of inhalable aerosol particle formation is determined, for example, by delivering aerosol phase drug amine into a confined chamber via an inhalation device. The delivery is for a set period of time (*e.g.*, 3 s), and the number of particles of a given size collected in the chamber is determined as outlined above. The rate of particle formation is equal to the number of 100 nm to 5 micron particles collected divided by the duration of the collection time.

Rate of aerosol formation is determined, for example, by delivering aerosol phase drug amine into a confined chamber via an inhalation device. The delivery is for a set period of time (*e.g.*, 3 s), and the mass of particulate matter collected is determined by

weighing the confined chamber before and after the delivery of the particulate matter. The rate of aerosol formation is equal to the increase in mass in the chamber divided by the duration of the collection time. Alternatively, where a change in mass of the delivery device or component thereof can only occur through release of the aerosol phase particulate matter, the mass of particulate matter may be equated with the mass lost from the device or component during the delivery of the aerosol. In this case, the rate of aerosol formation is equal to the decrease in mass of the device or component during the delivery event divided by the duration of the delivery event.

Rate of drug amine aerosol formation is determined, for example, by delivering a drug amine containing aerosol into a confined chamber via an inhalation device over a set period of time (*e.g.*, 3 s). Where the aerosol is pure drug amine, the amount of drug collected in the chamber is measured as described above. The rate of drug amine aerosol formation is equal to the amount of drug ester aerosol collected in the chamber divided by the duration of the collection time. Where the drug amine containing aerosol comprises a pharmaceutically acceptable excipient, multiplying the rate of aerosol formation by the percentage of drug ester in the aerosol provides the rate of drug aerosol formation.

The drug amine containing aerosols of the present invention are typically used for the same indication for which they are given orally. For instance, baclofen would be used to treat parkinsons disease and fexofenadine would be used to treat allergy symptoms.

As will be apparent to those of skill in the art upon reading of this disclosure, the present invention provides valuable methods relating to amine drug aerosols. The above description of necessity provides a limited and merely illustrative sampling of the specific compounds, substrates, and devices features and should not be construed as limiting the scope of the invention. Other features and advantages of the invention will be apparent from the following examples and claims.

## EXAMPLES

The following examples describe specific aspects of the invention to illustrate the invention and also provide a description of the methods used to select amine base salts suitable for forming condensation aerosols, and methods to generate amine drug aerosols and measure various physical properties of such aerosols to aid those of skill in the art in understanding and practicing the invention. The examples should not be construed as limiting the invention, in any manner.

Drug amine salts are typically commercially available from Sigma (www.sigma-aldrich.com), obtained in tablet form from a pharmacy and extracted, or synthesized using well known methods in the art.

## EXAMPLE 1

### General Procedure A for Volatilizing Drug Amines from Drug Amine Salts

### General Procedure for the Preparation of a Coating Solution

The concentration of a solution for coating of the substrate was typically 50-200 mg/ml. The amine drug salt was dissolved in an appropriate solvent. Common solvent choices included methanol, dichloromethane, and a 3:1 chloroform:methanol mixture, although DMF was used for less soluble amine drug salts and deionized water was used for amine drug salts that were insoluble in organic solvents. Occasionally sonication or heat was necessary to dissolve the compound.

### Volatilization

A solution of drug amine salt in a minimal amount of solvent was typically coated on a piece of aluminum foil (precleaned with acetone). The solvent was allowed to evaporate. The coated foil was wrapped around a 300 watt halogen tube (Feit Electric Company, Pico Rivera, CA), which was inserted into a glass tube sealed at one end with a rubber stopper. Running 60 V of alternating current (driven by line power controlled by a variac) through the bulb for 5-15 s or 90 V for 3.5-5 s afforded a thermal vapor (including aerosol), which was collected on the glass tube walls. (When desired, the system was flushed through with argon prior to volatilization.) Reverse-phase HPLC analysis with detection by absorption of UV light, generally at 225 nm, was used to determine the purity of the aerosol.

## EXAMPLE 2

### General Procedure B for Volatilizing Drug Amines from Drug Amine Salts

### Dip Coating

The substrate, consisting of a hollow stainless steel cylinder with thin walls, typically having a wall thickness of 0.12 mm, diameter 13 mm, and length 36 mm and conducive to resistance heating, was dip-coated with an amine drug salt coating solution (prepared as disclosed in Example 1) typically using a computerized dip-coating machine to produce a thin layer of drug on the outside of the substrate surface. Prior to using, the substrates were cleaned in dichloromethane, methanol, and acetone, then dried, and fired at

least once to remove any residual volatile material. The substrate was lowered into the drug solution and then removed from the solvent at a rate of typically 5-25cm/sec. The substrate was then allowed to dry for 30 minutes inside a fume hood. If either DMF or a water mixture was used as a dip coating solvent, the substrate was vacuum dried inside a desiccator for a minimum of one hour. Once the substrate was solvent free and only the drug remained, it was ready for volatilization. The drug-coated portion of the cylinder generally has a surface area of 8.5 $cm^2$. By assuming a unit density for the drug, the initial drug coating thickness were calculated.

**Volatilization**

A dip coated substrate was placed in a surrounding glass tube connected at the exit end via Tygon tubing to a filter holder fitted with a Savillex Teflon filter and the junction is sealed with paraffin film. The substrate was placed in a fitting which connects it to two 1 farad capacitors wired in series and controlled by a 12-volt relay. The capacitors were charged by a separate power source to about 16-21 volts and all the power was channeled to the substrate by closing a switch and allowing the capacitors to discharge into the substrate. The substrate was heated to a temperature of ~ 400°C in ~ 50 milliseconds. This heating process was done under an airflow of 15 L/min, which swept the vaporized drug aerosol into a 2 micron Teflon filter. After volatilization, the aerosol captured on the filter was recovered for analysis. Any material deposited on the glass sleeve or remaining on the substrate was also recovered. The recovered materials were analyzed by HPLC UV absorbance, generally at 225 nm, or alternatively at 250, 275, or 280 nm, using a gradient method aimed at detection of impurities. The samples were further analyzed by LC/MS to confirm the molecular weight of the drug and any degradants.

Table 1, which follows, provides data from drug amines volatilized using the above-recited general procedures A and B.

**TABLE 1**

| Generic Name | MW | Dose (mg) | Method | Sur-face Area | Thick-ness (μm) | Mass coated (mg) | Yield | % Pur-ity |
|---|---|---|---|---|---|---|---|---|
| Apomorphine HCl | 304 | 2 | B | 6 | 1.1 | 0.68 | 0.60 | 98.1 |
| Apomorphine HCl Diacetate | 388 | 2 | A | 20 | 1.0 | 1.9 | 1.65 | 94 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Brompheniramine Maleate | 435 | 2 | A | 20 | 2.8 | 5.60 | 3.4 | 99.6 |
| Brompheniramine Maleate | 435 | 2 | A under argon | 20 | 3.2 | 6.40 | 3.2 | 100 |
| Buprenorphine HCl | 504 | 0.3 | A | 20 | 1.1 | 2.10 | 1.37 | 91.4 |
| Buprenorphine HCl | 504 | 0.3 | A | 20 | 0.05 | 0.1 | 0.08 | 98.0 |
| Bupropion HCl | 276 | 100 | A | 20 | 1.1 | 2.30 | 2.1 | 98.5 |
| Bupropion HCl | 276 | 100 | A under argon | 20 | 1.1 | 2.30 | 1.8 | 99.1 |
| Buspirone HCl | 422 | 15 | A | 20 | 4.2 | 8.30 | 2.42 | 97.8 |
| Carbinoxamine Maleate | 407 | 4 | A | 20 | 3.9 | 7.70 | 4.8 | 99 |
| Carbinoxamine Maleate | 407 | 4 | A under argon | 20 | 3.4 | 6.8 | 3.0 | 100 |
| Chlorpheniramine Maleate | 391 | 8 | A | 20 | 1.6 | 3.20 | 2.1 | 99.6 |
| Chlorpheniramine Maleate | 391 | 8 | A under argon | 20 | 2.1 | 4.2 | 2.1 | 100 |
| Clemastine Fumarate | 460 | 1.34 | A | 20 | 2.9 | 5.70 | 1.8 | 76.6 |
| Cyproheptadine HCl | 324 | 4 | A | 20 | 2.2 | 4.30 | 2.6 | 99.6 |
| Cyproheptadine HCl | 324 | 4 | A under argon | 20 | 1.8 | 3.5 | 2.1 | 99.6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Diphenhydr-amine HCl | 292 | 25 | A | 20 | 2.5 | 4.9 | 3.7 | 90.3 |
| Diphenhydr-amine HCl | 292 | 25 | A under argon | 20 | 2.6 | 5.2 | 3.9 | 93.3 |
| Enalapril maleate | 493 | 5 | B | 8 | 1.1 | 0.85 | 0.29 | 61.0 |
| Fluphenazine 2HCl | 510 | 1 | B | 8 | 1.0 | 0.78 | 0.33 | 80.7 |
| Hydroxyzine 2HCl | 448 | 50 | A | 20 | 13.7 | 27.30 | 0.25 | 41.2 |
| Hydroxyzine 2HCl | 448 | 50 | A under argon | 20 | 12.8 | 25.60 | 1.4 | 70.8 |
| Meclizine 2HCl | 464 | 25 | A | 20 | 9.7 | 19.40 | 0.5 | 75.3 |
| Meclizine 2HCl | 464 | 25 | A under argon | 20 | 11.7 | 23.40 | 0.4 | 70.9 |
| Mexiletine HCl | 216 | 200 | B | 8 | 0.9 | 0.75 | 0.44 | 99.4 |
| Nicotine HCl | 198 | 1 | A | 32 | 3.2 | 10.3 | 5.4 | 99.9 |
| Nicotine 2HCl | 235 | 1 | A | 32 | 4.6 | 14.8 | 12.9 | 99.5 |
| Nicotine Sulfate | 260 | 1 | A | 32 | 2.5 | 8.0 | 1.8 | 97.0 |
| Prochlorpera-zine 2HCl | 446 | 5 | B | 8 | 0.8 | 0.65 | 0.24 | 72.4 |
| Protriptyline HCl | 299 | 15 | A | 20 | 1.1 | 2.20 | 0.99 | 99.7 |
| Protriptyline HCl | 299 | 15 | A under argon | 20 | 1.1 | 2.1 | 1.1 | 99.8 |
| Pyrilamine Maleate | 401 | 25 | A | 20 | 10.8 | 21.50 | 10.5 | 93.7 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pyrilamine Maleate | 401 | 25 | A under argon | 20 | 10.2 | 20.4 | 9.6 | 90.7 |
| Tranylcypro-mine HCl | 169 | 30 | A | 20 | 1.2 | 2.30 | 1.3 | 97.5 |
| Tranylcypro-mine HCl | 169 | 30 | A under argon | 20 | 1.0 | 2.0 | 1.2 | 97.2 |
| Trifluopera-zine 2HCl | 480 | 7.5 | B | 8 | 1.2 | 0.97 | 0.52 | 87.5 |
| Trimipramine Maleate | 411 | 50 | A | 20 | 1.2 | 2.40 | 1.6 | 95.9 |
| Trimipramine Maleate | 411 | 50 | A under argon | 20 | 1.1 | 2.20 | 2.1 | 97.4 |

## EXAMPLE 3

**General Procedure A for Screening Drug Amine Salts for Aerosolization Preferability**

Drug amine salt (1 mg) was dissolved or suspended in a minimal amount of solvent, such as for example, methanol. The solution or suspension was pipeted onto the middle portion of a 3 cm by 3 cm piece of aluminum foil. The coated foil was wrapped around the end of a 1½ cm diameter vial and secured with parafilm. A hot plate was preheated to approximately 300 °C, and the vial was placed on it foil side down. The vial was left on the hotplate for 10 s after volatilization or decomposition had begun. After removal from the hotplate, the vial was allowed to cool to room temperature. The foil was removed, and the vial was extracted with dichloromethane followed by saturated aqueous $NaHCO_3$. The organic and aqueous extracts were shaken together, separated, and the organic extract is dried over $Na_2SO_4$. An aliquot of the organic solution was removed and injected into a reverse-phase HPLC with detection by absorption of UV light, generally at 225 nm. A drug amine salt was preferred for aerosolization where the purity of the drug isolated by this method was greater than 85%. Such a drug amine salt has a decomposition index less than 0.15. The decomposition index was arrived at by substracting the fractional purity (*i.e.*, 0.85) from 1.

## EXAMPLE 4

**General Procedure B for Screening Drug Amine Salts for Aerosolization Preferability**

Volatilizations were done using a setup which consists of two 1 farad capacitors wired in series and controlled by a 12-volt relay. A dip coated substrate (prepared as described in Example 2) was placed in a surrounding tube connected at the exit end via Tygon tubing to a filter holder fitted with a Savillex Teflon filter and the junction is sealed with paraffin film. The substrate was placed in a fitting which connects it to the capacitors. The capacitors were charged by a separate power source to about 16-21 volts and all the power was channeled to the substrate by closing a switch and allowing the capacitors to discharge into the substrate. The substrate was heated to a temperature of ~ 400°C in ~ 50 milliseconds. This heating process was done under an airflow of 15 L/min, which swept the vaporized drug aerosol into a 2 micron Teflon filter. After volatilization, the aerosol captured on the filter was recovered for analysis. Any material deposited on the glass sleeve or remaining on the substrate was also recovered. The recovered materials were analyzed by HPLC UV absorbance, generally at 225 nm, or alternatively at 250, 275, or 280 nm, using a gradient method aimed at detection of impurities. The samples were further analyzed by LC/MS to confirm the molecular weight of the drug and any degradants. A drug amine salt was preferred for aerosolization where the purity of the drug isolated by this method was greater than 85%. Such a drug amine salt has a decomposition index less than 0.15. The decomposition index was arrived at by substracting the fractional purity (*i.e.*, 0.85) from 1.

## EXAMPLE 5

### Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Amine Drug Aerosol

A solution of 50-200 mg of amine drug salt per mL of solvent was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The solvent was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 3.5-6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. MMAD of the collected aerosol ranged between 1 and 3 microns with a

geometric standard deviation of less than 3. The number of particles collected on the various stages of the cascade impactor was given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 $g/cm^3$). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time.

## EXAMPLE 6

### Drug Mass Density of Amine Drug Aerosol From Amine Drug Salts

A solution of 50-200 mg of amine drug salt per mL of solvent was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The solvent was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after about 3.5-5 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of the amine drug revealed the purity of the amine drug that had been collected in the flask, resulting in a calculatable aerosol drug mass density.

Although certain embodiments and examples have been used to describe the present invention, it will be apparent to those of skill in the art that changes may be made to those described embodiments and examples without departing from the scope or spirit of the invention of the following claims.

What is Claimed:

1. A method of selecting an amine drug salt suitable for use in forming a condensation aerosol, comprising

a. dissolving or suspending an amine drug salt in a solvent,

b. coating the suspended or dissolved amine drug salt on a substrate,

c. heating the coated substrate to form a compound vapor,

d. cooling the vapor to form aerosol particles,

e. collecting the aerosol particles,

f. analyzing the collected particles to determine the purity of the aerosol particles; and

g. selecting the amine drug based on a decomposition index less than 0.15.

2. The method of Claim 1, wherein said substrate is metallic.

3. The method of Claim 2, wherein said metallic substrate is aluminum foil or stainless steel.

4. The method of Claim 2, wherein said heating is on a hot plate.

5. The method of Claim 4, wherein said heating is to a temperature approximately about 300 °C.

6. The method of Claim 1, wherein said heating is resistance heating.

7. The method of Claim 6, wherein said heating is to a temperature of approximately about 400 °C.

8. The method of Claim 1, wherein the amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

9. An aerosol comprising an amine drug from an amine drug salt selected by the method of Claim 2, wherein said amine drug salt is vaporized and condensed to form

amine drug aerosol particles having a mass median aerodynamic diameter between the range of 1 and 3, and has less than 10% amine drug decomposition products.

10. The aerosol of Claim 9, wherein said amine drug salt has a molecular weight between 200 to 600.

11. The aerosol of Claim 9, wherein said amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

12. A method of delivering an amine drug in an aerosol form, comprising

a. heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating,

b. by said heating, forming a amine drug vapor, and

c. during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.

13. The method according to claim 12, wherein said coating of amine drug salt has a thickness between about 0.2 and 20 μm.

14. The method according to Claim 13, wherein said aerosol particles have a mass median aerodynamic diameter between about 1 and 3 microns.

15. The method of Claim 14, wherein the amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

16. The method according to claim 15, wherein said amine drug salt has a molecular weight between 200 to 600.

17. A thermal vapor comprising gas and amine drug aerosol particles,

a. wherein said gas comprises an acid halide vapor, organic acid vapor, or organic acid decomposition product vapor, and

b. wherein said amine drug aerosol particles

i. comprise at least 10 micrograms of an amine drug and less than 10% amine drug decomposition products relative to said total mass of amine drug in the particles, and

ii. have a mass median aerodynamic diameter in the range 1 to 5 micrometers.

18. The thermal vapor of Claim 17, wherein said gas further comprises supersaturated drug amine vapor.

19. The thermal vapor of Claim 18, wherein said supersaturated drug amine vapor has a temperature of greater than 200°C.

20. The thermal vapor of Claim 17, wherein said drug amine aerosol particles have a mass median aerodynamic diameter in the range 1 to 3 micrometers.

21. The thermal vapor of Claim 17, wherein the amine drug is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

22. A method of forming an effective human therapeutic inhalation dose of drug amine aerosol particles having less than 10% degradation products and a drug amine particle mass median aerodynamic diameter between about 1 and 5 micrometers, comprising

a) providing a drug delivery article comprising a body defining an interior flow-through chamber having upstream and down stream chamber ends and a drug supply unit contained within such chamber, wherein said drug supply unit comprises a heat-conductive substrate coated with a composition comprising at least a therapeutic amount of amine drug salt having a decomposition index less than 0.10;

b) heating said heat-conductive substrate to a temperature of greater than 200°C over a period of less than 5 seconds, thereby producing a vapor of a therapeutic dose of said amine drug salt; and

c) flowing a gas through said chamber thereby cooling said vapor to form drug amine aerosol particles.

23. The method according to Claim 22, wherein the drug amine salt is a salt selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

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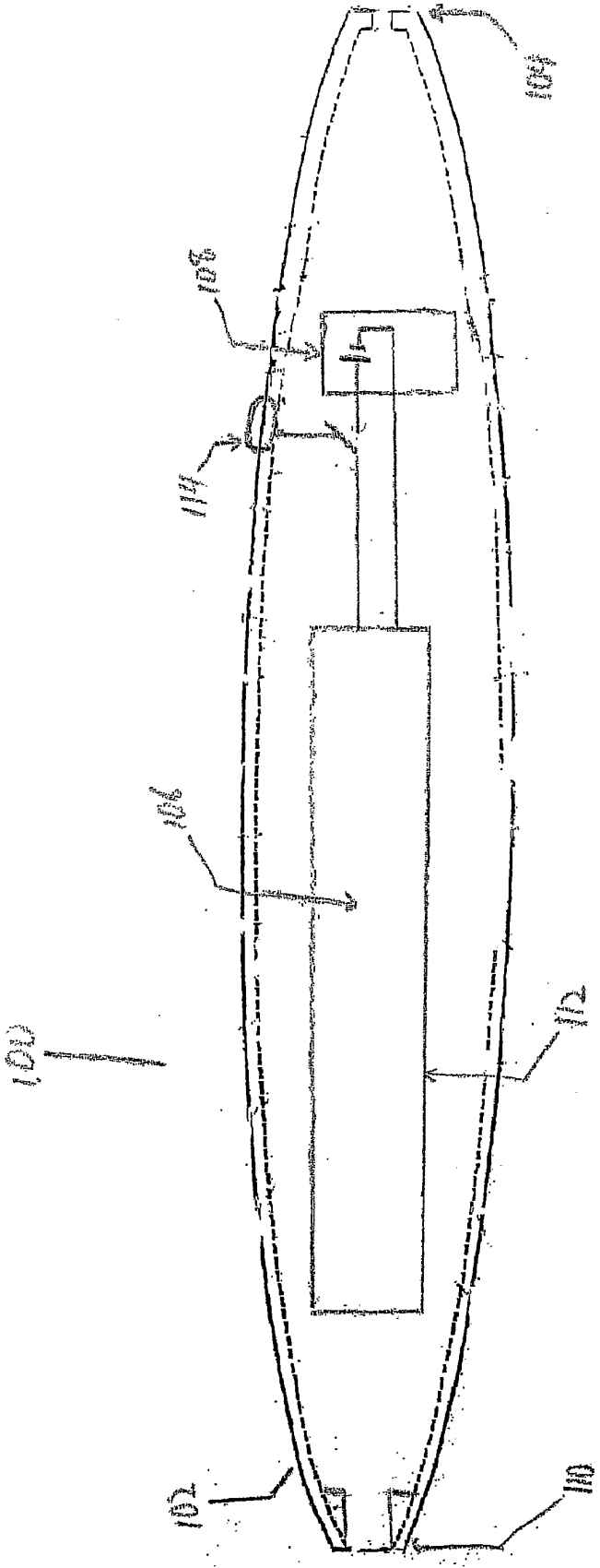



Fig. 1

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/14976

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/72 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 7 A61K 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)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | MENG YUN ET AL: "Pharmacological effects of methamphetamine and other stimulants via inhalation exposure." DRUG AND ALCOHOL DEPENDENCE, vol. 53, no. 2, 7 January 1999 (1999-01-07), pages 111-120, XP002255929 ISSN: 0376-8716 abstract paragraphs '02.3!,'02.5!,'03.1! page 118, right-hand column, last paragraph -page 119, left-hand column, paragraph 1 --- -/-- | 9-11, 17-21 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 29 September 2003 | 17/10/2003 |

| Name and mailing address of the ISA | Authorized officer |
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
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**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-16, 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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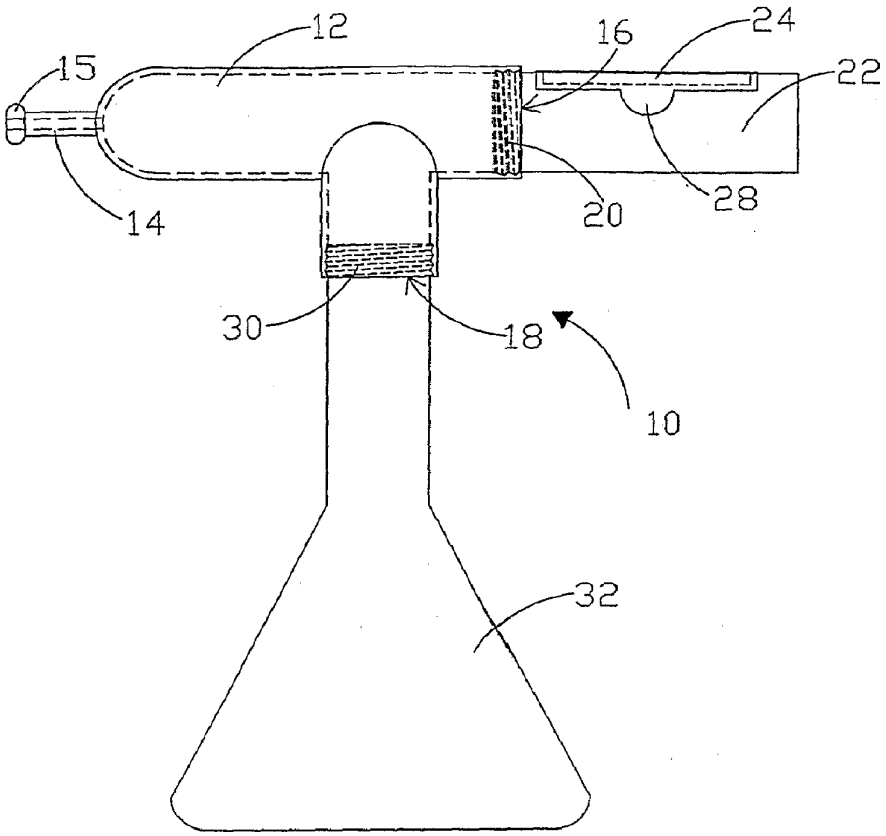
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(54) Title: SMOKING DEVICE




(57) Abstract: There is provided a personal and portable smoking device (10) which comprises a tube (12) provided with a first opening (20), a second opening (14) having a mouthpiece (15) through which smoke is inhaled and a plurality of disposable cartridges (22) with a port (28) through which burning products (24) engaged within the cartridge (22) are exposed to air. The cartridges (22) are connectable to the first opening of the tube (20) through one end. The smoking device (10) further comprises a container (32) with fluid aerodynamically connected to the tube, and a pipe (44) partially passing through the tube (12) and the second opening (18) and outwardly extended to be placed in the fluid. The user connects a cartridge (22) to the first opening (20) and burns the burning products (24). When the user inhales through the mouthpiece (15), the generated smoke from the combustion of the burning products (24) bubbles through the fluid in the connected container (32) and is inhaled through the mouthpiece (15).

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# SMOKING DEVICE

## FIELD OF THE INVENTION

The present invention relates to smoking devices. More particularly, the present invention relates to personal and portable hookah-based smoking device having a changeable and disposable tobacco cartridge and a method of using the same.

## BACKGROUND OF THE INVENTION

The traditional hookah or the water-pipe is a well known smoking device that was originally invented in Turkey and was used especially in oriental and middle-east countries. Since then, the hookah has become very popular in other cultures and penetrated into western countries for the last few decades. The hookah is related also to the traditional oriental custom of smoking in groups of several people in cafés or restaurants while using a single hookah having an inhaling pipe that is transferred from one individual to the others. Smoking hookah is a social custom that involves also the preparation of the tobacco mixture and the burning material as well as introducing the mixture and the burning material in a special part of the hookah.

The traditional hookahs as well as modern water-pipes generally comprise a bottle-like part that is adapted to receive water and a connectable tube having a portion that is adapted to receive the tobacco. The connectable tube is provided with a pipe having two openings wherein one of the openings is adapted to receive the smoke from the tobacco and the other end reaches the water in the bottle-like part so that smoke coming from the tobacco bubbles out through the water to the bottle and the connectable tube. The connectable tube is further provided with another flexible pipe through which

smoke is inhaled. The smoke passes through the water before it is inhaled by the smokers through a mouthpiece.

The passage of the tobacco smoke through water before inhaling the smoke into the mouth and lungs of the user has two objectives: First, some of the materials in the smoke are absorbed in the water without loosing the taste and aroma of the smoke. Therefore, the amount of harmful materials that reach the mouth and lungs of the user is reduced markedly. In fact, the water acts as a filter. Secondly, the water gives the smoke coolness that no cigarette, cigar or another pipe can provide.

One of the disadvantages of smoking a hookah in groups of people is that everyone has to smoke the same tobacco that has a certain taste and aroma. There are many types of tobacco as well as many types of fruit molasses and other flavor materials that smokers wish to mix in their tobacco. Each one of the mixtures has a certain taste and aroma. People develop preferences towards a certain tobacco mix and do not want to smoke a tobacco that is chosen by other smokers. This brought about the minimization of the hookah and presentation of a small hookah for which the user prepare his own favorite tobacco.

Another disadvantage of using a hookah in groups of people is that transferring the hookah from mouth to mouth is non-hygienic. There are many people that do not want to smoke from a water pipe that was used by other people. Again, the minimized hookah can partially solve the problem.

For smoking the traditional hookah as well as the minimized one, the smoker has to prepare his own mixture of tobacco and other tastes and flavors as well as the burning material while making some preparation in order to enable smoking. Not all people have the time or the delight to prepare the smoking mixtures and would have wanted to smoke tobacco and enjoy the advantages of smoking a hookah without having to make any preparations. Moreover, there is a need to provide a portable smoking device that is hookah-based and can be smoked at work and relatively rapidly without having to go through the tedious preparation of the mixtures and the burning materials.

## SUMMARY OF THE INVENTION

It is an object of the present invention to provide a new and unique hookah-based smoking device that is personal and portable.

It is another object of the present invention to provide a new and unique hookah-based smoking device having a tobacco cartridge that can be disposed of after use and changed to another tobacco cartridge.

It is yet another object of the present invention to provide a new hookah-based smoking device that is hygienic.

An additional object of the present invention is to provide a method of using the smoking device of the present invention.

It is therefore provided in accordance with a preferred embodiment of the present invention a smoking device which smoke pass through fluid, said smoking device comprising:

a tube provided with a first opening, a second opening and a mouthpiece through which the smoke is inhaled;

at least one of a plurality of cartridges connectable to said first opening through one end and wherein each one of said plurality of cartridges is provided with a port through which the burning products are exposed to air;

burning products engaged within said at least one of a plurality of cartridges;

a container adapted to receive the fluid wherein said container is connectable through an open upper end to said second opening and wherein said container is aerodynamically connected to said tube;

a pipe partially passing through said tube and said second opening and outwardly extended to be placed in the fluid received in said container, wherein said pipe is aerodynamically communicating with one of said plurality of cartridges that is

connected to first opening through a hole provided at said one end;

whereby after the user connects one of said plurality of cartridges to said first opening and burns the burning products, smoke generated from the combustion of the burning products passes through said hole into said pipe, and bubbles through the fluid in the connected container and then transferred into the tube and inhaled through said mouthpiece by the user, and wherein after the burning products are burnt out, the user disposes of the cartridge and replaces it with another one of said plurality of cartridges.

Furthermore, in accordance with yet another preferred embodiment of the present invention, the burning products comprise tobacco and coal.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein said tobacco resides in said bottom part and said coal resides in said upper part.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said tobacco is partially confined within a mesh screen so as to prevent its spreading.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said coal is in the shape of a stick that is positioned on top of said perforated sheet and is provided with a stopper that prevents its fully ejection from the cartridge.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said tobacco is mixed with fruit molasses or flavor materials.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is provided with a removable seal that seals said hole when the cartridge is not connected to said tube.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said port is sealed with a removable seal.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said removable seal is adhered to edges of said port.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is further provided with an additional opening substantially opposite said one end, wherein said additional opening is positioned so as to facilitate initiation of combustion of said burning products.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part and wherein said additional opening is positioned so as to allow said coal to be partially withdrawn through said additional opening.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is screwed to a corresponding screw provided in said first opening.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said open upper end is screwed to a corresponding screw provided in said second opening.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said container is provided with a broad base.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said container is an elongated tube provided with a flat base.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said fluid is water.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said at least one of a plurality of cartridges is made of a ceramic material.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said mouthpiece comprises a stem and a bit.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said container is provided with a cover adapted to cover said open upper end when said smoking device is not in use.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said first opening is provided with a plug through which said pipe passes.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said second opening is provided with a plug and wherein said plug is provided with a hole through which said pipe passes and at least one bore allowing said container to aerodynamically communicate with said tube.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said at least one bore is provided with a valve adapted to prevent fluid from the container to enter said tube.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said valve is a conical element provided with a confined float.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said float is a ball.

Furthermore, it is provided in accordance with yet another preferred embodiment of the present invention a disposable cartridge to be used in a personal smoking device in which smoke passes through fluid, said disposable cartridge comprises:

one end adapted to be connected to the smoking device;

burning products engaged within said disposable cartridge;

port through which said burning products are exposed to air;

Furthermore, in accordance with another preferred embodiment of the present invention, said disposable cartridge is further provided with an additional opening substantially opposite said one end, wherein said additional opening is positioned so as to facilitate initiation of combustion of said burning products.

Furthermore, in accordance with another preferred embodiment of the present invention, said disposable cartridge is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part and wherein said additional opening is positioned so as to allow said coal to be partially withdrawn through said additional opening.

It is furthermore provided in accordance with yet another preferred embodiment of the present invention, a method for smoking a smoking device in which smoke passes through fluid, said method comprising:

providing a smoking device comprising:

a tube provided with a first opening, a second opening, and a mouthpiece through which the smoke is inhaled;

at least one of a plurality of cartridges provided with burning products, said plurality of cartridges adapted to allow combustion of the burning products engaged within, wherein each one of said plurality of cartridges is connectable to said first opening through one end and wherein each one of said plurality of cartridges is provided with a port sealed with a first removable seal;

a container adapted to receive the fluid wherein said container is connectable through an open upper end to said second opening and wherein said container is aerodynamically connected to said tube;

a pipe partially passing through said tube and said second opening and outwardly extended to be placed in the fluid received in said container, wherein said pipe is aerodynamically communicating with each one of said plurality of cartridges that is connected to first opening through a hole provided at said one end;

a second removable seal provided on said hole;

removing said second removable seal from one of said plurality of cartridges;

connecting one of said plurality of cartridges through one end to said first opening;

removing said second seal;

providing fluid in said container;

connecting said container to said second opening;

removing said first seal;

lighting said burning products;

inhaling the smoke through said mouthpiece;

disconnecting said one of a plurality of cartridges after said burning products are burnt;

disposing said one of a plurality of cartridges;

providing another one of said plurality of cartridges;

whereby each one of said plurality of cartridges is connected to said tube and disposed after used in the same manner.

Furthermore, in accordance with yet another preferred embodiment of the present invention, said method further comprises providing to each one of said plurality of cartridges an additional opening opposite said one end, said additional opening is adapted to facilitate initiation of combustion of the burning products.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part and wherein said additional opening is positioned so as to allow said coal to be partially withdrawn through said additional opening.

Furthermore, in accordance with yet another preferred embodiment of the present invention, each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part.

Additionally, in accordance with yet another preferred embodiment of the present invention, said tobacco is confined in a mesh screen so as to prevent its spreading.

## BRIEF DESCRIPTION OF THE FIGURES

In order to better understand the present invention and appreciate its practical applications, the following Figures are attached and references herein. Like components are denoted by like reference numerals.

It should be noted that the figures are given as examples and preferred embodiments only and in no way limit the scope of the present invention as defined in the appending Description and Claims.

Figures 1a - c illustrate a frontal view, a side view and an upper view, respectively, of a hookah-based smoking device in accordance with a preferred embodiment of the present invention.

Figures 2a - c illustrate cross sectional frontal view and upper view of the tube of the hookah-based smoking device shown in Figure 1. An enlarged view of a valve provided in the plug of the smoking device is shown in Figure 2c.

Figure 3 illustrates a frontal view of a hookah-based smoking device in accordance with another preferred embodiment of the present invention.

Figure 4 illustrates a cross sectional view of the two optional containers in accordance with preferred embodiments of the present invention, disassembled from the hookah-based smoking device.

Figures 5a - e illustrate different views as well as cross sectional views of the tobacco cartridge of the hookah-based smoking device shown in Figure 1.

Figures 6 a - f illustrate different views and cross sectional views of a tobacco cartridge in accordance with another preferred embodiment of the present invention.

Figure 7 illustrates the smoking device shown in Figure 1, disassembled.

## DETAILED DESCRIPTION OF THE INVENTION AND THE FIGURES

The present invention provides a new and unique smoking device that is based on the traditional hookah; however, the smoking device of the present invention is portable. The Hookah-based smoking device is also personal in the sense that it is not designed to be transferred between a few smokers and an individual smoker can smoke it alone.

An additional unique feature of the hookah-based smoking device is in the possibility to provide the tobacco in a specially designed cartridge that is connected to the smoking device. The cartridge can contain tobacco having different tastes and aromas. This feature eliminates the need of the smoker to mix and prepare the tobacco mixture and the burning material on his own. The tobacco mixture and the burning material are provided in a disposable cartridge that is changeable. Cartridges of various tobacco types are available so that the smoker can change the cartridge according to his needs and taste.

In a preferred embodiment of the present invention, the hookah-based smoking device comprises a tube through which the user inhales the smoke. The smoke is originated from a connectable tobacco cartridge in which the burning products and preferably tobacco burns using a burning material such as coal. The coal has to be of such a kind that burns quickly. The tobacco cartridge is open to the air so as to facilitate an effective burning of the tobacco and the burning material. The tobacco cartridge can preferably be screwed onto the tube. The cartridge is disposable. The hookah-based smoking device further comprises a container that is connected to the tube. The container is adapted to receive a fluid such as water. The smoke generated in the tobacco cartridge enters the tube through a pipe having an opening that is positioned in the water in the container. The smoke that passes through the pipe bubbles out from the opening that is positioned in the water. The user, which inhales the smoke, receives smoke that is cooled by the water and is partially lack in some of the ingredients that are not desirable and are being absorbed by the water while passing through them. It should be

emphasized that the cartridge can be filled with materials other than tobacco. It can be filled with herbs of any kind such as healing or medicine herbs.

Reference is now made to Figures 1a, b, and c illustrating a frontal view, a side view and an upper view of a hookah-based smoking device in accordance with a preferred embodiment of the present invention. Smoking device 10 comprises a tube 12 having a mouthpiece preferably provided with a stem 14 and a bit 15 through which smoke that is received in tube 12 can be inhaled by a user. Tube 12 is provided with two openings; a first opening 16, which is concentric to the tube, and a second opening 18, which is preferably provided on the side of the tube. First opening 16 is provided with a screw 20 to which a complementary screw of a tobacco cartridge 22 can be connected. Tobacco cartridge 22 is concentric with respect to tube 12 and is provided with a side port 24. Side port 24 is provided with a seal 26 having a clasp 28 with which seal 26 can be removed of tobacco cartridge 22 (the seal is clearly shown in Figure 1c). Seal 26 is preferably a flexible sheet that is adhered on the edges of side port 24. A comprehensive explanation regarding tobacco cartridge 22 and other optional embodiments of tobacco cartridges are disclosed herein after.

Second opening 18 of tube 12 is provided with a screw 30 to which a complementary screw of a container 32 can be connected. Smoke generated in tobacco cartridge 22 is transferred into tube 12 through container 32. Container 32 is preferably filled with water (not shown in Figure 1) so that the smoke bubbles through the water before entering tube 12. While the smoke bubbles pass through the water, some of the materials that are generated by the burning process of the tobacco are absorbed by the water that acts as a filter. Moreover, the smoke in the bubbles is cooled by the water and the user inhales cooled smoke.

It is noted that the container may be filled with any fluid that may act as an absorbent or a solution that comprises an absorbent material as well as a mixture within an absorbent material is mixed. However, water is generally a common and efficient absorbent that can be found anywhere.

In order to better understand the passage of the smoke generated in the tobacco cartridge into the tube through the container, reference is now made to Figure 2 illustrating a cross sectional frontal view of the tube of the hookah-based smoking device shown in Figure 1. First opening 16 is provided with a plug 40 having a bore 42. A substantially L-shaped pipe 44, having a first opening 47 and a second opening 48, pass through tube 12. First opening 47 is placed in bore 42 of plug 40 so that smoke generated in tobacco cartridge (not shown in Figure 2) is communicating with pipe 44 and there is no direct aerodynamic connection between the tobacco cartridge and tube 12. A portion of pipe 44 that comes out of second opening 18 is positioned outside tube 12. The portion of pipe 44 that is outside tube 12 is adapted to be positioned in container 32 that is screwed onto screw 30 (the container is not shown in Figure 2). Second opening 48 is positioned in container 32 inside the water that is received in the container.

When the user inhales through the mouthpiece of smoking device 10, the pressure in the cavity of tube 12 is reduced as well as the pressure in container 32. Therefore, smoke is driven to pass through pipe 44 from tobacco cartridge 22 and into container 32. The smoke bubbles through the water in the container in order to equilibrate the pressure in the container and in the tube. Container 32 is fluidically connected to tube 12 so that the smoke that bubbles out from pipe 44 is free to fill the cavity in tube 12 and to be inhaled by the user through bit 15.

Since the container is filled with water and there is a possibility that the water will enter tube 12 if smoking device 10 is held in a declined manner, opening 18 is provided with a plug 50. Plug 50 is provided with a first hole 52 through which pipe 44 passes and preferably two additional bores provided with valves 54. In a preferred embodiment that is shown in Figure 2, valves 54 are operated such as a snorkel. The valves are clearly shown in Figure 2c, which is an enlargement of the valves in the bores. The walls of the bores as well as the valves are conical so that the upper openings of the valves that face tube 12 are smaller than the bottom openings that face container 32. Each one of valves 54 is provided with a light ball 56 that is caged in the valve

using preferably four hooks 60. When the water is in the container and the user inhales through the mouthpiece, the smoke is free to pass through valves 54. If the smoking device is inclined and the water reaches opening 18, light balls 56, which are light enough to float on the water surface, are upwardly advancing towards the upper openings of valves 54. Since the diameter of the balls 56 is slightly longer than the diameter of the upper openings of the valve, balls 56 seal the openings so that water cannot enter tube 12.

In order for the hookah-based smoking device 10 to be stable in a position where the device is not decline, container 32 is shaped so that it is provided with a broad base. The device can be mounted on a surface while it is supported by the broad base and water cannot enter the tube.

Reference is now made to Figure 3 illustrating a frontal view of a hookah-based smoking device in accordance with another preferred embodiment of the present invention. Hookah-based smoking device 100 generally comprises similar parts as smoking device 10, however, smoking device 100 is provided with a tube-like container 102 that is screwed onto screw 30. Tube-like container is provided with a flat base 104 that supports smoking device 100 when it is mounted on a surface. In this way, the possibility of water entering the tube is lessened.

Reference is now made to Figure 4 illustrating a cross sectional view of the two optional containers in accordance with preferred embodiments of the present invention, disassembled from the hookah-based smoking device. Generally, the container that is adapted to receive water can be of any shape. As mentioned herein, container 32 as well as container 102 are provided with a broad base adapted to support the smoking device when placed on a surface. When the containers are disassembled from the smoking device, they can be supported also by the broad base. A cover 106 is provided as an accessory to the hookah-based smoking device assembly so that when the smoking device is not in use, the container is kept closed. Cover 106 is provided with a screw 108 that corresponds the screw that is provided on the container.

As mentioned herein before, one of the objects of the water is to filter the smoke. Some of the materials in the smoke bubbles that pass through the water are absorbed in the water. The amount of absorbed materials depends on the time the bubbles travels in the water, a factor that depends on the height of the water above opening 48 of pipe 44 (the pipe is not shown in Figure 4). For example, the time in which the bubbles travel in water 110 in container 102 is longer than the time the bubbles travel in the water 112 in container 32. The user can choose the containers shape and size according to his needs and desires as well as the height of the water. The same is applied on the coolness of the smoke that will be inhaled by the user. The more time the bubbles are in the water, the cooler the smoke will be.

The tobacco cartridge can be an empty cartridge that is filled by the user with tobacco and burning material or a cartridge that can be supplied as a disposable cartridge that can be changed in every use.

Reference is now made to Figures 5a - e illustrating different views as well as cross sectional views of the tobacco cartridge of the hookah-based smoking device shown in Figure 1. Figures 5 a, b illustrate an upper and frontal views of tobacco cartridge 22 provided with seal 26. Seal 26 is removed from port 24 when the user wishes to use the smoking device while port 24 has two purposes. The first is to light the burning material and the tobacco that is placed within tobacco cartridge 22 and the second purpose is to allow air with oxygen to be in contact with the burning material so as to enable the heating of the tobacco. Tobacco cartridge 22 has a connection 150 that is provided with a screw 157 that is screwed onto a tube such as tube 12 (not shown in Figure 5). Tobacco cartridge 22 is provided with a seal 154 that seals the cartridge when the smoking device is not in use in order to preserve the tobacco's freshness inside the cartridge. Seal 154 can be replaced by a cover that is screwed onto screw 157. When the cartridge is provided with a single port for lighting, the preferred method of lighting the coal is to hold the cartridge upside down while it is lighted and turning it back afterwards.

Figures 5c and d are frontal and side cross sectional views of tobacco cartridge 22, respectively. Tobacco cartridge 22 is provided with tobacco 156 that resides at the bottom part of the cartridge. Tobacco 156 can be of any kind or can be a mixture of tobacco and other materials that enriches the taste and the aroma of the tobacco. Tobacco 156 is confined in the cartridge so it will not spread out upon removal of seal 154 by a mesh screen 170 that is provided adjacent a hole 168 on the bottom part of the cartridge. Hole 168 allows communication of smoke between the cartridge where the tobacco resided and pipe 44 that is adjacent to connection 150 that connects the cartridge and the tube. A mesh screen 172 adjacent to the bottom of cartridge 22 is adapted to prevent the tobacco from spreading out. Burning material 158 that is preferably coal is placed on top of tobacco 156 so that when burning material 158 is lighten and burns, tobacco 156 is heated. As can be seen from Figure 5d, burning material is preferably designed as a stick so as to facilitate clean and uniform combustion.

A perforated sheet 160 is placed between tobacco 156 and burning material 158. Figure 5e is an upper cross sectional view of tobacco cartridge 22. Perforated sheet 160 is clearly shown in the figure. Perforated sheet 160 is adapted to separate tobacco 156 and burning material 158 so that they will not mix and the taste of the tobacco will be purer. The perforations facilitate the smoke from the burning material to pass through the tobacco as well as oxygen from the air to be in good contact with the tobacco.

It is optional to provide a tobacco cartridge having separate openings; a first opening for lighting the burning material and a second opening allowing air to be in contact with the burning material.

Reference is now made to Figures 6 a-f illustrating different views and cross sectional views of a tobacco cartridge in accordance with another preferred embodiment of the present invention. In tobacco cartridge 200 side port 24 is adapted only for allowing air to be in contact with the coal and the tobacco so as to facilitate efficient combustion. In order to light the coal, an additional opening 202 is provided opposite connection 150. A coal stick 204

is accommodated within the upper part of tobacco cartridge 200. Coal stick 204 can be withdrawn from the cartridge through additional opening 202 so as to facilitate its lighting (clearly shown in Figure 6f which is a side view of the cartridge). Coal stick 204 is provided with a stopper 206 that prevents the complete ejection of the coal stick from tobacco cartridge 200. Additional opening 202 is provided with a screwed cover 208 that keeps the cartridge closed at all times except the time the coal is lighted.

It is emphasized again that the tobacco cartridge in the hookah-based smoking device can be designed as a disposable cartridge so that plurality of cartridges in which different types of burning products are provided, is supplied. Each cartridge can be provided with the tobacco or tobacco mixture of certain taste and aroma. The user can change the cartridge when the tobacco is fully burnt or when he desires for another taste. The tobacco cartridge is disposable so that when the tobacco is fully burnt, the user disposes of the cartridge and connects another one to the tube of the smoking device. The other option is to supply an empty tobacco cartridge in which the user fills in the tobacco as well as the burning material. The tobacco cartridges are preferably made of a material that is adapted to allow combustion of the burning products that are engages within. It is preferably made from a ceramic material, however any other material is covered by the scope of the present invention.

Reference is now made to Figure 7, illustrating the smoking device shown in Figure 1, disassembled. In the method of the present invention, the seal that closes connection 150 (seal 154) is removed before the cartridge is screwed onto opening 16. After the cartridge is connected to the tube, container 32 is filled with water (the water is not shown in Figure 7) and is ready to be screwed onto opening 18 while pipe 44 is positioned in the water. Then port 24 of tobacco cartridge 22 is removed and the coal can be lighten so that air and eventually smoke can be inhaled by the user through bit 15. It is optional to provide the container with water or with any other fluid that act as a filter as mentioned herein before.

It is an optional to provide cartridges having a diameter that corresponds the diameter of the container's upper opening so that before disposal of the cartridge, it is inserted into the fluid container to be cooled.

It should be noted that the burning products may be tobacco or tobacco mixtures. Any mixture of tobacco and other materials such as fruit molasses and other flavor materials or other herbs that are desired to be smoked are covered by the scope of the present invention. The burning material that burns the tobacco or tobacco mixture can be coal, however any other appropriate material can be used in order to establish combustion.

It should be clear that the description of the embodiments and attached Figures set forth in this specification serves only for a better understanding of the invention, without limiting its scope as covered by the following Claims.

It should also be clear that a person skilled in the art, after reading the present specification can make adjustments or amendments to the attached Figures and above described embodiments that would still be covered by the following Claims.

# CLAIMS

1. A smoking device which smoke pass through fluid, said smoking device comprising:

a tube provided with a first opening, a second opening and a mouthpiece through which the smoke is inhaled;

at least one of a plurality of cartridges connectable to said first opening through one end and wherein each one of said plurality of cartridges is provided with a port through which the burning products are exposed to air;

burning products engaged within said at least one of a plurality of cartridges;

a container adapted to receive the fluid wherein said container is connectable through an open upper end to said second opening and wherein said container is aerodynamically connected to said tube;

a pipe partially passing through said tube and said second opening and outwardly extended to be placed in the fluid received in said container, wherein said pipe is aerodynamically communicating with one of said plurality of cartridges that is connected to first opening through a hole provided at said one end;

whereby after the user connects one of said plurality of cartridges to said first opening and burns the burning products, smoke generated from the combustion of the burning products passes through said hole into said pipe, and bubbles through the fluid in the connected container and then transferred into the tube and inhaled through said mouthpiece by the user, and wherein after the burning products are burnt out, the user disposes of the cartridge and replaces it with another one of said plurality of cartridges.

2. The smoking device as claimed in Claim 1, wherein the burning products comprise tobacco and coal.

3. The smoking device as claimed in Claim 2, wherein each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein said tobacco resides in said bottom part and said coal resides in said upper part.

4. The smoking device as claimed in Claim 3, wherein said tobacco is partially confined within a mesh screen so as to prevent its spreading.

5. The smoking device as claimed in Claim 3, wherein said coal is in the shape of a stick that is positioned on top of said perforated sheet and is provided with a stopper that prevents its fully ejection from the cartridge.

6. The smoking device as claimed in Claim 2, wherein said tobacco is mixed with fruit molasses or flavor materials.

7. The smoking device as claimed in Claim 1, wherein each one of said plurality of cartridges is provided with a removable seal that seals said hole when the cartridge is not connected to said tube.

8. The smoking device as claimed in Claim 1, wherein said port is sealed with a removable seal.

9. The smoking device as claimed in Claim 8, wherein said removable seal is adhered to edges of said port.

10. The smoking device as claimed in Claim 1, wherein each one of said plurality of cartridges is further provided with an additional opening substantially opposite said one end, wherein said additional opening is positioned so as to facilitate initiation of combustion of said burning products.

11. The smoking device as claimed in Claim 10, wherein each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part and wherein said additional opening is positioned so as to allow said coal to be partially withdrawn through said additional opening.

12. The smoking device as claimed in Claim 1, wherein each one of said plurality of cartridges is screwed to a corresponding screw provided in said first opening.

13. The smoking device as claimed in Claim 1, wherein said open upper end is screwed to a corresponding screw provided in said second opening.

14. The smoking device as claimed in Claim 1, wherein said container is provided with a broad base.

15. The smoking device as claimed in Claim 1, wherein said container is an elongated tube provided with a flat base.

16. The smoking device as claimed in Claim 1, wherein said fluid is water.

17. The smoking device as claimed in Claim 1, wherein said at least one of a plurality of cartridges is made of a ceramic material.

18. The smoking device as claimed in Claim 1, wherein said mouthpiece comprises a stem and a bit.

19. The smoking device as claimed in Claim 1, wherein said container is provided with a cover adapted to cover said open upper end when said smoking device is not in use.

20. The smoking device as claimed in Claim 1, wherein said first opening is provided with a plug through which said pipe passes.

21. The smoking device as claimed in Claim 1, wherein said second opening is provided with a plug and wherein said plug is provided with a hole through which said pipe passes and at least one bore allowing said container to aerodynamically communicate with said tube.

22. The smoking device as claimed in Claim 1, wherein said at least one bore is provided with a valve adapted to prevent fluid from the container to enter said tube.

23. The smoking device as claimed in Claim 22, wherein said valve is a conical element provided with a confined float.

24. The smoking device as claimed in Claim 23, wherein said float is a ball.

25. A disposable cartridge to be used in a personal smoking device in which smoke passes through fluid, said disposable cartridge comprises:

one end adapted to be connected to the smoking device;

burning products engaged within said disposable cartridge;

port through which said burning products are exposed to air;

26. The disposable cartridge as claimed in Claim 25, wherein said disposable cartridge is further provided with an additional opening substantially opposite said one end, wherein said additional opening is positioned so as to facilitate initiation of combustion of said burning products.

27. The disposable cartridge as claimed in Claim 26, wherein said disposable cartridge is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part and wherein said additional opening is positioned so as to allow said coal to be partially withdrawn through said additional opening.

28. A method for smoking a smoking device in which smoke passes through fluid, said method comprising:

providing a smoking device comprising:

a tube provided with a first opening, a second opening, and a mouthpiece through which the smoke is inhaled;

at least one of a plurality of cartridges provided with burning products, said plurality of cartridges adapted to allow combustion of the burning products engaged within, wherein each one of said plurality of cartridges is connectable to said first opening through one end and wherein each one of said plurality of cartridges is provided with a port sealed with a first removable seal;

a container adapted to receive the fluid wherein said container is connectable through an open upper end to said second opening and wherein said container is aerodynamically connected to said tube;

a pipe partially passing through said tube and said second opening and outwardly extended to be placed in the fluid received in said container, wherein said pipe is aerodynamically communicating with each one of said plurality of cartridges that is connected to first opening through a hole provided at said one end;

a second removable seal provided on said hole;

removing said second removable seal from one of said plurality of cartridges;

connecting one of said plurality of cartridges through one end to said first opening;

removing said first seal;

providing fluid in said container;

connecting said container to said second opening;

removing said first seal;

lighting said burning products;

inhaling the smoke through said mouthpiece;

disconnecting said one of a plurality of cartridges after said burning products are burnt;

disposing said one of a plurality of cartridges;

providing another one of said plurality of cartridges;

whereby each one of said plurality of cartridges is connected to said tube and disposed after used in the same manner.

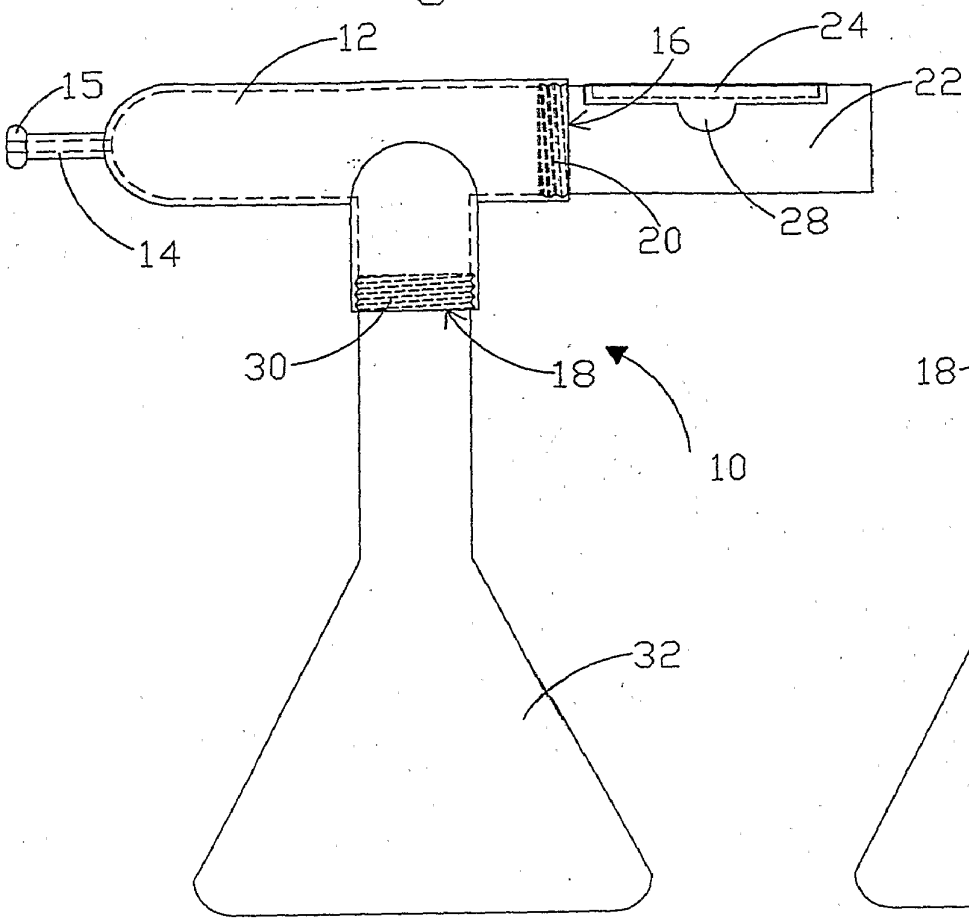
29. The method as claimed in Claim 28, wherein said method further comprises providing to each one of said plurality of cartridges an additional opening opposite said one end, said additional opening is adapted to facilitate initiation of combustion of the burning products.

30. The method as claimed in Claim 29, wherein each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part and wherein said additional opening is positioned so as to allow said coal to be partially withdrawn through said additional opening.

31. The method as claimed in Claim 28, wherein each one of said plurality of cartridges is divided into an upper part and a bottom part by a perforated sheet and wherein the burning products comprise tobacco that resides in said bottom part and coal that resides in said upper part.

32. The method as claimed in Claim 31, wherein said tobacco is confined in a mesh screen so as to prevent its spreading.

Figure 1a



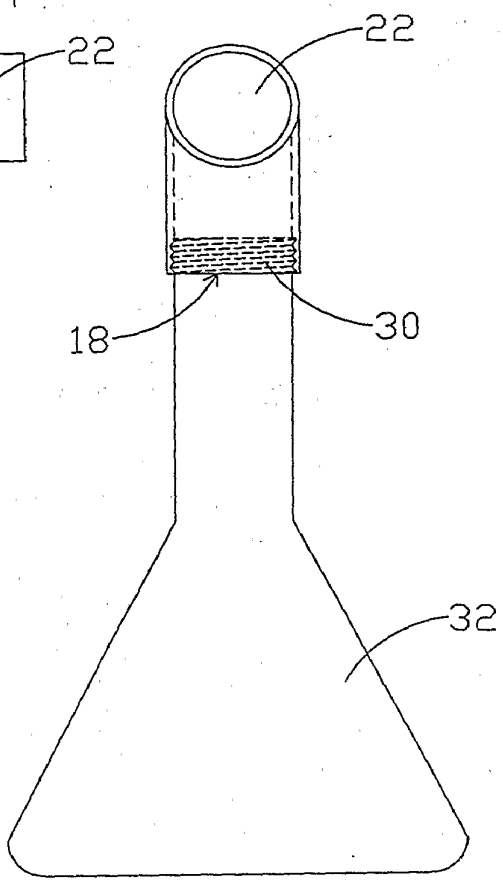




Figure 1b

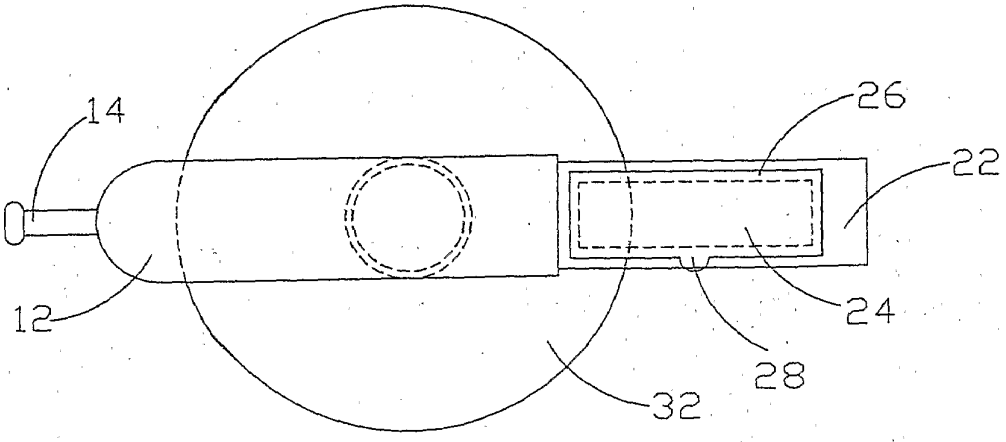
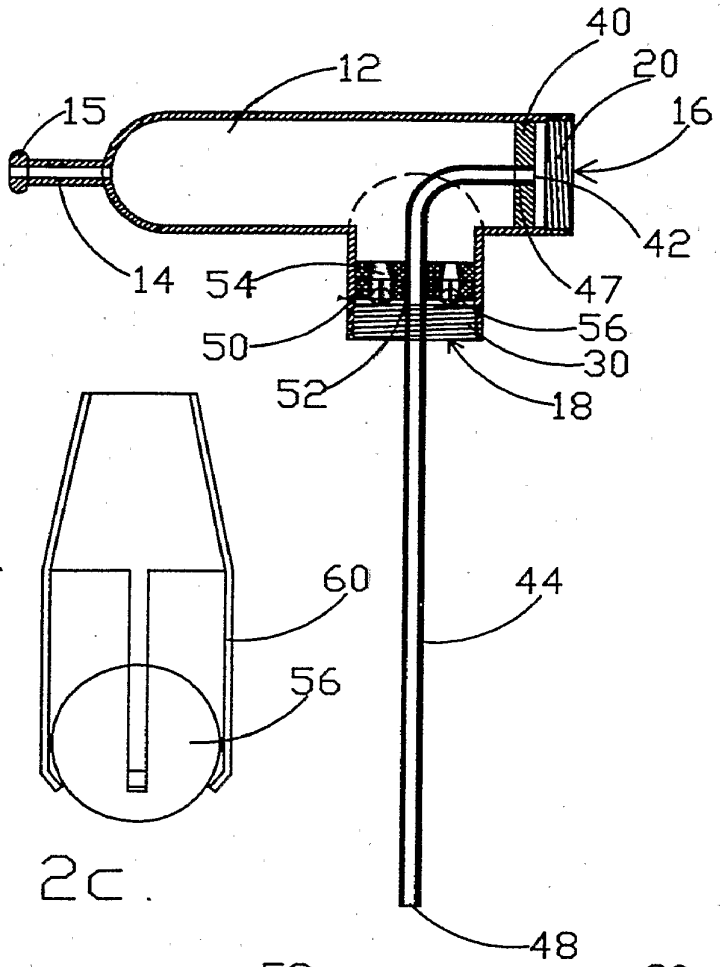



Figure 1c

Figure 2a



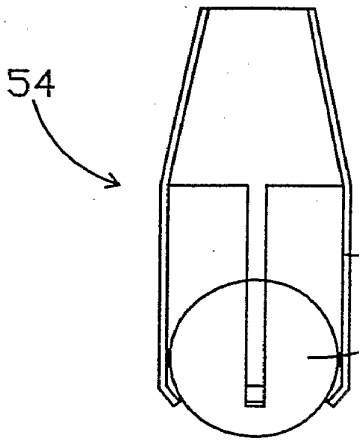




Figure 2c.

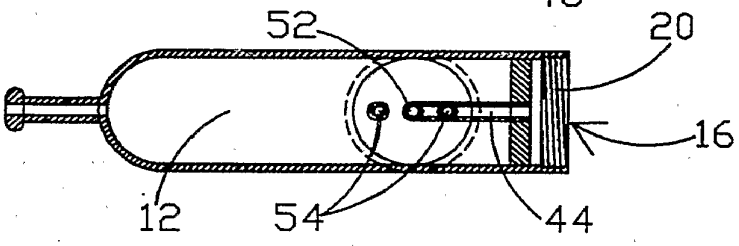



Figure 2b

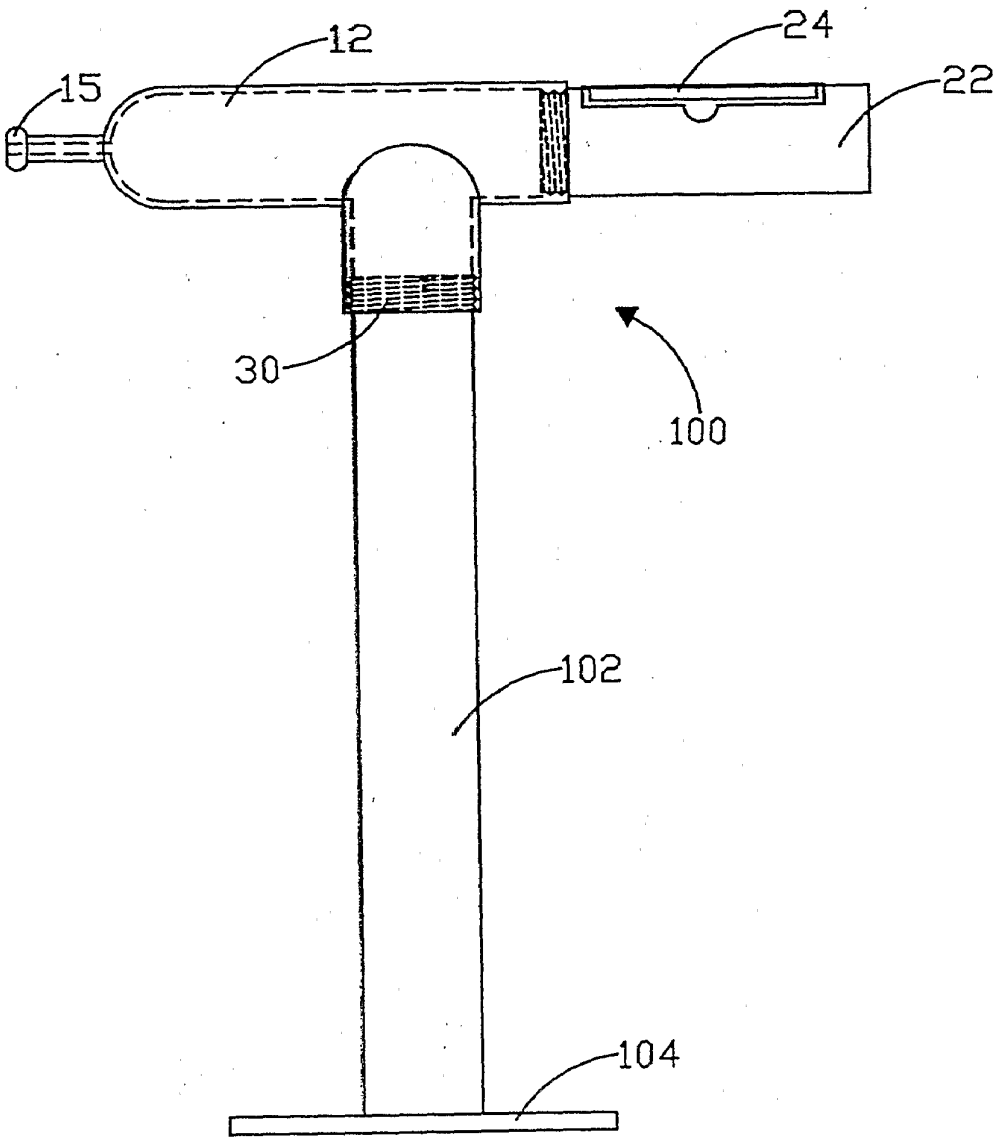



Figure 3

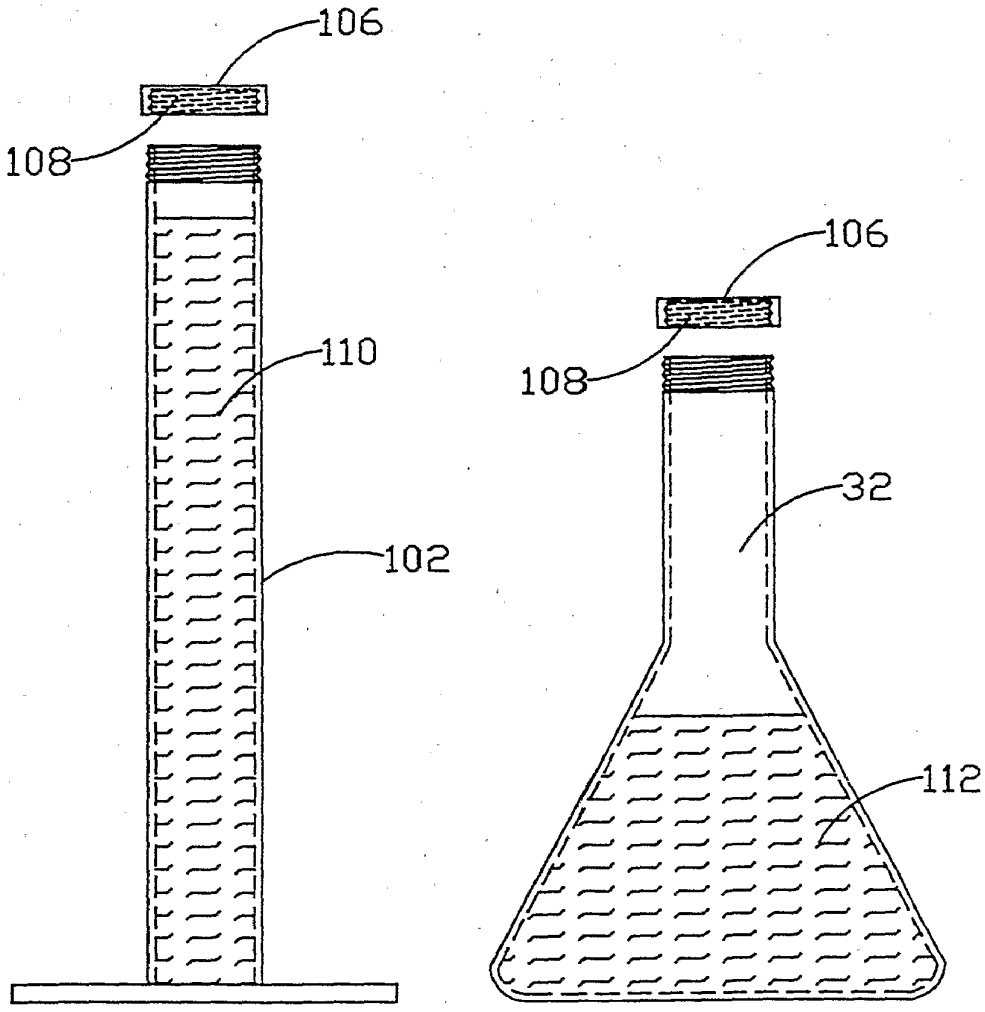



Figure 4

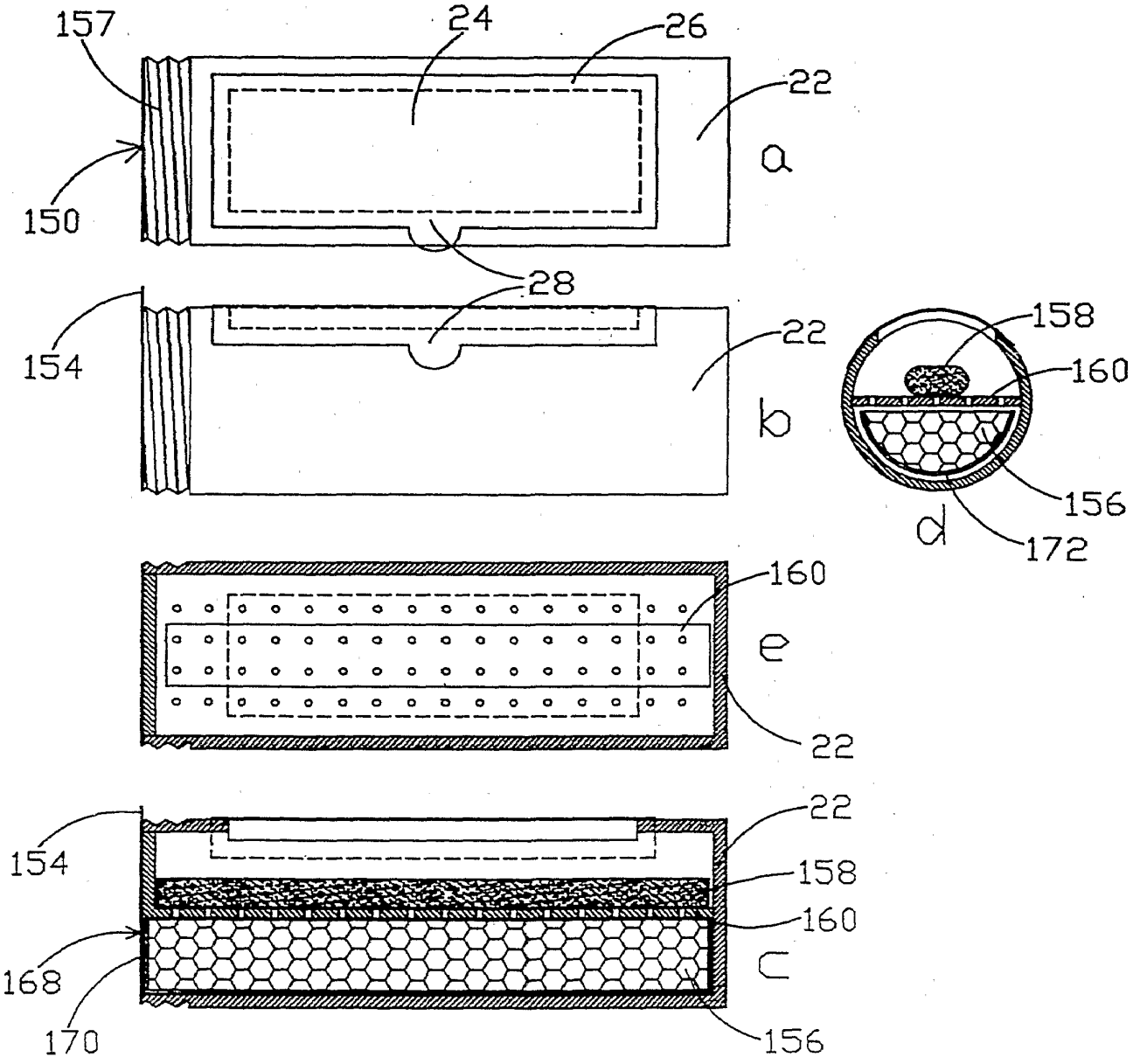

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Figure 5

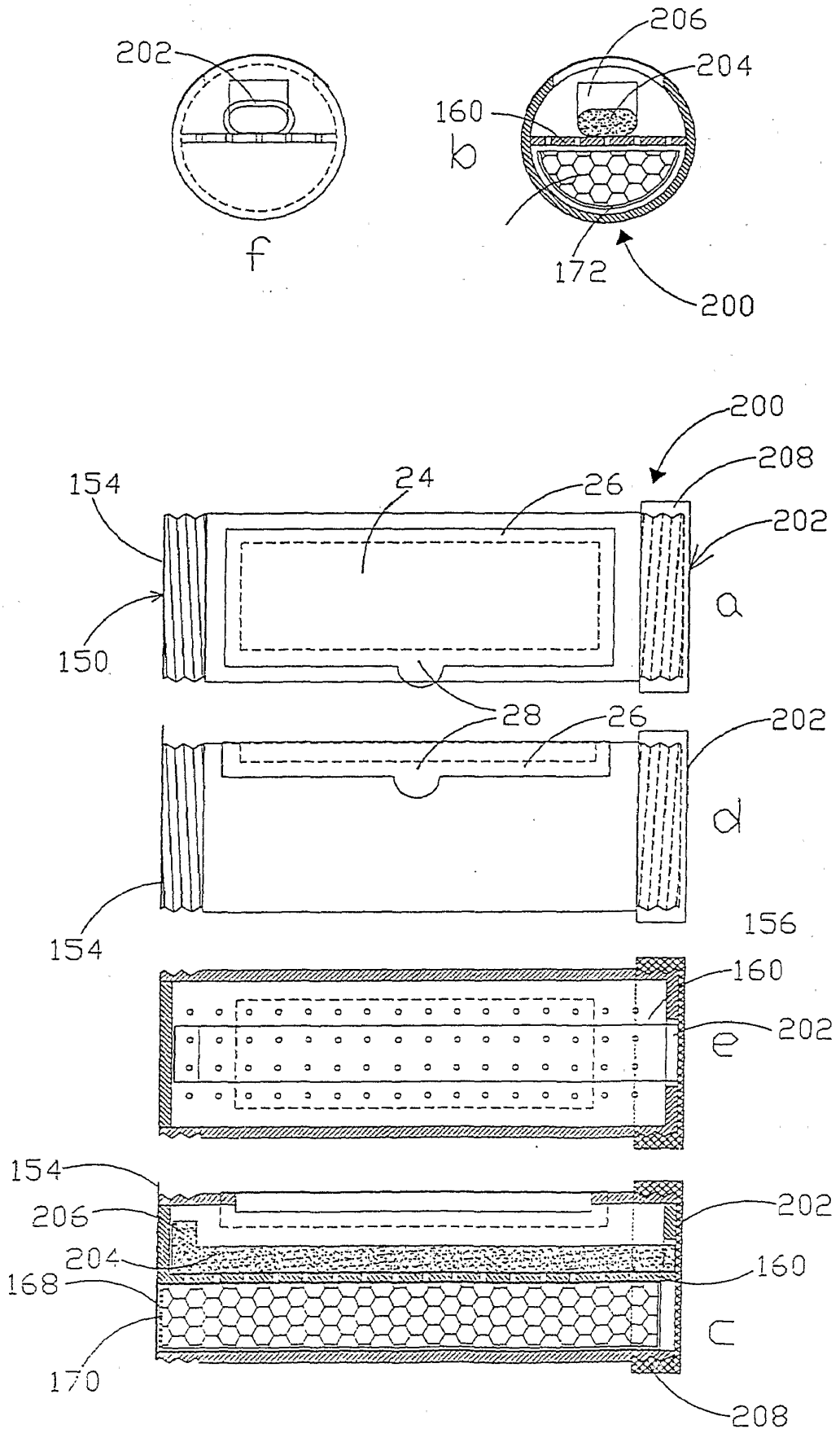

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Figure 6

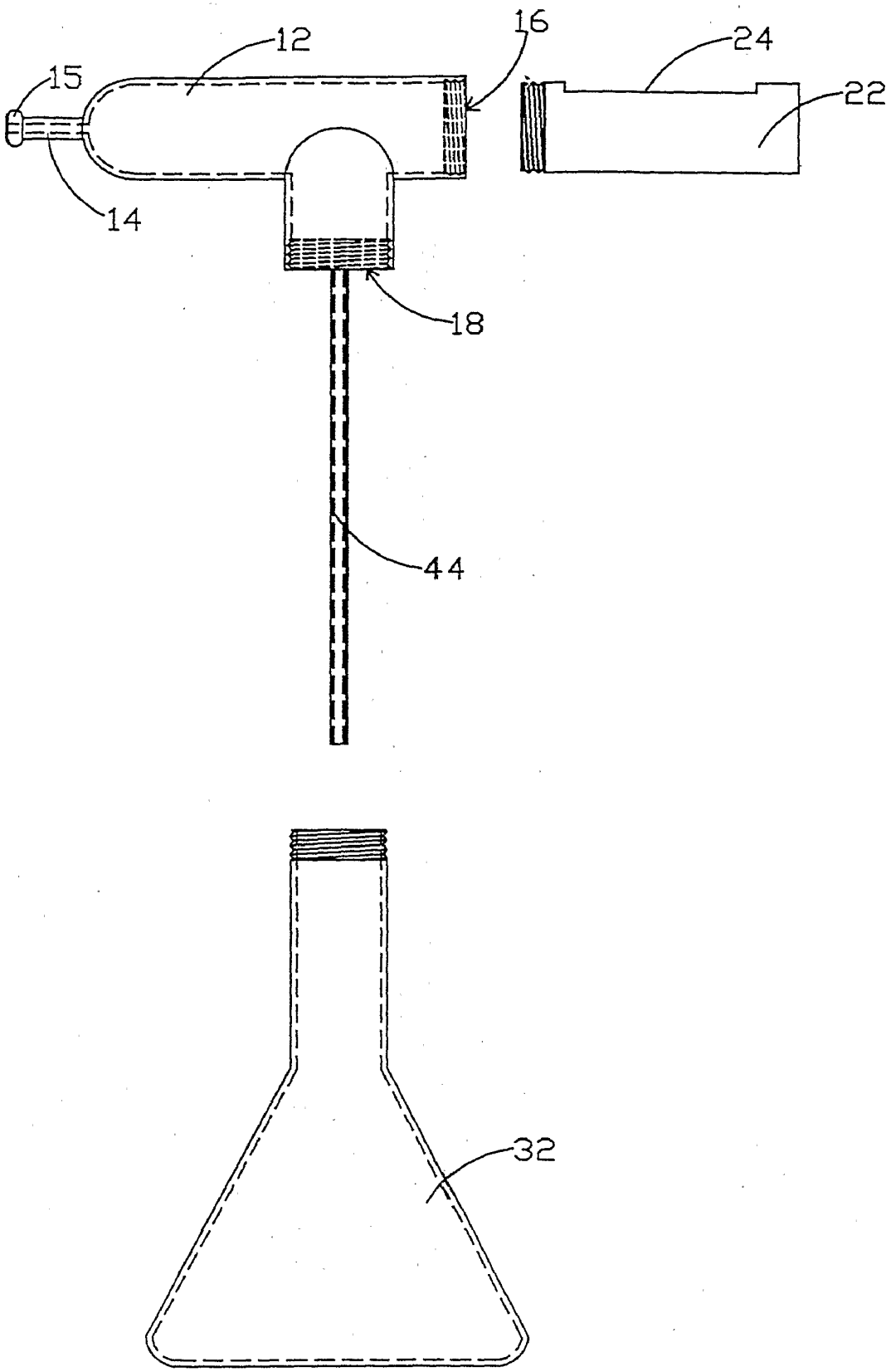



Figure 7

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL03/01121

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A24F 01/14
US CL : 131/173,329

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)
U.S. : 131/173,329

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 practicable, 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 | US 4,638,815 A (YOSHIOKA) 27 January 1987 (27.01.1987), see colums 2 and 3; and see figs) | 1,12-16,18-22 |
| --- | | --- |
| A | | 2-11,17,23-32 |
| A | US 55,321 A (MASSON) 05 June 1866 (05.06.1866), see entire document. | 1-32 |

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 01 May 2004 (01.05.2004) | 17 MAY 2004 |
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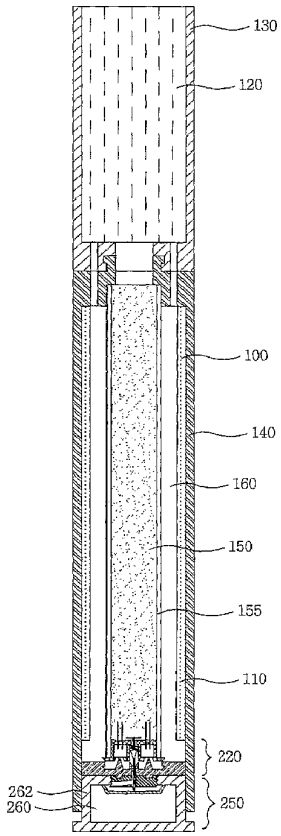
(74) Agent: **HWANG, Eui In**; 10th Floor, Hankook Tire Bldg., 647-15 Yeoksam-dong, Gangnam-gu, Seoul 135-723 (KR).

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*[Continued on next page]*

(54) Title: CLOSED-TYPE SMOKING DEVICE




(57) **Abstract:** Disclosed herein is a closed-type smoking device for inhaling aerosols and gasses, such as cigarette smoke. The smoking device comprises a body and a combustible generating gasses and aerosols upon combustion inside the body in such a manner that the flame and smoke are not spread outside. The smoking device is less harmful to humans, minimizes the damage of second-hand smoke, has no risk of causing a fore or burns, provides various cigarette flavors, is convenient to use without the need for a lighter, is sanitary because no ash falls, and is high quality. Specifically, the closed-type smoking device comprises: a body defining an appearance of the smoking device, the body being closed at one side and opened or filled with a filter at the other side; a combustible inserted inside the body, the combustible being continuously heated or burned to generate gasses and aerosols after ignition; and an igniter for initial ignition of the combustible.

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**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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# CLOSED-TYPE SMOKING DEVICE

## Technical Field

The present invention relates to a smoking device for inhaling aerosols and gasses, such as cigarette smoke. More particularly, the present invention relates to a smoking device which comprises a body and a combustible generating gasses and aerosols upon combustion inside the body in such a manner that flame and smoke are not spread outside. The smoking device of the present invention is less harmful to humans, minimizes the damage of second-hand smoke, has no risk of causing a fire or burns, provides various cigarette flavors, is convenient to use without the need for a lighter, is sanitary because no ash falls, and is high quality.

## Background Art

In general, ideal smoking devices must satisfy the following requirements.

First, smoking devices must be less harmful to habitual smokers themselves.

Conventional cigarettes contain a variety of flavorants for better cigarette flavor, humectants, e.g., glycerin, for maintaining humidity at a constant level to soften the cigarette flavors, a combustion aids for preventing the cigarette from being extinguished, and the like, other than a pure leaf tobacco.

Conventional cigarette paper (paper wrappings and rolling leaf tobacco) contain an organic fiber consisting essentially of hemp, a filler (e.g., hard calcium carbonate), and a combustion aids (e.g., ammonium phosphate) for improving combustibility and improving the shape of ashes. In addition, an adhesive is used to maintain the cylindrical shape of the cigarette paper. Accordingly, smokers inevitably inhale cigarette smoke evolved from the cigarette paper and the adhesive. According to a report from the U.S.A, cigarettes made in the U.S.A prior to being burned contain 599 ingredients, which generate about 4,000 substances upon pyrolysis. Of these, 20 or more substances have been shown to be carcinogenic. Since the generation of carbon monooxide (CO) is inevitable, smoking is recognized to be a great hazard to the health of smokers.

Now conceptual cigarettes which are less harmful than conventional cigarettes are defined as "safer cigarettes". The safer cigarettes are divided into smokeless cigarettes and harmful substance-free cigarettes. In addition, the safer cigarettes include patch-, spray-, inhalation- and aerosol-type cigarettes in terms of their form. Methods for catalytically converting carcinogenic substances into non-carcinogenic substances by the addition of catalysts, methods for reducing the formation of carcinogenic substances in cigarettes by the addition of catalysts, such as titanium, tin, iron, copper, palladium,

vanadium, etc., methods for delivering nicotine to smokers using heating instead of combustion, methods using nicotine analogues having similar functions and being less harmful to smokers, smokeless cigarettes, and low-smoke cigarettes have been developed until now. However, since these prior arts use processes other than combustion, flavors inherent to cigarettes and smoking satisfaction are poor, and there is a risk of side effects due to the additives.

Secondly, smoking devices must be less offensive to others. With the increasing public perception that smoking is offensive to others, non-smokers strongly feel hatred toward smoking. This perception prevents smokers from freely enjoy smoking. Cigarette smoke includes main-stream smoke directly entering the mouth of a smoker by the inhalation of the smoker, and side-stream smoke naturally evolved during combustion in air, i.e., during burning a raw tobacco. Depending on habits and attitudes of smokers, side-stream smoke accounts for 55~70% of the total cigarette smoke. Accordingly, considerable attention has focused on environmental pollution and second-hand smoking problems caused by the side-stream smoke. Main-stream smoke, which are inhaled into the bronchi of smokers and then exhaled, and side-stream smoke are collectively defined as "environmental tobacco smoke (ETS)". The main-stream smoke occupies only about 13% of ETS and the side-stream smoke comprises the remainder (about 87%).

An example of prior arts for reducing the evolution of side-stream smoke is the use of a low side-stream smoke cigarette paper. For this purpose, a method of using special cigarette paper which is heavier than general cigarette paper, a method for reducing the formation of side-stream smoke particles by the use of cigarette paper containing an inorganic filler such as $CaCO_3$ $Al(OH)_3$ or $Mg(OH)_2$, a method for filtering tar using cigarette paper, a method for promoting the moisture condensation in the inner surface of cigarette paper, or a method for thermally decomposing side-stream smoke into invisible volatile low-molecular materials, have been utilized. However, these methods have problems of complicated processes. In addition, since the shape of cigarette ashes is changed into that of scorched rice, scattering is likely to happen and contaminate clothes, causing displeasure to others. Further, since particulate materials are hardly released and accumulated, the combustion temperature is increased, causing the formation of a large amount of carbon monooxide. Further, since moisture acting as an abirritant is absorbed in the cigarette paper upon smoking, the irritation is severe. Furthermore, the additives may cause safety problems.

Thirdly, smoking devices must be safe.

Because most conventional cigarettes have a burning section exposed to the outside, physical risks exist. Cigarettes are responsible for unknown fires including

forest fires. The temperature of a burning cigarette reaches 700~950°C in an oxygen-short burning section, but 200~600°C in an oxygen-rich section in the rear portion of the burning section due to pyrolysis and distillation phenomena. Nicotine is formed at a temperature less than 250°C. Since a burning cigarette is accidentally dropped, or a lump of a burning section, i.e., spark, falls during driving, it causes the driver embarrassment. This is because the burning section is exposed to the outside. In addition, the burning cigarette may damage passers-by, particularly, children, against the smoker's will. Recently, smoking has been prohibited in airplanes, oil tankers, gas stations and other public areas due to the danger of fire. Thus, there is a need for a smoking device which can protect people from physical risks and allow a smoker to freely and comfortably enjoy smoking regardless of place.

Fourthly, smoking devices must be convenient to use.

A lighter or match as an ignition source is essential to ignite conventional cigarettes. In addition, an ashtray is required while a smoker is smoking indoors. Furthermore, conventional cigarettes have disadvantages that it is impossible to smoke in the midst of rain and the original cigarette flavors are maintained upon smoking in a severely windy place. Thus, there is a need for a smoking device which can solve the aforementioned problems encountered during smoking and is simple to use.

Fifthly, smoking devices must satisfy habitual smokers' diverse needs associated with cigarette flavors.

According to conventional cigarettes, air dilution rate (i.e. dilution rate of cigarette smoke (main-stream smoke) inhaled into the mouth of a smoker by air introduced through apertures formed on a tip paper of a filter and apertures formed on cigarette paper) and the amount of flavorants added are fixed. Accordingly, since smokers cannot control the air dilution rate and the amount of the flavorants, they cannot feel stronger or milder taste at their will. Thus, there is a need for a smoking device which allows smokers to control the air dilution rate and the amount of flavorants depending on various preferences of the smokers.

Sixthly, smoking devices must be highly sanitary.

Once conventional cigarettes have been smoked, they inherently leave behind ashes and butts, thus polluting the ambient environment. In order to prevent cigarette ashes from being blown out of the ashtray, a piece of wet tissue paper may be placed on the ashtray. However, tar permeates the tissue paper, an adhesion portion of cigarette paper is torn and shredded tobacco pours from the cigarette, making the ashtray dirty within a few minutes. Particularly, a completely closed ashtray must be prepared inside a car in order to block the spread of odor generated from cigarette butts. Even after the ashtray is empty, the offensive odor still remains inside the car. When a smoker speaks

after smoking, a bad cigarette smell arises from the mouth of the smoker and is soaked in the hands of the smoker, strongly causing an unclean impression to others. Cigarette smoke smell disgusts non-smokers, irrespective of main-stream smoke or side-stream smoke. Since smoke essentially spreads during smoking, it is preferred that the smoke is covered with a favorable fragrance. To this end, the addition of an additive is required. Therefore, there may be a possibility of formation of harmful substances. Thus, there is a need for a smoking device which can satisfy smokers' latent needs toward sanitation, which could not have been accomplished by conventional cigarettes.

Finally, smoking devices must be high quality.

There is a need for a smoking device which solves or diminishes the above-mentioned aversive factors and shortcomings of conventional cigarettes, thereby eliminating negative image of smoking, allowing a habitual smoker to enjoy flavors inherent to cigarettes without the worries of harmfulness, improving the consideration for the health of others, and allowing a smoker to comfortably and gracefully enjoy various cigarette flavors according to his or her own tastes without mental burden such as risk of fire.

**Disclosure of the Invention**

Therefore, the present invention has been made in view of the above-mentioned aversive factors and shortcomings of conventional cigarettes, and it is an object of the present invention to provide a smoking device which eliminates the negative image of smoking, allows a habitual smoker to enjoy flavors inherent to cigarettes without the worries of harmfulness, removes harmful factors to the health of others, allows a smoker to conveniently and gracefully enjoy various cigarette flavors according to his or her own tastes without mental burden such as risk of fire, and at the same time, solves decisive problems, for example, loss of inherent cigarette flavors and smoking satisfaction, of conventional cigarette substitutes.

In order to accomplish the above object of the present invention, there is provided a smoking device for inhaling gasses and aerosols generated by burning and heating a material, comprising:

a body defining an appearance of the smoking device, the body being closed at one side and opened or filled with a filter at the other side;

a combustible inserted inside the body, the combustible being continuously burned to generate gasses and aerosols after ignition; and

an igniter for initial ignition of the combustible.

The combustible is preferably a mixture of shredded tobacco, a combustion aids and an oxygen-supplying material. The combustible itself generates oxygen while

being burned without the supply of additional oxygen from the outside. That is, the combustible can be continuously burned using the generated oxygen.

In accordance with another aspect of the present invention, there is provided a smoking device for inhaling gasses and aerosols generated by burning and heating a material, comprising:

a body defining an appearance of the smoking device, the body being closed at one side and filled with a filter at the other side;

a combustible inserted inside the body, the combustible being continuously burned to generate gasses and aerosols after ignition;

an oxygen-supplier for supplying oxygen such that the combustible is continuously burned; and

an igniter for initial ignition of the combustible.

The body is divided into a body including the filter (hereinafter, abbreviated as a "smoking body") and a body including the combustible (hereinafter, abbreviated as a "combustible body"). The smoking body and the combustible body are rotatably engaged relative to each other. A flavor-generating material capable of generating a flavor by combustion heat released from the combustible is applied on the inner surface of the smoking body. The combustible body and the smoking body are formed with respective central apertures through which gasses and aerosols generated by the combustion of the combustible are passed. Further, the combustible body and the smoking body are formed with a plurality of circumferential apertures through which a fragrance generated from the flavor-generating material is passed, respectively. As the smoking body is rotated in a direction opposite to that of the combustible body, the opening degree between the circumferential apertures is varied. Accordingly, the rotation of the two bodies enables the control of the mixing ratio between the gasses and aerosols generated from the combustible and the fragrance generated from the flavor-generating material.

**Brief Description of the Drawings**

The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

Fig. 1 is a cross-sectional view showing the basic structure of a closed-type smoking device according to the present invention;

Fig. 2 is an exploded perspective view of the closed-type smoking device of Fig. 1;

Figs. 3, 4 and 5 are cross-sectional views showing the structure of a closed-type

smoking device according to one embodiment of the present invention which is provided with means for controlling the ratio of gasses and aerosols inhaled;

Figs. 6, 7 and 8 are cross-sectional views showing various igniters usable in a smoking device of the present invention;

Fig. 9 is a cross-sectional view showing the structure of a closed-type smoking device according to another embodiment of the present invention which is provided with an oxygen supplier;

Figs. 10, 11 and 12 are cross-sectional views showing a structure configured to control the amount of oxygen supplied by the oxygen supplier of Fig. 9; and.

Fig. 13 is a diagrammatic view showing a filter-enclosing part of a smoking device of the present invention.

**Best Mode for Carrying Out the Invention**

Detailed description will be made of preferred embodiments of the present invention with reference to the accompanying drawings.

Fig. 1 is a cross-sectional view showing the basic structure of a closed-type smoking device according to the present invention, and Fig. 2 is an exploded perspective view of the closed-type smoking device of Fig. 1.

The closed-type smoking device of the present invention comprises a body 100 defining an appearance of the smoking device, a combustible 150 inserted inside the body and generating gasses and aerosols upon combustion, an igniter 200 for igniting the combustible, and a filter 120 for filtering the gasses and aerosols.

The body 100 is substantially cylindrical. Since the filter 120 is inserted into one side of the body 100 and the igniter 200 is fitted into the other side of the body 100 to separate the inner space of the body 100 from ambient air, problems associated with the evolution of side-stream smoke in conventional cigarettes can be completely solved. Gasses and aerosols generated from the combustion of the combustible 150 are exhausted to the outside (or inhaled by the smoker) only through the filter 120. When filtering is unnecessary, i.e. tar or nicotine is not generated, the filter 120 may be omitted.

The body 100 is preferably made of an incombustible or flame-resistant material so that when the combustible 150 is burned, no deformation takes place or no harmful gasses are generated by combustion heat. Glass is preferably used. A holder 102 for fixing the combustible 150 is formed at a predetermined location of the inner side of the body so that the combustible is spaced apart from the inner wall of the body 100 by a fixed distance to form a space 160. Accordingly, since the space 160, the body 100 and an inner cylindrical body 155 block direct delivery of combustion heat released from the combustible 150 to the outside, problems associated with the exposure of the burning

section to the outside, i.e. a fire or burns, of conventional cigarettes can be solved. If necessary, an insulation material and a heat-absorbing material may be filled into the space 160. A mixture of a flavor-generating material and an oxygen-generating material may be further filled into the space 160 or applied on the space 160. For example, when the space 160 is filled with peppermint leaves, the smoking device generates a peppermint flavor while absorbing and blocking the generated combustion heat. At the same time, a plurality of intake pores 104 are formed through which the peppermint flavor spreads outside and covers a bad cigarette smell arising from the mouth of the smoker. Accordingly, the smoking device of the present invention can reduce unpleasantness to others.

The combustible 150 inserted into the body 100 functions as a fuel generating gasses and aerosols when a smoker inhales, and may be a combination of shredded tobacco (leaf tobacco cut at a uniform width), sheet tobacco (artificial leaf tobacco obtained by shaping leaf tobacco by-products into a paper form), charcoal and the like. It is preferred that the combustible 150 is continuously burned using air defined in the body 100 without the supply of ambient air. For this purpose, a mixture of an oxygen-generating material and shredded tobacco is preferably added as the combustible. A combustion aids which helps the combustible burn may be further added. Examples of oxygen-generating materials include potassium chloride, potassium perchlorate, potassium nitrate, potassium peroxide and the like. Of these, potassium peroxide is a yellow paramagnetic solid obtained by burning potassium in the presence of a large excess of oxygen. Specifically, potassium peroxide is obtained by slowly passing oxygen through a solution of potassium in ammonia at -50°C until the solution is colorless, or by evaporating an equivalent mixture of potassium hydroxide and hydrogen peroxide in concentrated sulfuric acid under vacuum. U.S. Patent No. 4,867,902 discloses an oxygen-generating microcapsule in which potassium hydroxide is encapsulated. The oxygen-generating microcapsule can continuously and uniformly generate oxygen without the danger of explosion. In the present invention, a mixture of potassium hydroxide and shredded tobacco encapsulated in a microcapsule is used as the combustible 150. Accordingly, the combustible can be burned even in a closed state without the supply of additional oxygen from the outside.

The combustible 150 essentially composed of shredded tobacco, the oxygen-generating material and the combustion aids may be shaped into a bar. Alternatively, the combustible 150 may be rolled using cigarette paper, cigar wrapper or "tubular" tobacco (sheet tobacco), like conventional cigarettes. Alternatively, the combustible 150 may be filled into the inner cylindrical body 155. The inner cylindrical body 155 may be made in the form of a wire net, a metal tube, a glass tube or the like. In the case

where the combustible 150 includes an oxygen-generating material and a combustion aids, substances harmful to humans may be formed, as previously stated. Accordingly, it is preferred that the combustible 150 is composed of shredded tobacco only, and the oxygen-generating material and the combustion aids are applied on the inner surface of a combustible body 140 so as to be spaced apart from the combustible 150 at a regular interval 160. Accordingly, a smoker can inhale gasses and aerosols generated from the shredded tobacco together with oxygen.

Although shredded tobacco has been illustrated as a representative raw material of the combustible 150, it should be understood that a person skilled in the art can use shredded tobacco analogues, such as mugwort as a smoking cessation product, materials generating aerosols and gasses useful to treat various diseases (particularly, pulmonary diseases), materials for use in aroma therapy, and the like, instead of shredded tobacco.

The combustible 150 is continuously burned after ignition, but since the combustible 150 is completely closed from the outside in order to block the formation of side-stream smoke, the igniter 200 must be embedded. Examples of the igniter 200 used to ignite the combustible 150 include battery-powered igniters (mercury, lithium, dry cells, etc.), igniters using electric heating wires, igniters using inflammable chemical substances, electric lighters, etc. Details concerning these igniters will be described hereinafter.

The filter 120 is one commonly used in general cigarettes, and acts to filter gasses or aerosols generated from the combustion of the combustible. However, when harmful substances, including tar and nicotine, are not generated, the filter 120 may be omitted.

The plurality of intake pores 104 formed on the side surface of the body 100 are not essential elements constituting the smoking device. The intake pores 104 having a predetermined diameter help ambient air enter the smoking device in proportion to the inhalation pressure of the smoker. Accordingly, the intake pores 104 allow a smoker to experience smoking enjoyment to a degree similar to a general cigarette. In addition, the intake pores 104 function to release a fragrance generated from the flavor-generating material, and act as passageways through which the combustion heat of the combustible 150 is released, thereby preventing overheating of the body. In this case, the inner cylindrical body 155 is preferably made of a metal tube or glass tube in order to prevent the escape of side-stream smoke. The inner cylindrical body 155 should be adhered closely to the igniter 200 when the igniter 200 is fitted into the body, and the oxygen-supplying material should be incorporated into the combustible 150.

Figs. 3, 4 and 5 are cross-sectional views showing the structure of a closed-type smoking device according to one embodiment of the present invention which is provided

with means for controlling the ratio of gasses and aerosols inhaled.

According to the smoking device of this embodiment, a flavor-generating material 110 is applied on the inner wall of the body 100 such that the flavor-generating material 110 is heated by the combustion heat of the combustible 150 to generate gasses and/or aerosols (hereinafter, referred to as "fragrance"). Accordingly, a smoker can control the mixing ratio between gasses and aerosols generated from the combustible 150 and the fragrance generated from the flavor-generating material 110.

For this purpose, the body includes a smoking body 130 and a combustible body 140 separated from each other. Two partitions 132 and 142 are formed between the bodies 130 and 140. The partitions 132 and 142 are formed with a groove 135 and a protrusion 145, respectively, so that the bodies 130 and 140 are rotatably engaged relative to each other. A pair of central apertures 134 and 144 through which gasses and aerosols are passed are formed at the center of the respective partitions 132 and 142, and a plurality of circumferential apertures 136 and 146 through which gasses and aerosols generated from the flavor-generating material 110 are passed are formed in the vicinity of the respective central apertures. The smoking body 130 is rotated in a direction opposite to that of the combustible body 140 in such a manner that the opening degree between the central apertures 134 and 144 and the circumferential apertures 136 and 146 is varied.

Referring specifically to Fig. 4, the opening degree between the circumferential apertures 136 and 146 is high, but that between the central apertures 134 and 144 is low. According to this structure, a large quantity of aerosols and gasses generated from the flavor-generating material 110 pass through the circumferential apertures 136 and 146. Referring to Fig. 5, the opening degree between the circumferential apertures 136 and 146 is low, but that between the central apertures 134 and 144 is high. Accordingly, a relatively small quantity of aerosols and gasses generated from the flavor-generating material 110 pass through the circumferential apertures 136 and 146.

The control of the opening degree between the central apertures 134 and 144 and that between the circumferential apertures 136 and 146 enables the control of the mixing ratio between gasses and aerosols generated from the combustible 150 and fragrance generated from the flavor-generating material 110. Accordingly, a smoker can easily control the cigarette flavor according to his or her own tastes. Although the central apertures 134 and 144 and the circumferential apertures 136 and 146 are shown by triangular forms in Fig. 3, it should be understood that a person skilled in the art can modify the form and arrangement of the apertures. Unlike in the case where the combustible 150 is composed of shredded tobacco only, when the object of the combustible 150 is to heat the flavor-generating material, that is, the inhalation of gasses and aerosols generated from the combustible 150 is unnecessary, the formation of the

central apertures may be omitted.

Figs. 6, 7 and 8 are cross-sectional views showing various igniters usable in the smoking device of the present invention;

Fig. 6 is a cross-sectional view of an electric heat-type igniter using a cell.

As shown in Fig. 6, the igniter includes a cell 212 for supplying electric power to the igniter, a plurality of ignition pins 214 heated by the electric power supplied from the cell 212, and a switch (not shown) for controlling the power supply. The ignition pins 214 are electric heating wires, and generate heat by the electric power supplied from the cell. Alternatively, the ignition pins 214 are made of a heat conductive material so that the heat generated from the electric heating wires can be delivered to the combustible.

Before ignition, the igniter 210 is spaced from the body 100 by a fixed interval. When the igniter 210 is fitted into the body by an external force to turn the switch ON, the ignition pins are heated. The switch may be a sliding switch or push switch. The sliding switch is operated by sliding along with the movement of the igniter 210, and the push switch is operated by being pushed when the igniter is fitted into the body. Since the configuration of switches is well understood by a person skilled in the art, further description is omitted.

Reference numerals 215 and 216 denote a fixing protrusion and a fixing groove, respectively, which serve to fix the igniter 210 to the body 100 when the igniter 210 is fitted into the body 100.

Fig. 7 is a cross-sectional view of an igniter using chemical substances.

A chemical substance generates heat at a high temperature when mixed with another chemical substance. In particular, many chemical substances are widely known to explosively react with oxygen and generate heat at a high temperature. Of these, two chemical substances are selected and used in the present invention. The selected chemical substances 226 and 227 are separated from each other in the initial stage. When a plurality of push plates 222 of the igniter 220 are pushed toward the body, protrusions 223 formed on the push plates 222 rupture a diaphragm 225. This rupture enables the mixing of the chemical substance (A) 226 and the chemical substance (B) 227 to generate heat at a high temperature. The heat is delivered to the combustible 150 through the ignition pins 214 to ignite the combustible 150. At this time, a receptacle of the chemical substance A (226) is preferably evacuated such that the chemical substance (B) 227 is rapidly introduced into the receptacle.

Fig. 8 is a cross-sectional view of an electric lighter used as the igniter.

The electric lighter uses a piezoelectric device for ignition and ignites the combustible by pressing the piezoelectric device. As shown in Fig. 8, the smoking

device is provided with a push switch 232 below the body 100, a gas vent nozzle 236 below the combustible 150, and a spark generator 234 in the vicinity of the gas vent nozzle 236. By pressing the push switch, the combustible 150 is ignited.

It should, of course, be understood that various modifications are possible other than the three igniter types as described above.

Fig. 9 is a cross-sectional view showing the structure of a closed-type smoking device according to another embodiment of the present invention which is provided with an oxygen supplier.

In the previous embodiment shown in Fig. 1, the smoking device comprises the oxygen-supplying material for supplying oxygen to the combustible 150, or the oxygen-supplying material applied on the inner surface of the combustible body 140. In this embodiment, the smoking device further comprises an oxygen-supplier 250 for supplying oxygen-containing air to the smoking device.

The smoking device according to this embodiment of the present invention comprises a body 100 defining an appearance of the smoking device, a combustible 150 inserted inside the body and generating gasses and aerosols upon combustion, an igniter 200 for igniting the combustible, an oxygen-supplier 250 for supplying oxygen such that the combustible is continuously burned in a closed state, a filter 120 for filtering gasses and aerosols generated from the combustion of the combustible 150, and a flavor-generating material 110 generating a fragrance by combustion heat released from the combustible.

As explained in the smoking device shown in Fig. 3, the body 100 includes a smoking body 140 and a combustible body 130 separated from each other so that the mixing ratio between the gasses and aerosols generated from the combustible 150 and the fragrance generated from the flavor-generating material 110 can be controlled.

The combustible 150 may be pure shredded tobacco, or a mixture of shredded tobacco and a combustion aids. Since the smoking device comprises the oxygen-supplier 250, an oxygen-supplying material is not required.

Igniters which can be used in the embodiment include those shown Figs. 6 to 8. In this embodiment, the igniter using chemical substances shown in Fig. 7 is used as the igniter 220, as shown in Fig. 9.

The oxygen supplier 250 includes an oxygen receptacle 260 and an oxygen supply tube 262. Exemplary gas and liquids included in the oxygen receptacle 260 include compressed air, liquefied air, liquefied oxygen, liquefied oxygen, liquid oxygen, and oxygen-containing gas and liquid mixtures. The purity of oxygen can be controlled considering the combustion speed of the combustible 150. Oxygen is supplied using the oxygen supplier 250 by an operator. At this time, it is preferred that the igniter is

concurrently operated. Like the operation of the igniter, the oxygen supply is initiated by fitting a portion exposed to the outside of the body into the body.

As can be seen from Fig. 5, the oxygen supplier 250 is formed at one end of the body 140 together with the igniter 220, but the location of the oxygen supplier 250 is particularly not limited. For example, the oxygen supplier 250 is disposed in a space 160 formed between the combustible 150 and the body 100. It should, of course, be understood that various modifications to the location of the oxygen supplier are possible.

Figs. 10, 11 and 12 are cross-sectional views showing a structure configured to control the amount of oxygen supplied by the oxygen supplier of Fig. 9. Fig. 10 shows a state before the smoking device is used, and Fig. 11 shows a state after ignition of the smoking device.

When the oxygen supplier 250 is fitted inside the combustible body 140, the push plates 222 of the igniter 220 at the upper side of the oxygen supplier rupture the diaphragm 225 to mix the chemical substances 226 and 227, thereby generating heat. The generated heat ignites the combustible 150, and simultaneously an operation pin 270 is thrust into the oxygen receptacle. The operation pin 270 pushes a cover plate 280 closely sealing the oxygen supplier 250. One end of the cover plate 280 is firmly adhered to an upper wall of the oxygen receptacle, and the other end is relatively weakly adhered to the upper wall of the oxygen receptacle. When the cover plate is pushed by the pin 280, it is thrust into the oxygen receptacle.

After oxygen supply begins, the amount of the oxygen supplied can be controlled as follows. An auxiliary supply tube 264 inclinedly formed on the oxygen supply tube 262 is initially open halfway. When the lower side of the oxygen supplier 250 exposed to the outside of the combustible body 140 is rotated, the oxygen supply tube 262 ascends or descends along a thread line to increase or decrease the opening degree of the auxiliary supply tube 264. Accordingly, a great deal of oxygen can be supplied to the combustible through a vertical oxygen supply tube 263. This configuration of the oxygen supplier allows a smoker to control the amount of oxygen supplied according to his or her own smoking habits.

The oxygen supplier is provided with an inhalation plate 275 formed on the operation pin 270, which is fixed by a spring 280. When a smoker inhales, the inhalation plate 275 moves upwardly. Referring again to Fig. 10, the operation pin 270 is formed with a conical protrusion. When the operation pin 270 moves upwardly together with the conical protrusion, the conical protrusion reduces the resistance to a gas, e.g., oxygen, supplied from the oxygen supplier and thus a great deal of oxygen can be inhaled by the smoker. The inhalation plate 275 is not an essential element constituting the smoking device. It is apparent to a person skilled in the art that since the operation

pin 270 can move upwardly by a negative pressure applied only to the protrusion, the same effects as the inhalation plate 275 are achieved.

Since the rotation of the oxygen supplier allows a smoker to control the amount of oxygen supplied depending on various preferences of the smoker, the smoking device of the present invention can overcome the limitations (e.g. fixed air dilution rate) of conventional cigarettes. In addition, since the smoker can inhale a great deal of oxygen upon smoking, the smoker can enjoy smoking enjoyment to a degree similar to a general cigarette.

In this embodiment, since the igniter 220 releasing heat and the oxygen supplier 250 are adjacent to each other, an insulation material is preferably interposed between the igniter 220 and the oxygen supplier 250 to prevent overheating of the oxygen supplier 250. More preferably, both the igniter 220 and the oxygen supplier 250 are made of an insulation material.

The object of the smoking device according to this embodiment is to control the amount of oxygen supplied from the oxygen supplier 250. It should be understood that various modifications are possible. In addition, general structures, such as portable butane containers, can be used in the present invention so long as a uniform amount of oxygen can be supplied only by pressing.

Fig. 12 is a horizontal cross-sectional view showing the arrangement of the ignition pins 214, the push plates 222 and the inhalation plate 275. As shown in Fig. 12, the ignition pins 214 and the push plates 222 are arranged in such a manner that they form different concentric circles, thereby overcoming problems associated with the small space.

Fig. 13 is a diagrammatic view showing a filter-enclosing part of the smoking device of the present invention.

As shown in Fig. 13, the filter-enclosing part 300 has the same plane as the body, and is extended toward the rear of the filter 120. The filter-enclosing part 300 hermetically seals a portion of the filter exposed to the outside to prevent a bad smell of the filter 120 after smoking from spreading. The filter-enclosing part 300 is preferably made of a shape memory material. As the combustible is burned and the burning location is closer to the filter 120, the filter-enclosing part 120 seals the filter by heat released from the combustible. The filter-enclosing part 120 may be made of a relatively hard paper and thin metal plate capable of being bent sufficiently to enclose the filter by hand.

13-a (left of Fig. 13) illustrates an initial shape memorized by the filter-enclosing part 300. The central part of the filter-enclosing part 300 is lower than the upper surface of the filter. This is to closely adhere the filter-enclosing part 300 to the

filter 120. 13-b (center of Fig. 13) illustrates the initial state and a state during smoking. 13-c (right of Fig. 13) illustrates a state where the combustion heat released from the combustible is delivered to the filter-enclosing part 300 to change the shape of the filter-enclosing part 300 into the initially memorized shape and to permit the filter-enclosing part 300 to enclose the filter.

**Industrial Applicability**

As apparent from the above description, since the closed-type smoking device of the present invention uses shredded tobacco and additives, including a combustion aids and an oxygen-supplying material, separated from the shredded tobacco, it can reduce a possibility of formation of harmful substances due to chemical reactions between shredded tobacco and additives. Since the closed-type smoking device can reduce the formation of side-stream smoke evolved during burning a raw tobacco, it minimizes the damage of second-hand smoke. Since flame is not spread outside the closed-type smoking device after ignition, it does not cause the risk of causing a fire or burns.

In addition, the closed-type smoking device of the present invention is convenient to use and allows a smoker to conveniently enjoy smoking without the need of a lighter and an ashtray. Using the closed-type smoking device, a smoker can easily control the amount of air and a fragrance inhaled according to his own tastes. Furthermore, since the closed-type smoking device of the present invention is provided with a filter-enclosing part to hermetically seal the filter opening, it can prevent a bad smell of the filter 120 after smoking from spreading.

In conclusion, the closed-type smoking device of the present invention minimizes direct and indirect damages to the smoker and others, allows the smoker to comfortably enjoy various cigarette flavors without mental and physical burdens, and is advantageous in terms of cleanness.

Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

**Claims:**

1. A closed-type smoking device for inhaling gasses and aerosols generated by burning and heating a material, comprising:

a body defining an appearance of the smoking device, the body being closed at one side and opened or filled with a filter at the other side;

a combustible inserted inside the body, the combustible being continuously burned to generate gasses and aerosols after ignition; and

an igniter for initial ignition of the combustible.

2. The closed-type smoking device according to claim 1, wherein the combustible consists of shredded tobacco, a combustion aids and an oxygen-supplying material such that it generates oxygen while being burned without the supply of additional oxygen from the outside and is continuously burned using the generated oxygen.

3. The closed-type smoking device according to claim 1, wherein the body is made of an incombustible or flame-resistant material.

4. The closed-type smoking device according to claim 1, wherein the body is made of glass.

5. A closed-type smoking device for inhaling gasses and aerosols generated by burning and heating a material, comprising:

a body defining an appearance of the smoking device, the body being closed at one side and filled with a filter at the other side;

a combustible inserted inside the body, the combustible being continuously burned to generate gasses and aerosols after ignition;

an oxygen-supplier for supplying oxygen such that the combustible is continuously burned; and

an igniter for initial ignition of the combustible.

6. The closed-type smoking device according to claim 1 or 5, wherein the body is divided into a body including the filter and a body including the combustible rotatably engaged relative to each other, a flavor-generating material generating a flavor by combustion heat released from the combustible is applied on the inner surface of the body including the filter, and the body including the combustible and the body including the filter are formed with respective central apertures through which gasses and aerosols

generated from the combustion of the combustible are passed and a plurality of circumferential apertures through which a fragrance generated from the flavor-generating material is passed, respectively.

7. The closed-type smoking device according to claim 1 or 5, wherein the body is formed with a plurality of intake pores through which ambient air is introduced into the smoking device upon inhalation by a smoker.

8. The closed-type smoking device according to claim 5, wherein the oxygen supplier is provided with a cover plate and the igniter is provided with an operation pin, and the cover plate descends to initiate the oxygen supply when the operation pin is inserted into the igniter.

9. The closed-type smoking device according to claim 8, wherein the oxygen supplier is provided with a vertical oxygen supply tube and an auxiliary supply tube connected to and inclinedly formed on the vertical oxygen supply tube, the auxiliary supply tube is initially open halfway, and the opening degree of the auxiliary supply tube is adjusted by rotating the oxygen supplier relative to the body, thereby controlling the amount of oxygen supplied.

10. The closed-type smoking device according to claim 8, wherein the operation pin is provided with a circular inhalation plate at its upper side, and ascends to increase the opening degree of the oxygen supplier upon inhalation by a smoker.

11. The closed-type smoking device according to claim 1 or 5, further comprising a filter-enclosing part for sealing the rear portion of the filter after smoking.

12. The closed-type smoking device according to claim 11, wherein the filter-enclosing part is made of a shape memory material, and seals the filter by heat delivered from the combustible.

13. The closed-type smoking device according to claim 1 or 5, wherein the igniter is provided with a cell and a plurality of electric heating wires, and the electric heating wires act to supply electric power to ignite the combustible when a switch is turned on.

14. The closed-type smoking device according to claim 1 or 5, wherein the

igniter and the oxygen supplier include chemical substances rapidly oxidized and generating heat upon being contacted with oxygen, and the chemical substances generate heat by oxygen supplied from the oxygen supplier and the combustible is ignited by the generated heat after the igniter and the oxygen supplier are fitted into the body.

FIG. 1

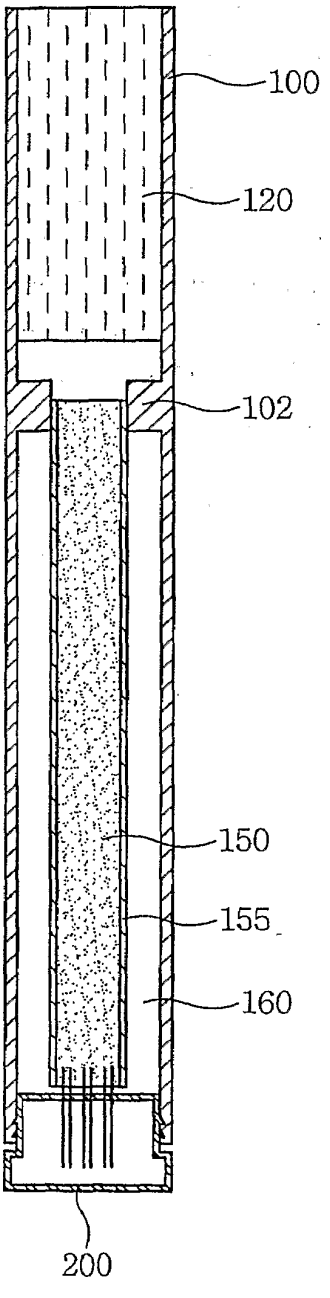


FIG. 2

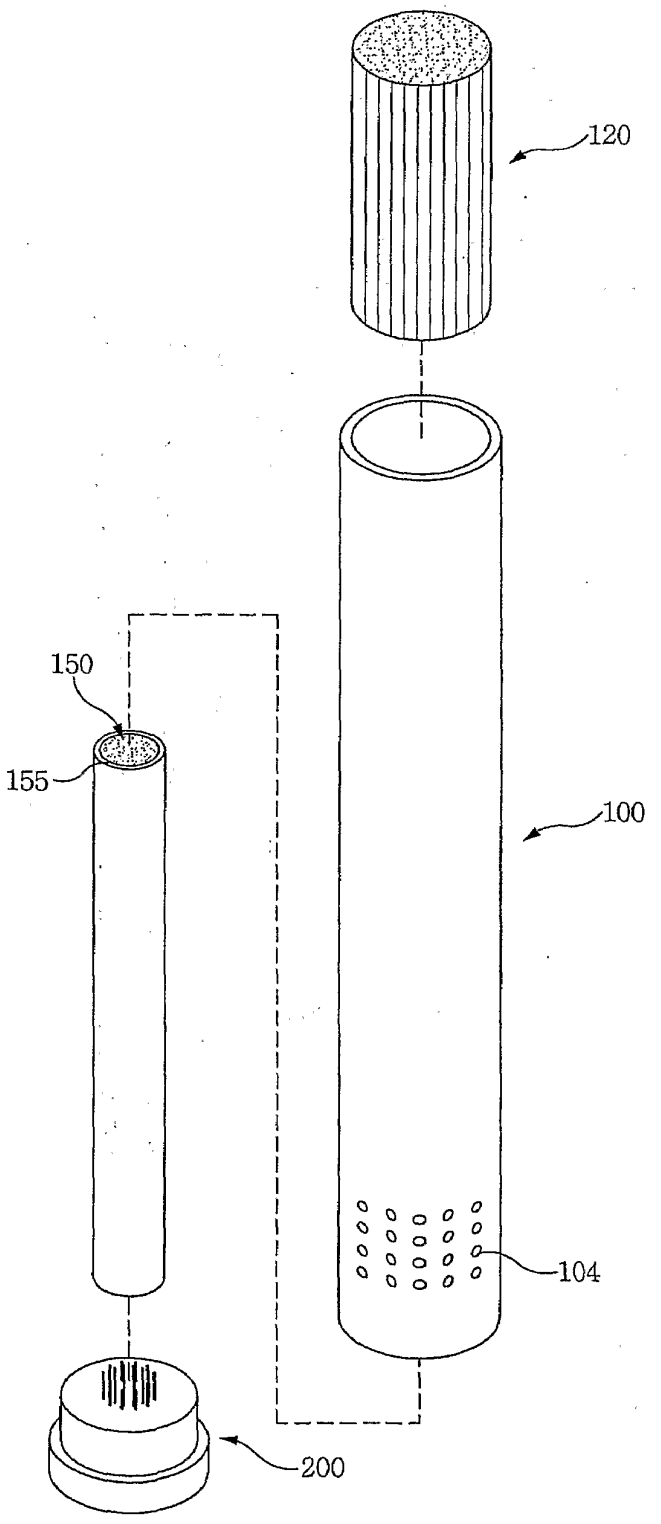


FIG. 3

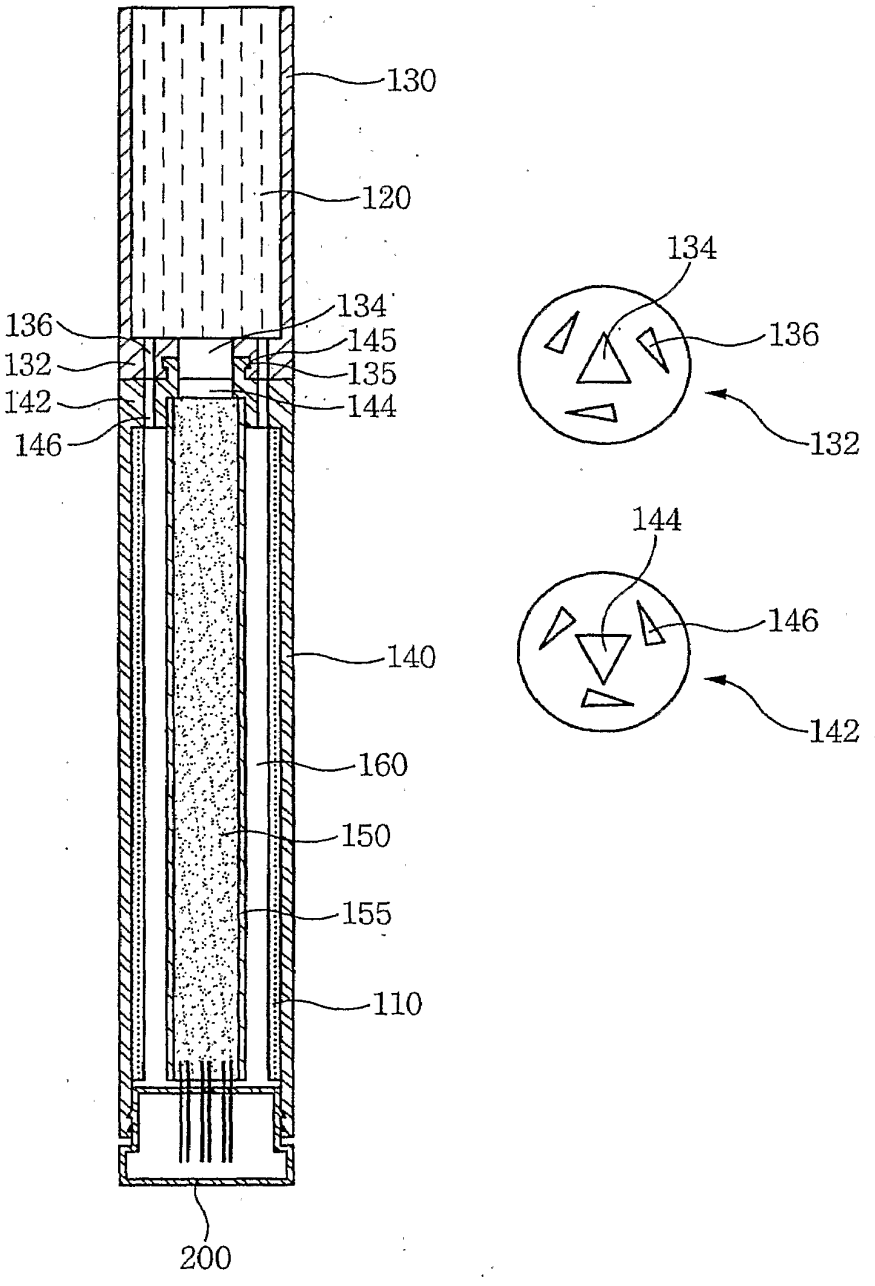

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FIG. 4

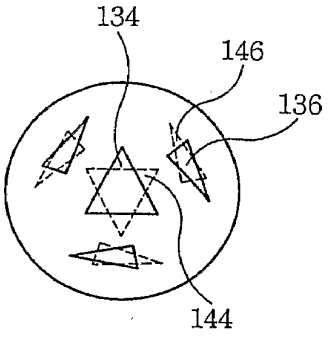



FIG. 5

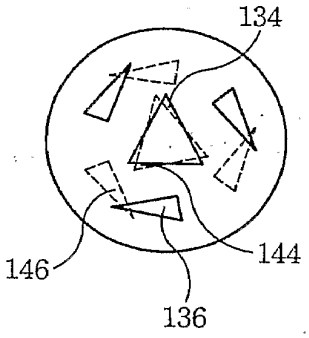



FIG. 6

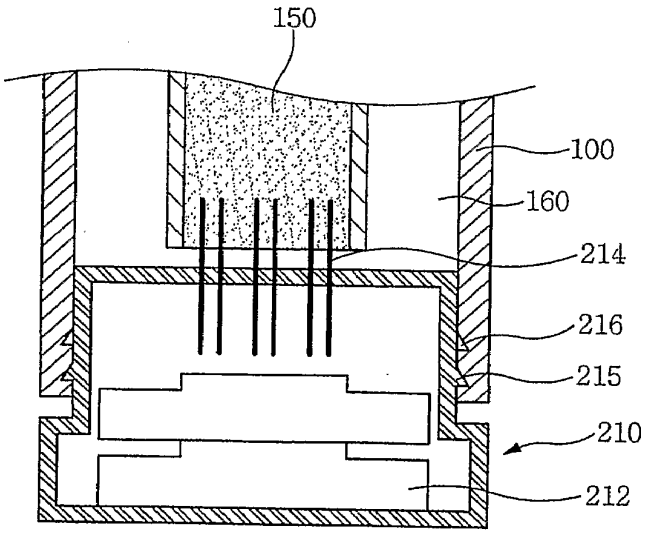


FIG. 7

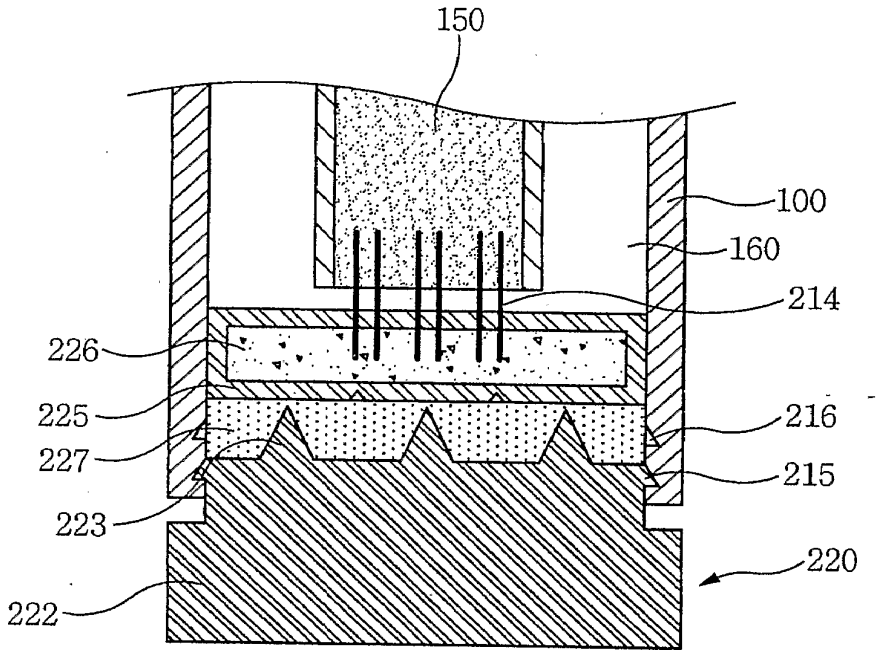

150
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222

FIG. 8

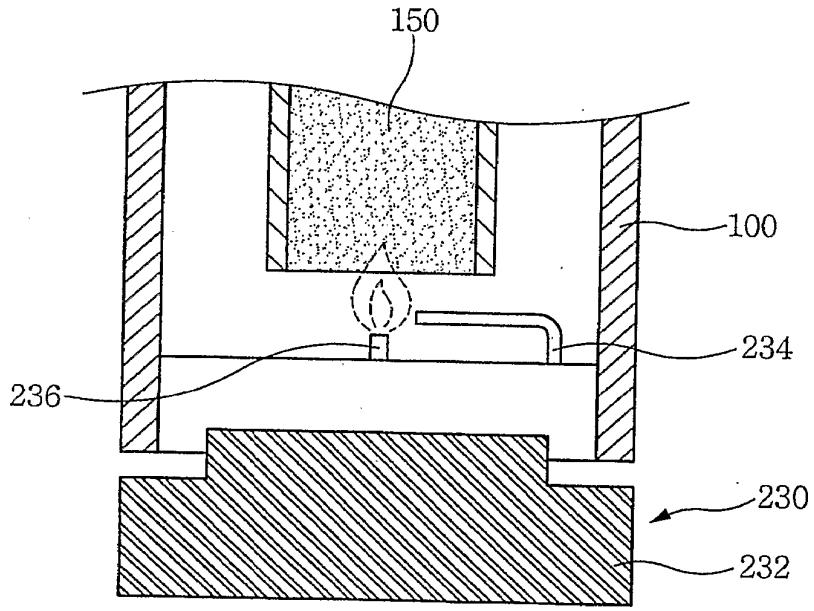

150
100
234
236
230
232

FIG. 9

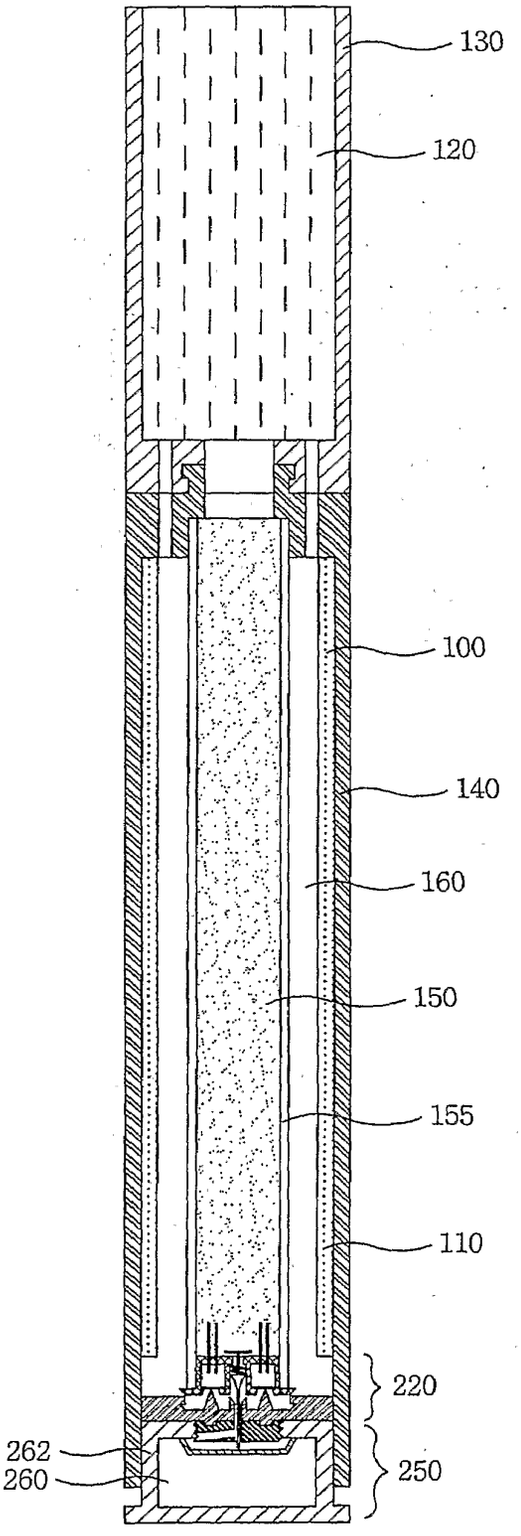


FIG. 10

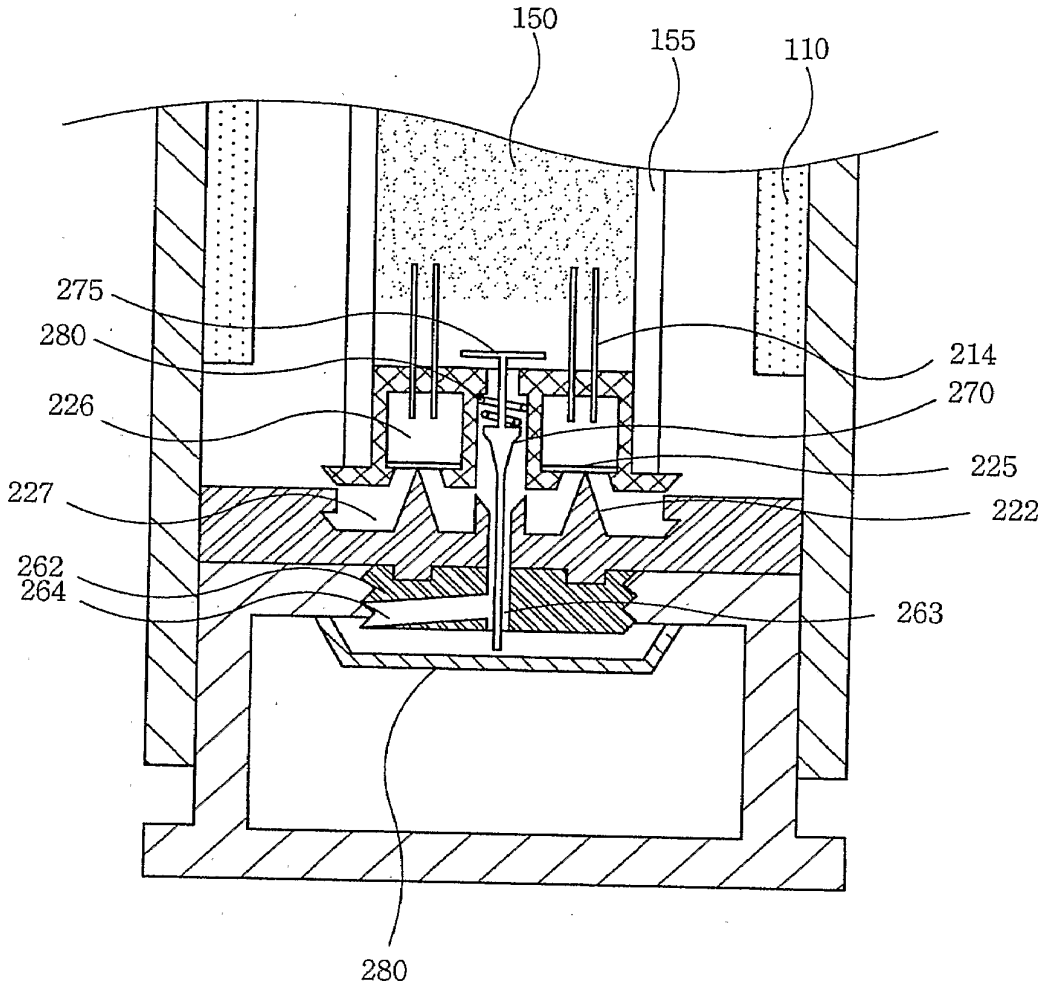


FIG. 11

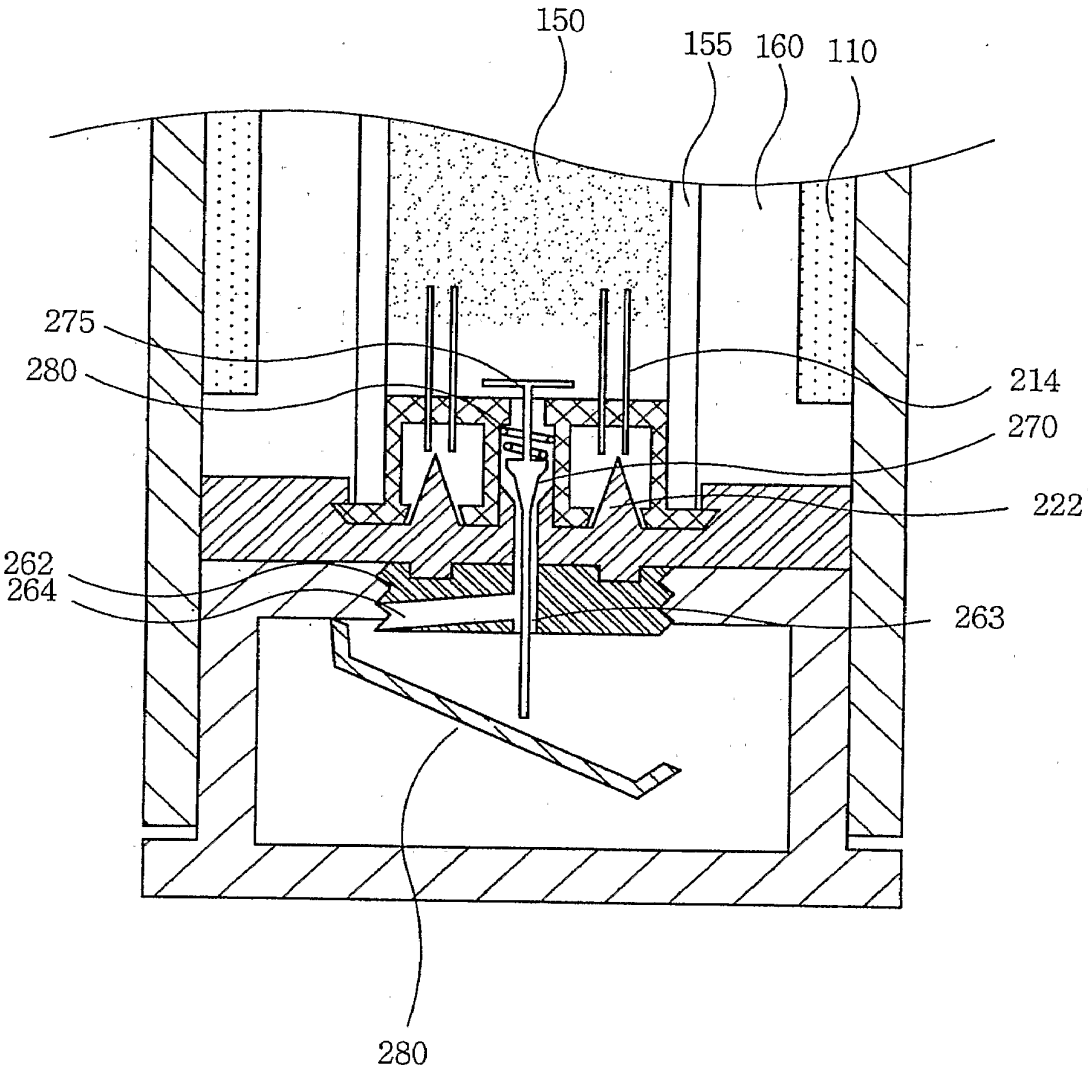


FIG. 12

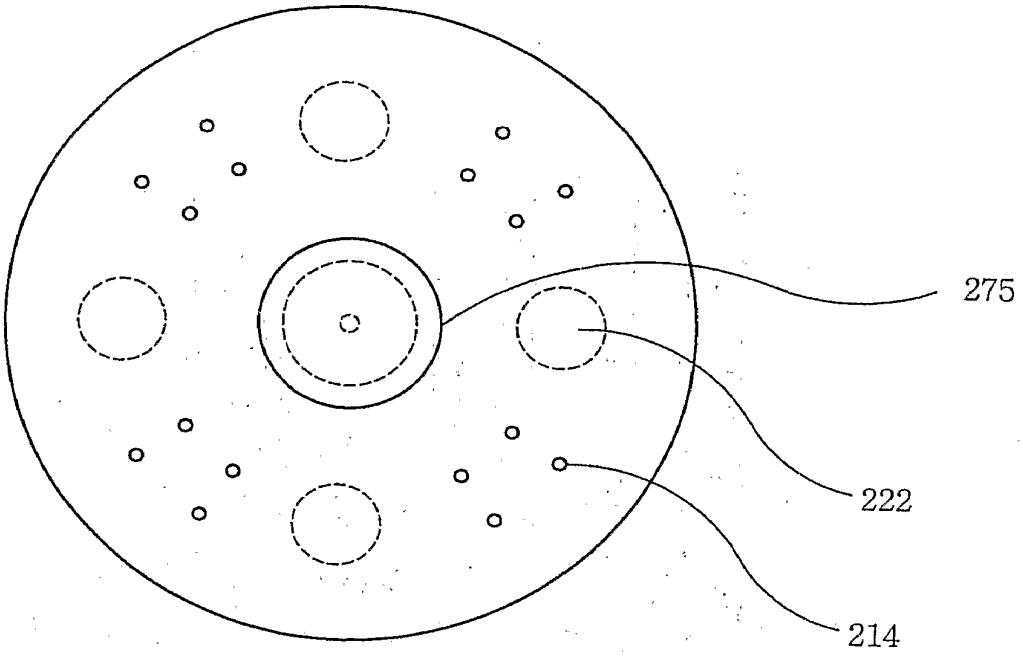
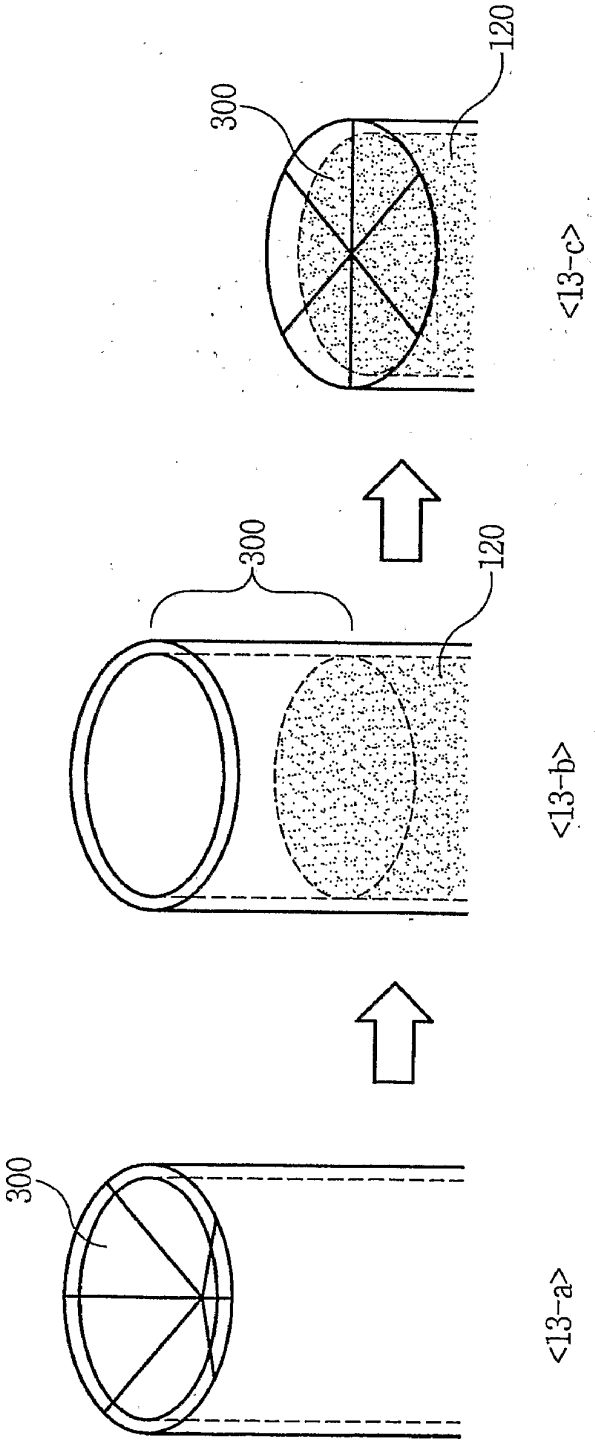


FIG. 13



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/002196

A. CLASSIFICATION OF SUBJECT MATTER

**IPC7 A24F 13/22**

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 7 A24B 15/00, A24D 1/02, A24D 1/12, A24F 1/00, A24F 13/06, A24F 13/08, A24F 13/16, A24F 13/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Utility models and applications for Utility models since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
eKIPASS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | KR 1998-0006261 U(Lee, Myoung-Hoon)<br>30 April 1998<br>see page 2, line 20 - line 25; claim 1; figs. 1, 2 | 1, 3, 4 |
| Y | US 4,585,014 A(Arnold H. Fry)<br>29 April 1986<br>see column 4, line 45 - column 5, line 32; fig. 1 | 1, 3, 4 |
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Information on patent family members

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|---|---|---|---|
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| JP 04-121179 A | 22.04.1992 | None | |
| JP 61-242571 A | 28.10.1986 | None | |

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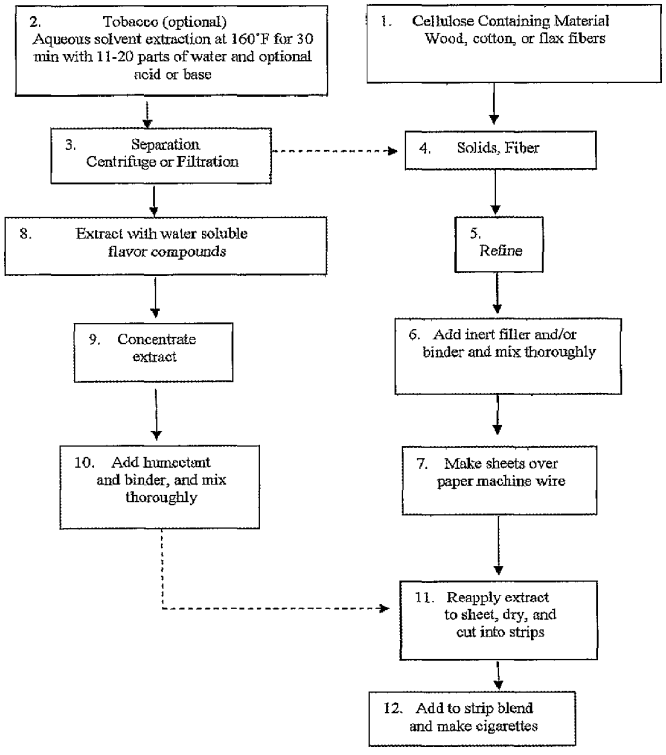
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*[Continued on next page]*

(54) Title: SMOKEABLE TOBACCO SUBSTITUTE FILLER HAVING AN INCREASED FILL VALUE AND METHOD OF MAKING SAME




*Paper Recon Process*

(57) Abstract: The invention relates to a smokeable filler material having an increased fill value and processes for making the smokeable filler. The smokeable filler has a fill value of at least 5 cc/g and comprises a cellulose material, a humectant, an inert filler, a binder, and optionally a tobacco containing material.

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RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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# SMOKEABLE TOBACCO SUBSTITUTE FILLER HAVING AN INCREASED FILL VALUE AND METHOD OF MAKING SAME

## CROSS-REFERENCE TO RELATED APPLICATIONS

This international patent application is a continuation of and claims priority to and benefit from U.S. Patent Application Serial Number 10/902,760, filed on 30 July 2004.

## STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

## FIELD OF INVENTION

This invention relates to smokeable filler material for smoking articles, and in particular to a smokeable filler material for a smoking article where the filler has an increased fill value and closely exhibits properties of tobacco in a smoking article while reducing the Hoffman Analytes associated with tobacco.

## BACKGROUND OF THE INVENTION

In the many efforts which have been made to provide alternative smokeable filler materials with reduced Hoffman Analyte delivery very few, if any, have been found which

produce a smoke taste and flavor which is acceptable to smokers of conventional tobacco containing products. Many of these fillers contain mostly, if not entirely, chalk or other inert fillers. Therefore, most alternative filler materials have been used in conjunction with cut tobacco leaf or tobacco-containing reconstituted products. However, even in this form, the unacceptable taste of these filler materials is noticeable and detracts from smoking pleasure. Additionally, many of the non-tobacco filler materials have a low fill value which results in a heavy smoking article with a low burn rate, low smoke delivery, and high propensity to extinguish.

## SUMMARY OF THE INVENTION

The Smokeable Tobacco Substitute Filler Having an Increased Fill Value and Method of Making Same claimed herein has a cellulose containing material, a humectant, optionally a tobacco containing material wherein a portion of the tobacco containing material may be a tobacco extract, optionally an inert material, and a binder. Additionally, the filler material of the present invention may have flavorants and casings added as desired.

The filler material claimed herein may be produced via a paper making process, bandcast process, or an extrusion process. The filler material of the present invention has a fill value of at least 5 cc/g and more closely exhibits the properties exhibited by natural tobacco.

It is an object of the present invention to provide a smokeable tobacco substitute that has an increased fill value.

It is also an object of the present invention to provide a smokeable filler material having improved tobacco taste and flavor characteristics with minimal Hoffman Analyte deliveries. It is a further object of the invention to provide a smokeable filler material having an improved burn rate, smoke delivery, and propensity to resist extinguishing.

The present invention meets these objectives and provides additional benefits to the smoking article by replacing the large natural granular chalk found in the prior art fillers with precipitated and refined chalk having a smaller particle size and replacing at least a portion of the chalk with a less dense filler having a cellulose containing material.

The present invention provides for a smokeable filler material for a smoking article where the filler material has an increased fill value and tobacco characteristics and methods for making the smoking filler material.

More particularly, the present invention provides a smokeable filler having a fill value of at least 5 cc/g, wherein the smokeable filler has a humectant, a substantially non-combustible inert filler material, a binder, a cellulose fibrous material, and optionally a tobacco containing material.

Even more particularly, the present invention provides a process for making a smokeable filler comprising. The process comprises mixing and refining a cellulose containing material and an inert material. The inert material may be organic, inorganic or a combination of organic and inorganic. Tobacco, tobacco extract, humectant, binders, flavorants, and casings may be added at particular steps in the process to form a fiber containing material. The fiber containing material is cast into sheets via a paper making process, bandcast process, or an extrusion porcess. The sheet is cut into sheets into strips forming a smokeable filler having a fill value in excess of 5 cc/g.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a block diagram of the process steps representative of the present invention incorporating a paper making process.

FIG. 2 is a block diagram of the process steps representative of the present invention incorporating bandcast and extrusion processes.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. 1 shows a method of making a smoking article, such as a cigarette, according to the presently claimed invention wherein the sheet is produced via a paper making process. In step 1, a cellulose containing material derived from wood, cotton, or flax is provided. The cellulose containing material in step 1 is in an amount that makes up about 5% to 50% by weight of the sheet material obtained in step 11. Particularly, the cellulose containing material in step 1 makes up to about 10% to 15% by weight of the sheet material obtained in step 11. The use of cellulose in step 1 serves to improve the fill value of the filler material and also enables or improves the process of making sheet via a paper making process. Step 2 is an optional step of extracting tobacco. The tobacco extraction method in Step 2, used to obtain a tobacco extract and tobacco solids, may be an aqueous extraction using solely water or an aqueous extraction using other additives in the extraction process, for example, acids or bases. Typically, extraction of tobacco in Step 2 is carried out by extracting one part of tobacco with about 11 to 20 parts of an aqueous solution at about 140° to 180° F for about 15 to 45 minutes. The aqueous solution may be acidic or basic for the release of tobacco pectin (binder) which increases sheet tensile strength, improves sheet pliability, and reduces the amount of added binder, e.g. alginate, during sheet making. In Step 3 the tobacco solids are separated from the tobacco extract by either centrifugation or filtration.

Step 4 is an optional step where the tobacco solids from Step 3 are added to the cellulose containing material of Step 1. The cellulose containing material of step 1 and, optionally, added tobacco solids in step 4 are refined in step 5. After refining in step 5, inert fillers and/or binders are mixed in step 6 with the refined material obtained in step 5. The inert materials in step 6 may be organic and/or inorganic. The organic fillers used in step 5 include chitosan and liposan while the inorganic filler materials, include, for example, calcium carbonate, magnesium carbonate, calcium oxide, and magnesium oxide. These inorganic filler materials are precipitated and refined resulting in a small particle size. Refining of the inert fillers typically involves milling the fillers to a very fine particle size such as a range of about 0.5μm to 1 μm. This small particle size allows for making a thin sheet material and hence helps to increase the fill value of the smokeable filler when cut or shredded into strips. The inert materials in step 6 may be a single organic or inorganic inert material or may be a combination of inert materials whether organic or inorganic. The inert materials added in step 6 are in an amount that makes up to 35% by weight of the sheet material obtained in step 11. Preferably, the inert materials in step 6 make up about 20% to 25% by weight of the sheet material obtained in step 11.

In step 7 the material resulting from step 6 is formed into sheets via a paper making process. The sheet material derived from step 7 may, optionally, have a tobacco extract containing material added to the sheet in step 11. The tobacco extract in step 8 obtained by the separation from the tobacco solids in step 3 are concentrated in step 9. In step 10 a humectant and binder is mixed thoroughly with the concentrated tobacco extract of step 9. The humectant in step 10 may be added at a concentration where the resulting sheet from step 11 comprises up to 15% by weight humectant on a dry weight basis. Generally, the humectant in step 10 is added at a concentration where the resulting sheet from step 11 comprises about 12.5% by weight humectant on a dry weight basis. The binder in step 10 is

in an amount that makes up about 5% to 25% by weight of the sheet material obtained in step 11. Preferabley, the binder step 10 makes up to about 6% to 10% by weight of the sheet material obtained in step 11. The resulting tobacco extract containing material of step 10 is the tobacco extract that is, optionally, added to the sheet in step 11 and may make up to 30% by weight of the sheet resulting from step 11. Additionally, the sheet resulting from step 11 may contain up to 50% by weight tobacco containing materials which are, optionally, added in the process at process steps 4 and / or 11. The sheet resulting from step 11 has a fill value in excess of 4 cc/g. Preferably, the fill value of the sheet resulting from step 11 has a fill value in a range of about 6 to 10 cc/g. The sheet resulting from step 11 is then cut into strips and added to a strip blend in step 12 for making a smoking article.

FIG. 2 shows other embodiments that may be followed in practicing the present invention. The block diagram in FIG. 2 shows the process steps to be taken to produce a tobacco substitute filler having an increased fill value where the sheet is produced via a bandcast or extruding process.

In step 100, a cellulose containing material derived from wood, cotton, or flax and refined is provided. The cellulose containing material in step 100 is in an amount that makes up to 25% by weight of the sheet material to be shredded in step 109. Step 101 is an optional step of adding a tobacco containing material such as fines, slurry, extract or combinations thereof, and an inert filler. The tobacco containing material added in step 101 is in such an amount that the finished sheet to be shredded in step 109 may contain up to 50% by weight of tobacco containing material. The tobacco containing material in step 101 may have tobacco extract in an amount that makes up to 30% by weight of the sheet material obtained in step 109. Preferably, the tobacco extract material in step 101 makes up from about 10% to 20% by weight of the sheet material obtained in step 109. The inert filler that is added in step 101 is in an amount needed to produce a sheet to be shredded in step 109 having up to 70% by

weight inert filler. Preferably, the inert material in step 101 makes up from about 10% to 70% by weight of the sheet material obtained in step 109. The inert filler added to the cellulose containing material in step 101 may be either organic or inorganic. The inorganic chalk fillers are precipitated and refined resulting in a small particle size, i.e. about 0.5 μm to 1 μm in diameter, which allows for the forming of a thinner sheet having an increased fill value when shredded.

In step 102 the materials resulting from steps 100 and 101 are mixed thoroughly. In step 103 a binder solution (e.g. alginate, carboxymethyl cellulose, etc.) is added to the material resulting from step 102 and mixed in step 104. The binder solution added in step 103 is in such an amount that the finished sheet to be shredded in step 109 contains from about 5% to 25% binder on a dry weight basis. In step 105, a humectant (e.g. glycerol, propylene glycol, etc.) is added in such an amount that the finished sheet to be shredded in step 109 contains from about 8% to 15% humectant. Advantageously, the finished sheet to be shredded in step 109 contains about 12.5% humectant by weight. Optionally, In step 106 casings and flavorings may be added to the mixture.

The mixture resulting from step 106 may be formed into a sheet by either an extruder in step 107 or by a bandcast process in step 108. The resulting sheet is then shredded and added to strip blend for cigarette fabrication in step 109.

The smokeable tobacco substitute filler having an increased fill value is produced by the processes shown in FIG. 1 and FIG. 2. The smokeable filler material typically comprises a cellulose containing material, a humectant, a substantially non-combustible inert filler material, a binder, and optionally a tobacco containing material, casings, and flavorings.

The humectant comprise up to 15% by weight of the filler of the present invention. However, it has been determined that a concentration of humectant over 20% may cause the wrapper of the smoking article to spot. The precise concentration at which spotting occurs

depends on the concentration of other materials in the filler. In order to avoid spotting, advantageous concentrations of humectant have been determined for various embodiments of the present invention as indicated herein.

The filler material of the present invention has about 5% to 25% binder. Suitable binder materials for the present invention include the well known cellulosic or cellulosic derivative binders, alginic or pectinaceous binders. The cellulosic derivative binders include binders such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose or cellulose ethers. The alginic binders include binders such as ammonium alginate, sodium alginate, sodium calcium alginate, calcium ammonium alginate, potassium alginate, magnesium alginate, triethanol-amine alginate and propylene glycol alginate, or insoluble alginates which can be rendered soluble by the addition of solubilising agents, such as ammonium hydroxide. Examples of these include aluminium, copper, zinc and silver alginates. Alginates which are initially soluble but which, during processing, undergo treatment to render them insoluble in the final product may also be used, e.g. sodium alginate going to calcium alginate. Other organic binders include gums such as gum arabic, gum ghatti, gum tragacanth, Karaya, locust bean, acacia, guar, quince seed or xantham gums, or gels such as agar, agarose, carrageenans, fucoidan and furcellaran. Pectins and pectinaceous materials can also be used as binders. Starches can also be used as organic binders. Other suitable gums can be selected. Inorganic non-combustible binders, such as potassium silicate, magnesium oxide in combination with potassium silicate, or some cements, for example, and mixtures thereof, may also be used, usually in the alternative. Combinations of all of the above may also be used as an effective binder.

Cellulose fibers may be derived from wood, cotton, or flax and typically make up approximately 5% to 50% by weight of the filler of the present invention. Preferable ranges of cellulose have been determined for the different processes in practicing the present

invention as indicated herein. These ranges of cellulose in conjunction with the precipitated and refined inert materials has been determined to produce a filler material having a fill value above 4 cc/g and approximates the fill value found in natural tobacco. Additionally, these cellulose fibers have been found to reduce the spotting that is often times associated with use of humectants. Tobacco containing materials may make up to 50% by weight of the filler material of the present invention. The source of tobacco may be in the form of tobacco fines, stems, tobacco containing slurry, extract of tobacco, concentrated extract, extracted tobacco solids, or other tobacco sources known in the art. The tobacco containing material may have tobacco extract in an amount that makes up to 30% by weight of the sheet material obtained in the processes claimed herein.

Additionally, flavorants and casings may be added to the smokeable filler as desired. Flavorants or taste materials may include menthol, licorice, coffee, tobacco, tobacco extract or other flavorings known in the art. The filler material may be cased using conventional techniques known in the art.

In order that the invention may be easily understood and readily carried into effect the following examples were performed to illustrate the invention and aspects thereof. The following Examples are incorporated herein to illustrate the present invention with no intention of being unduly limited thereby.

EXAMPLES 1-10

Several embodiments of the present invention were made according to the processes described herein and the fill value of these embodiments were measured and compared to the fill value of the tobacco filler material found in the prior art. The fill value was determined by placing a 10 g to 20 g sample of filler material into a densimeter and compressing the filler with a 2 kg piston for 30 seconds. The height of the piston in the densimeter as well as the

moisture content of the samples were measured. The fill value of the samples were calculated according to the following formulas:

$UFV\ (cc/g) = (2.78 \times H) / W$

$CFV\ (cc/g) = UFV + (-0.76 \times (T - M) + 0.01 \times (T^2 - M^2)$

Wherein UFV in an uncorrected fill value, H is the final compressed height of the piston in the densimeter, W is the weight of the sample in grams., CFV is the corrected fill value, M is the percent moisture content of the sample, and T is a target moisture of 14%.

The compositions of the filler found in the prior art and the compositions of several examples of the present invention are listed in the following tables. The examples include sheets having a basis weight from 55 $g/m^2$ to 100 $g/m^2$. The sheet materials in the following examples were made via the paper making process in FIG. 1 and the bandcast process in FIG. 2 as indicated. The results of the corrected fill value measurements of each sample is listed at the bottom of each table.

**Table 1**

Sheet basis weight of 100 g/m$^2$
Sheet made via bandcast process

| Material | Prior Art Filler | Increased Fill Value Ex. 1 | Increased Fill Value Ex. 2 | Increased Fill Value Ex. 3 | Increased Fill Value Ex. 4 |
|---|---|---|---|---|---|
| Tobacco (%) | 0.0 | 0.0 | 0.0 | 10.0 | 10.0 |
| Alginate (%) | 7.5 | 10.0 | 10.0 | 8.0 | 8.0 |
| Precipitated Refined Chalk (%) | 0.0 | 61.5 | 61.5 | 55.0 | 55.0 |
| Granular Chalk (%) | 78.5 | 0.0 | 0.0 | 0.0 | 0.0 |
| Cellulose Fiber from Cotton (%) | 0.0 | 15.0 | 0.0 | 13.0 | 0.0 |
| Cellulose Fiber from Wood (%) | 0.0 | 0.0 | 15.0 | 0.0 | 13.0 |
| Glycerin (%) | 12.5 | 12.0 | 12.0 | 12.0 | 12.0 |
| Caramel (%) | 1.5 | 1.5 | 1.5 | 0.0 | 0.0 |
| Corrected Fill Value (cc/g) | 4.0 | 5.8 | 6.8 | 5.7 | 6.9 |

**Table 2**

Sheet basis weight of 75 g/m$^2$
Sheet made via bandcast process

| Material | Prior Art Filler | Increased Fill Value Ex. 5 | Increased Fill Value Ex. 6 | Increased Fill Value Ex. 7 |
|---|---|---|---|---|
| Tobacco (%) | 0.0 | 0.0 | 0.0 | 0.0 |
| Alginate (%) | 7.5 | 10.0 | 10.0 | 10.0 |
| Precipitated Refined Chalk (%) | 0.0 | 60.0 | 60.0 | 60.0 |
| Granular Chalk (%) | 78.5 | 0.0 | 0.0 | 0.0 |
| Cellulose Fiber from Cotton (%) | 0.0 | 15.0 | 0.0 | 0.0 |
| Cellulose Fiber from Wood (%) | 0.0 | 0.0 | 15.0 | 0.0 |
| Cellulose Fiber from Flax (%) | 0.0 | 0.0 | 0.0 | 15.0 |
| Glycerin (%) | 12.5 | 13.0 | 13.0 | 13.0 |
| Caramel (%) | 1.5 | 2.0 | 2.0 | 2.0 |
| Corrected Fill Value (cc/g) | 4.48 | 8.51 | 8.62 | 8.88 |

**Table 3**

Sheet basis weight of 85 g/m$^2$

| Material | Prior Art Filler[a] | Increased Fill Value Ex. 8[a] | Increased Fill Value Ex. 9[a] | Increased Fill Value Ex. 10[b] |
|---|---|---|---|---|
| Tobacco (%) | 0.0 | 0.0 | 10.0 | 10.0 |
| Alginate (%) | 7.5 | 10.0 | 8.0 | 8.0 |
| Precipitated Refined Chalk (%) | 0.0 | 61.5 | 55.0 | 55.0 |
| Granular Chalk (%) | 78.5 | 0.0 | 0.0 | 0.0 |
| Cellulose Fiber from Cotton (%) | 0.0 | 15.0 | 13.0 | 13.0 |
| Cellulose Fiber from Wood (%) | 0.0 | 0.0 | 0.0 | 0.0 |
| Glycerin (%) | 12.5 | 12.0 | 12.0 | 12.0 |
| Caramel (%) | 1.5 | 1.5 | 0.0 | 0.0 |
| Corrected Fill Value (cc/g) | 4.3 | 7.3 | 7.6 | 7.8 |

[a] Sheet made from bandcast process
[b] Sheet made from paper process

**Table 4**

Sheet basis weight of 55 g/m$^2$
Sheet made via paper process

| Material | Increased Fill Value Ex. 11 |
|---|---|
| Tobacco (%) | 0.0 |
| Alginate (%) | 10.0 |
| Precipitated Refined Chalk (%) | 61.5 |
| Granular Chalk (%) | 0.0 |
| Cellulose Fiber from Cotton (%) | 15.0 |
| Cellulose Fiber from Wood (%) | 0.0 |
| Glycerin (%) | 12.0 |
| Caramel (%) | 1.5 |
| Corrected Fill Value (cc/g) | 8.5 |

The examples show the increased fill value obtained by the present invention. Typically, tobacco cut rag exhibits a fill value of about 6 to 7 cc/g where the filler of the prior art has a fill value of about 4 to 4.5 cc/g. The low fill value of the filler material in the prior art results in a heavy smoking article that has a poor burn rate and smoke delivery as well as a propensity to extinguish. The fill value of the filler material presently claimed was shown in the examples to be from 5.7 to 8.88 cc/g which is in a range more closely approximating what is found in tobacco cut rag. This filler material with an increased fill value produces a smoking article having a weight and other properties that more closely approximates tobacco. Additionally, the filler material has a good burn rate and smoke delivery as well as a reduced propensity to extinguish. Another advantage discovered with the present invention is the filler material has an increased tensile strength that better withstands shredding and other

cigarette making processes than the filler material of the prior art. Also, an advantage of the present invention over the prior art is that the present invention reduces or eliminates spotting of the cigarette paper.

The Smokeable Tobacco Substitute Filler Having an Increased Fill Value and Method of Making Same claimed herein has a cellulose containing material in a range of 5% to 50%, a humectant in a range of up to 15%, a tobacco containing material in a range of up to 50% wherein a portion of the tobacco containing material may be a tobacco extract in a range of up to 30%, an inert material of up to 70%, and a binder in a range of 5% to 25%. The percentages of each of the constituents is based on a dry weight percentage of the final sheet. Additionally, the filler material of the present invention may have flavorants and casings added as desired.

The filler material claimed herein may be produced via a paper making process, bandcast process, or an extrusion process. The advantageous concentrations of the constituents making up the filler material vary based upon the process employed to practice this invention. The filler material of the present invention has a fill value of at least 4 cc/g and more closely exhibits the properties exhibited by natural tobacco.

We Claim:

1. A smokeable filler comprising up to about 15% humectant by weight, up to 70% by weight of non-combustible inert filler material, from about 5% to about 25% by weight binder, up to about 50% by weight cellulose fiber, all on a dry weight basis, wherein said smokeable filler has a fill value of at least 5 cc/g .

2. The smokeable filler in Claim 1 wherein said inert filler material is selected from the group consisting of chitosan, liposan, calcium carbonate, magnesium carbonate, calcium oxide, magnesium oxide, and combinations thereof.

3. The smokeable filler in Claim 2 wherein said calcium carbonate, magnesium carbonate, calcium oxide, and magnesium oxide have been precipitated and refined.

4. The smokeable filler in Claim 2 wherein said inert filler is in a range from about 10% to 70% by weight of said smokeable filler.

5. The smokeable filler in Claim 4 wherein said inert filler is in a range from about 20% to 25% by weight of said smokeable filler.

6. The smokeable filler in Claim 2 wherein said inert filler is in a range of up to 35% by weight of said smokeable filler.

7. The smokeable filler in Claim 1 wherein said cellulose is present in a range from about 5% to about 50% by weight of said smokeable filler.

8. The smokeable filler in Claim 1 wherein said cellulose is present in a range of up to 25% by weight of said smokeable filler.

9. The smokeable filler in Claim 8 wherein said cellulose is present in a range from about 10% to about 15% by weight of said smokeable filler.

10. The smokeable filler in Claim 1 wherein said humectant is present in a range of about 8% to 15% by weight of said smokeable filler.

11. The smokeable filler in Claim 10 wherein said humectant is present at about 12.5% on a dry weight basis of said smokeable filler.

12. The smokeable filler in Claim 1 wherein said tobacco containing material has a tobacco extract, wherein said tobacco extract is present in a range of up to 30% by weight of said smokeable filler.

13. The smokeable filler in Claim 12 wherein said tobacco extract is present in a range from about 10% to 20% by weight of said smokeable filler.

14. The smokeable filler in Claim 1 wherein said binder is present in a range from about 5% to 25% by weight of said smokeable filler.

15. The smokeable filler in Claim 14 wherein said binder is present in a range from about 6% to 10% by weight of said smokeable filler.

16. The smokeable filler in Claim 1 wherein said cellulose fiber is derived from wood.

17. The smokeable filler in Claim 1 wherein said cellulose fiber is derived from cotton.

18. The smokeable filler in Claim 1 wherein said cellulose fiber is derived from flax.

19. The smokeable filler in Claim 1 wherein said filler is in the form of a sheet.

20. The smokeable filler in Claim 19 wherein said sheet is formed by a paper making process.

21. The smokeable filler in Claim 19 wherein said sheet is formed by a bandcast process.

22. The smokeable filler material in Claim 19 wherein said sheet is formed by an extrusion process.

23. A process for making a smokeable filler comprising the steps of:

mixing a cellulose containing material to form a fibrous material product;

refining said fibrous material product;

mixing an inert material selected from the group consisting of chitosan, liposan, calcium carbonate, calcium oxide, magnesium oxide, and combinations thereof with said fibrous material product to form a fiber containing material;

making said fiber containing material into sheets via a paper making process; and

cutting said sheets into strips forming said smokeable filler, wherein said smokeable filler has a fill value in excess of 5 cc/g.

24. The process for making a smokeable filler in Claim 23 wherein said mixing step further comprises the mixing of a tobacco containing material wherein said tobacco containing material may make up to 50% by weight of said smokeable filler.

25. The process for making a smokeable filler in Claim 23 wherein said sheets are sprayed with a tobacco extract prior to said cutting of said sheets.

26. The process for making a smokeable filler in Claim 23 wherein said tobacco extract further has a humectant.

27. The process for making a smokeable filler in Claim 26 wherein said humectant is in an amount that makes up to 15% by weight of said smokeable filler.

28. A process for making a smokeable filler comprising the steps of:

mixing a refined cellulose containing material, a tobacco containing material, and an inert material forming a fibrous material product;

mixing a binder solution with said fibrous material product to form a fiber containing material;

adding a humectant to said fiber containing material;

making said fiber containing material into sheets; and

cutting said sheets into strips forming said smokeable filler, wherein said smokeable filler has a fill value in excess of 5 cc/g.

29. The smokeable filler in Claim 28 wherein said sheet is formed by a bandcast process.

30. The smokeable filler material in Claim 28 wherein said sheet is formed by an extrusion process.

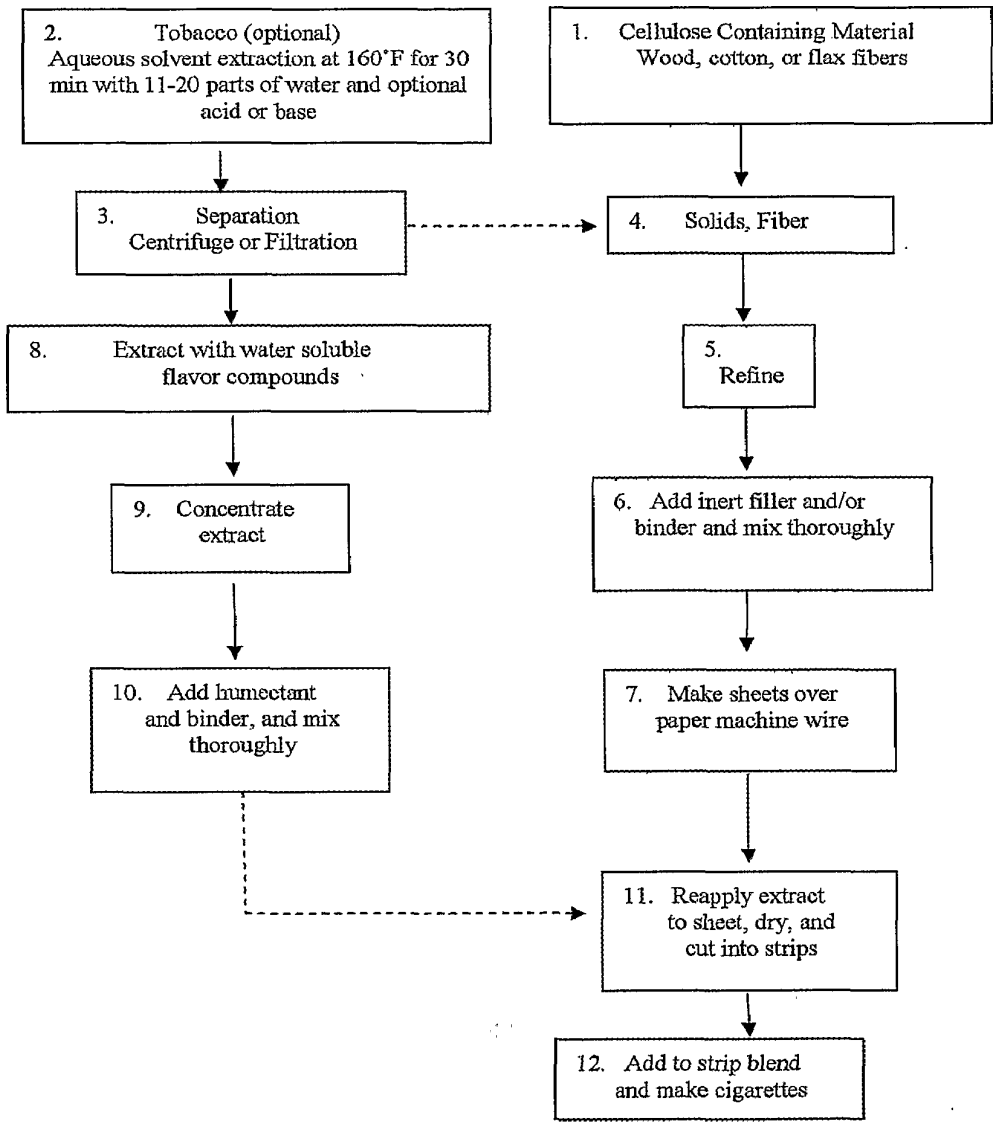



*Figure 1. Paper Recon Process*

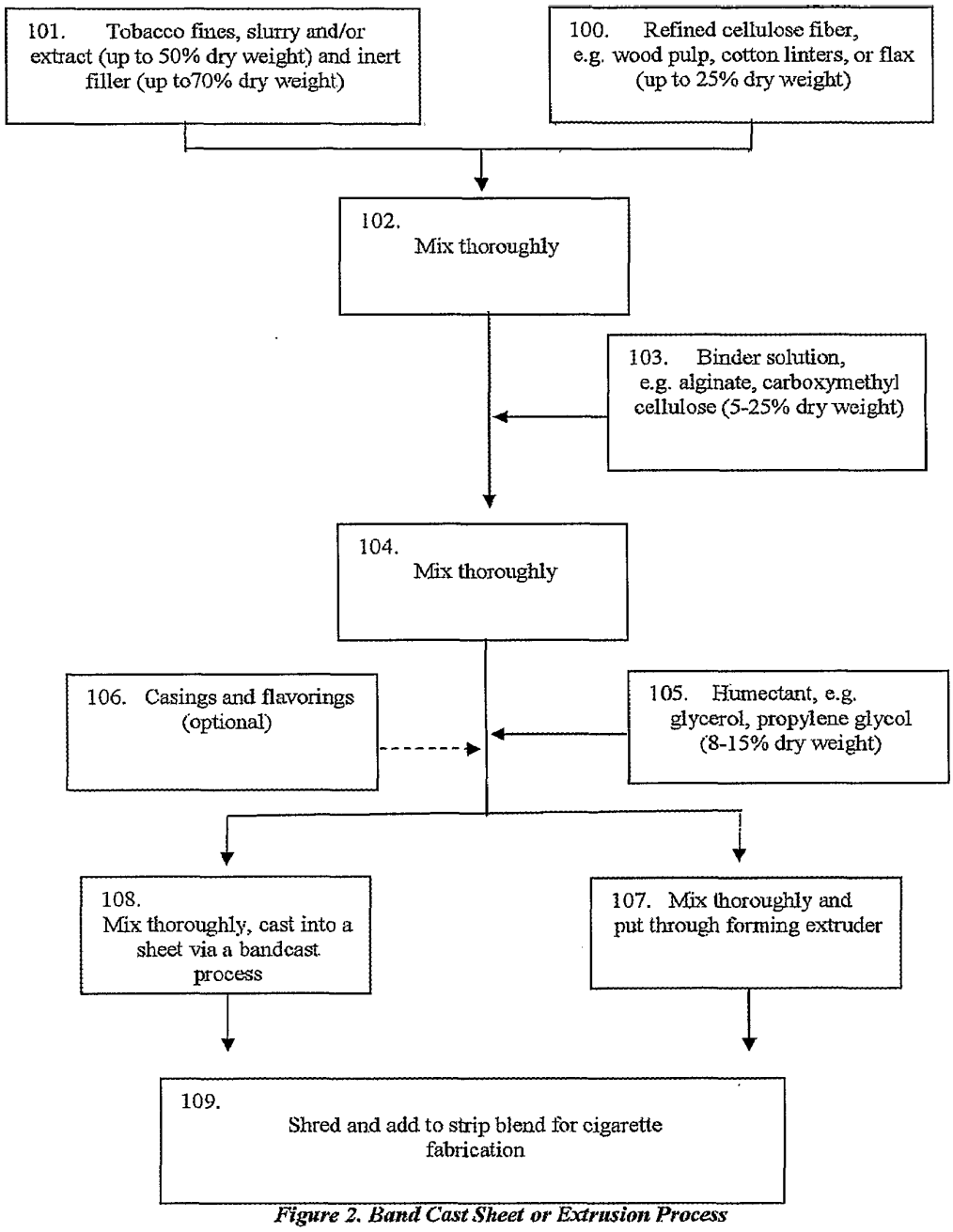



***Figure 2. Band Cast Sheet or Extrusion Process***

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Minimum documentation searched (classification system followed by classification symbols)
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 03/055337 A (BRITISH AMERICAN TOBACCO LIMITED; MCADAM, KEVIN, GERARD; GRIERSON, GO) 10 July 2003 (2003-07-10) the whole document | 1-30 |
| A | EP 0 419 975 A (R.J. REYNOLDS TOBACCO COMPANY) 3 April 1991 (1991-04-03) the whole document | 1-30 |
| A | US 6 408 856 B1 (MCADAM KEVIN GERARD) 25 June 2002 (2002-06-25) the whole document | 1-30 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"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

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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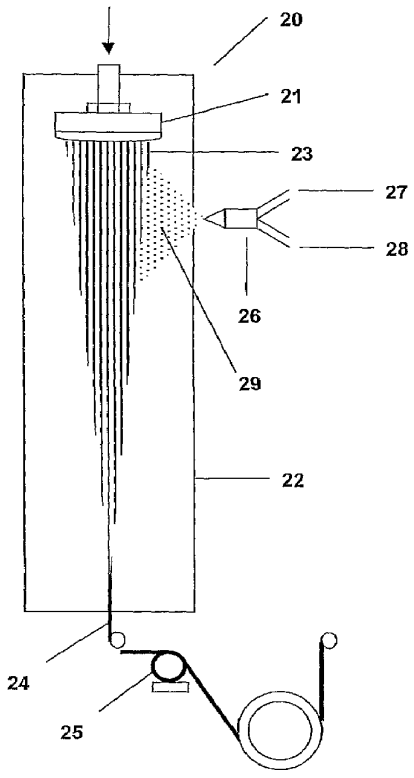
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*[Continued on next page]*

(54) Title: PROCESSING FOR MAKING FILTER TOW




(57) Abstract: A method of preparing a crimped tow of cellulose acetate filaments comprising the steps of: a) providing cellulose acetate dope b) forming filaments (23) from the dope c) applying at least one additive to the filaments d) crimping the filaments to form a crimped tow wherein the at least one additive is capable of removing a component from cigarette smoke. Preferably, the component is a Hoffmann analyte. The additive may comprise a solution, liquid, emulsion or particulate material or combinations thereof. Preferably, the additive comprises an acidic compound or an alkaline compound. The additive may comprise malic acid, potassium carbonate, citric acid, tartaric acid, lactic acid, ascorbic acid, polyethyleneimine, cyclodextrin, sodium hydroxide, sulphamic acid, sodium sulphamate, polyvinyl acetate and carboxylated acrylate, carbon, silica, zeolite, clay, alumina, metal, molecular sieves or an ion exchange resin. The product tow can be processed on standard equipment to make efficient filter rods from which cigarette filter tips can be made which give significantly increased and selective retention of key smoke constituents.

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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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# PROCESS FOR MAKING FILTER TOW

## Field of the Invention

This invention relates to a process for making a crimped tow of filaments, known as filter tow, suitable for conversion into filter rods for use as tobacco smoke filters. The most commonly used filter tows comprise cellulose acetate filaments which are valued for their ability to produce high quality filters.

## Background of the Invention

Manufacturers in the tobacco industry are seeking to develop means of selective filtration in order to reduce the levels of certain constituents of main-stream cigarette smoke. For this purpose, various constructions of filter rods have been devised, involving in many cases the use of porous particles having adsorbent surfaces, particularly activated carbon particles. The inclusion of such particles in a filter rod can have a major impact on the efficiency of the filter but can involve more complicated and expensive filter rod manufacturing processes.

One approach has been to have a multi-section filter in which carbon particles are confined to an inner section of the filter, with the part of the filter which goes in the mouth being a standard cellulose acetate filament filter. In a triple-section filter, for example, the middle section may comprise a bed of loose carbon particles. However, a loose bed of particles in the cigarette filter may sometimes be by-passed as a filtration medium by channelling of the smoke stream passing through it.

Another approach has been to include carbon in filter rods by adhering the carbon particles to the filaments through use of plasticisers or adhesives sprayed onto the crimped tow at the filter rod making stage. This approach can however lead to variability in the application of the particles.



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Traditionally, additional components for incorporation into cigarette filters have been added at or after the stage of forming filter rods from crimped tow. For example, US 6,145,511 discloses the addition of various compounds to filters during conventional filter rod manufacture. It is stated that the additional components are mixed with the traditional plasticiser triacetin in the rod maker process.

The processes described above which involve the incorporation of additional components at the rod making stage add complexity to the rod making process. Furthermore, some processes are inflexible in that the rod making machine often needs to be custom designed or require extensive modification to perform the step of adding the particular substance in question.

Another approach to incorporating additional components is disclosed in WO 91/12737. This document discloses the step of dissolving acidic compounds into a cellulose acetate spinning solution prior to spinning filaments for use in the manufacture of a filter. The incorporation of acidic materials into the spinning solution is intended to alter the nicotine to tar ratio in filtered cigarette smoke.

The present invention seeks to provide an improved method for the manufacture of filter tow, which may be used in the manufacture of filter rods and cigarettes. The present invention also seeks to provide improved filter tow.

Disclosure of the Invention

According to one aspect of the present invention, there is provided a method of preparing a crimped tow of cellulose acetate filaments comprising the steps of:

providing cellulose acetate dope

forming filaments from the dope

applying at least one additive to the filaments

crimping the filaments to form a crimped tow

wherein the at least one additive is capable of removing a component from cigarette smoke.

Preferably, the at least one additive comprises a solution, emulsion, liquid, or particulate material or combinations thereof.

Conveniently, the at least one additive comprises an acidic compound or an alkaline compound.

Advantageously, the at least one additive comprises malic acid, potassium carbonate, citric acid, tartaric acid, lactic acid, ascorbic acid, polyethyleneimine, cyclodextrin, sodium hydroxide, sulphamic acid, sodium sulphamate, polyvinyl acetate and carboxylated acrylate.

Preferably, the at least one additive comprises particles of carbon, silica, zeolite, clay, alumina, metal, molecular sieves or an ion exchange resin.

Conveniently, the carbon comprises activated carbon.

Advantageously, the particles comprise a material capable of generating a gaseous emission.

Preferably, the material is a liquid which can volatilized to generate a gas or vapour by the action of heat and/or reduced pressure.

Conveniently, the material is water.

Advantageously, the method further comprises the step of steeping the particles in water before application to the filaments.

Preferably, the at least one additive is applied to the filaments using an adhesive.

Conveniently, the adhesive comprises a cellulose ether.

Advantageously, the adhesive comprises methyl cellulose.

Preferably, the method further comprises the step of applying a shed suppressor to the filaments.

Conveniently, the shed suppressor is glycerol.

Advantageously, the filaments have a non-circular cross-section.

Preferably, the filaments have a multi-lobal cross-section.

Conveniently, the component is a Hoffmann analyte.

Advantageously, the component comprises hydrogen cyanide, formaldehyde, pyridine, quinoline or phenol.

Preferably, the step of forming filaments from the dope comprises extruding the dope through a spinneret to form an array of filaments, and drying the filaments to remove a dope solvent.

Conveniently, the at least one additive is applied to the filaments during the drying step.

Advantageously, the at least one additive is applied to the filaments after the drying step.

Preferably, the method comprises the step of combining the filaments produced by a plurality of spinnerets to produce a banded tow of filaments.

Conveniently, the at least one additive is applied to the filaments before formation of the banded tow.

Advantageously, the at least one additive is applied to the filaments after formation of the banded tow.

Preferably, the at least one additive is applied to the filaments immediately before the step of crimping to form the crimped tow.

Conveniently, the at least one additive comprises a plurality of additives.

Advantageously, the plurality of additives comprises two additives.

Preferably, the plurality of additives comprises three additives.

Conveniently, the plurality of additives are applied separately to the filaments.

Advantageously, the plurality of additives are applied concurrently to the filaments.

Preferably, the plurality of additives are applied sequentially to the filaments.

Conveniently, each of the plurality of additives is incorporated into a substantially separate portion of the filaments.

Advantageously, the method comprises the step of applying the plurality of additives to the banded tow in stripes.

Preferably, the step of applying the plurality of additives to the banded tow in stripes further comprises the application of a barrier material between adjacent stripes.

Conveniently, the barrier material comprises white oil.

Advantageously, the step of forming filaments from the dope comprises extruding the dope through a spinneret to form an array of filaments, and drying the filaments to remove a dope solvent.

Preferably, one of the plurality of additives is applied to the filaments during the drying step and another of the plurality of additives is applied to the filaments after the drying step.

Conveniently, one of the plurality of additives is applied to the filaments formed by a first spinnerette and another of the plurality of additives is applied to the filaments formed by a second spinnerette.

Advantageously, the step of providing cellulose acetate dope comprises incorporating at least one additive into the dope.

Preferably, the method further comprises the step of plaiting the crimped tow of filaments into a bale.

Advantageously, the method further comprises the step of forming a filter rod from the crimped tow of filaments.

Preferably, the step of forming a filter rod further comprises incorporating at least one additive into the filter rod.

Advantageously, a particulate additive is incorporated into the tow of filaments.

Preferably, a particulate additive is incorporated into a cavity in the filter rod.

Conveniently, the step of forming a filter rod comprises combining a plurality of filter rod segments together to form the filter rod.

Preferably, each of the plurality of filter rod segments comprises filaments that incorporate a different additive.

Conveniently, the filter rod comprises three filter rod segments.

Advantageously, the method further comprises the step of forming a cigarette from the filter rod.

According to another aspect of the invention, there is provided a crimped tow of cellulose acetate filaments obtainable by a method as defined above.

According to a further aspect of the invention, there is provided a bale of tow obtainable by a method as defined above.

Preferably, the bale of tow is suitable for use on a conventional rod-maker with little or no modification being necessary.

According to a yet further aspect of the present invention, there is provided a filter rod obtainable by a method as defined above

According to yet another aspect of the present invention, there is provided a cigarette obtainable by a method as defined above.

The invention may include one or more of the following preferred features.

Preferably, if the at least one additive comprises particles, then the particles are applied to the filaments before the formation of a banded tow.

Conveniently, if the at least one additive comprises particles, then the particles are not pre-treated to load them with a material capable of generating a gaseous emission from the particles.

Advantageously, if the at least one additive comprises particles, then an adhesive is not used to bond the particles to the filaments.

The present invention will now be described, by way of example, with reference to the accompanying drawings in which:

Figure 1 is a schematic diagram showing the typical production of cellulose acetate tow;

Figure 2 is a schematic view of a solution of additive being introduced into a spinning cell;

Figure 3 is a schematic view of a particulate additive being introduced into a spinning cell;

Figure 4 is a schematic view of an additive being applied to filaments immediately after leaving a spinning cell;

Figure 5 is a plan view of an applicator for applying an additive to a tow of filaments;

Figure 6 is a cross-sectional view of a banded tow of filaments passing through a pair of applicators as shown in Figure 5;

Figure 7 is a plan view of an applicator for applying two additives to a tow of filaments;

Figure 8 is a cross-sectional view of a banded tow of filaments passing through a pair of applicators as shown in Figure 7;

Figure 9 is a plan view of a banded tow being treated with two additives;

Figure 10 is a plan view of a banded tow being treated with three additives;

Figure 11 is a plan view of four arrays of treated filaments being banded together to form a banded tow;

Figure 12 is a scanning electron micrograph of a control filament without an additive at 1000x magnification;

Figure 13 is a scanning electron micrograph of a filament treated with malic acid at 1000x magnification; and

Figure 14 is a scanning electron micrograph of the treated filament shown in Figure 13 but at 10000x magnification.

The conventional method of manufacturing cellulose acetate filter tow will now be described with reference to Figure 1. The starting material is typically cellulose acetate flake which has been prepared from wood pulp. The cellulose acetate flake is dissolved in a solvent comprising about ~97% acetone and ~3% water in a mixer 1 to form a relatively viscous solution known as spinning dope. After dissolution, the dope typically undergoes a two stage filtration process by being pumped through a filter system 2 in order to remove fibrous or particulate matter which would otherwise cause problems with the subsequent spinning step. After filtration, the filtered dope is passed into a storage tank 3 before being preheated and pumped to an array of spinning cells 4.

Each spinning cell 4 comprises a spinneret 5 positioned above a relatively long drying chamber 6. The spinneret 5 has a head which typically comprises several hundred small holes through which the dope is extruded under pressure. The holes may be, for example, circular, triangular, square or rectangular that give rise to filaments having crenelated, "Y", "X" and dog-bone shaped cross-sections respectively. After being extruded through the spinneret 5, the dope forms an array of filaments 7 which are passed down through the drying chamber 6 which acts to remove the majority of the dope solvent. This normally involved the passing of a counter current of heated air which serves to evaporate most of the acetone from the extruded array of filaments 7. During the drying step, the array

of filaments 7 is gathered together to form a gathered array of filaments 8 which leaves the drying chamber 6.

After leaving the drying spinning cell 4, it is normal to apply "spin finish" to the gathered array of filaments 8 in order to provide beneficial properties. The spin finish normally comprises an oil-in-water emulsion containing white oil and surfactants. This serves to protect the filaments from abrasion, imparts reduced friction and avoids electrostatic problems. Spin finish is applied by passing the gathered array of filaments 8 over a roller 9 which dips into a reservoir of spin finish.

As each spinning cell produces a relatively small amount of filaments, the output from a number of spinning cells, for example from 25 to 100 but typically in the region of 50, is consolidated to form a ribbon or band of filaments known as a banded tow. For clarity, only four spinning cells are shown in Figure 1. As shown, the output of each of the spinning cells 4 is consolidated by a series of guides 10 to form the banded tow 11.

The banded tow 11 contains a large number of individual filaments, typically in the region of 2,000 to 40,000. In order to form a coherent banded tow that opens as a coherent web at the filter rod making stage and to impart properties to the tow that enables a stable filter rod to be made, the banded tow undergoes a crimping step involving the passage of the banded tow through a crimper 12 which imparts a generally sinusoidal shaped crimp along the length of the tow. This is typically performed by passing the banded tow 11 through a pair of rollers and box known as "stuffer-box" crimping.

The crimped banded tow 13 is then passed through a conditioner 14 which contains a number of zones of different temperature and humidity in order to ensure that the crimped tow 13 has had most of the residual solvent removed and has been restored to the tow's natural regain of moisture.

Although not a normal step in traditional tow manufacture, the conditioned crimped tow 15 may be subjected to a stretching step by passing through a pair of rollers 16 operating at slightly different speeds. This stretching step may be useful in the method of the present invention, as discussed in more detail below.

The crimped tow 15 is then carefully plaited into a container 17 and subsequently compressed by a hydraulic press 18 in order to give a bale of crimped tow 19. The bale 19 may then be sold to filter rod or cigarette manufacturers for processing into cigarette filter rods and subsequent incorporation into cigarettes.

The compressed tow 19 provides a convenient compact unit known as a bale containing a relatively long length of crimped tow 15 for the preparation of cigarette filter rods. This process involves the pulling of one end of the crimped tow 15 from the bale 19 and passage through a rod maker machine which produces the cigarette filter rods. In this process, the crimped tow 15 passes over a number of mechanical and/or air spreading devices to open up the web of the tow. During the final spreading step the web of stretched tow is sprayed with a plasticiser (typically triacetin) before passing through a garniture which funnels the stretched web of tow into a circular shape and packages the circular plug of filter with a paper casing. The paper-wrapped filter plug is then chopped into individual filter rods for use in subsequent steps to prepare cigarettes. These subsequent steps typically involve the cutting of the filter rods into individual cigarette filters followed by their combination with rods of tobacco to form complete filter cigarettes.

As previously mentioned, there are numerous examples in the prior art of the incorporation of additional components to the crimped tow at the rod making stage. This may involve the stretched plasticised web of tow being showered with carbon particles. Some of the carbon particles will thus become entrapped within the filaments of the web of filtered tow before formation of the filters.

This process results in a proportion of the carbon particles either passing through the web or being bounced off the web. These excess particles need to be safely collected within the manufacturing environment for recycling or disposal.

It would be very beneficial to provide a bale of crimped tow which already incorporates an additional component or components which may then be used on traditional rod-making machines with no or minimal changes to produce filters that can or have the potential to remove or reduce the level of certain constituents of mainstream smoke.

Furthermore, this approach also allows the use of dispersions, solutions, liquids or emulsions which would not be compatible with addition at the rod making stage. The speed that filter tow passes through a rod maker machine means that there is only a fraction of a second between the addition of a component to the stretched web of tow and the formation of a filter rod from that tow. Thus, a solution, liquid, emulsion or dispersion of an additive introduced at the rod-maker stage would have little time to dry before the formation of the final filter rod. This could lead to many problems such as the deterioration of the paper casing, clogging of the garniture, tape, cutting and rod feed mechanisms and/or retraction of fibre in the rods. However, if the solution of filter tow is applied at a stage in the manufacture before the rod maker, then sufficient time may be allowed for necessary drying of the various additives.

There has been increased interest in the selective reduction of levels of certain components of cigarette smoke. In particular, a group of compounds known as the Hoffmann analytes have been identified as targets for selective reduction. The list of Hoffmann analytes comprises a wide range of different chemicals and components which are present in various quantities in cigarette smoke. Currently listed compounds of particular interest include hydrogen cyanide, pyridine, quinoline, phenol, acetaldehyde, methanol, isoprene, acetone, acrolein, and various aldehydes such as propionaldehyde, crotonaldehyde, butyraldehyde, methyl ethyl ketone, 1,3-butadiene, acrylonitrile, benzene, toluene and styrene. It is also of

interest to reduce and/or differentially modify the levels of tar and nicotine in the smoke.

One definition of the Hoffmann list of analytes is set out below:

INORGANIC GASES

Carbon Monoxide (CO)

Hydrogen cyanide (HCN)

Cyanogen $(CN)_2$

Carbon disulphide $(CS)_2$

Ammonia $(NH)_3$

Oxides of nitrogen $(NO_x)$

Hydogen sulphide $(H_2S)$

Hydrazine $(N_2H_4)$

METALS

Mercury

Nickel

Lead

Cadmium

Chromium

Arsenic

Selenium

ALDEHYDES

Formaldehyde $(H_2CO)$

Acetaldehyde $(CH_3CHO)$

Acrolein $(CH_2=CHCHO)$

Crotonaldehyde $(CH_3CH=CHCHO)$

Proprionaldehde $(CH_3CH_2CHO)$

POLY AROMATIC HYDROCARBONS

Benz(a)anthracene $(C_{18}H_{12})$

Benzo(b)flouroanthene ($C_{20}H_{12}$)

Benzo(l)fluoroanthene ($C_{20}H_{12}$)

Benzo(k)fluoroanthene ($C_{20}H_{12}$)

Benzo(a)pyrene ($C_{20}H_{12}$)

Dibenzo(a,h)anthracene

Dibenzo(a,l)pyrene

Dibenzo(a,e)pyrene

Indeno(1,2,3-cd)pyrene

5-Methylchrysene ($C_{19}H_{14}$)

VOLATILE HYDROCARBONS

1,3-Butadiene

Isoprene

Benzene

Styrene

HETEROCYCLIC COMPOUNDS

Pyridine ($C_5H_5N$)

Nicotine ($C_6H_4NC_4H_7NCH_2$)

Quinoline ($C_9H_7N$)

Dibenz(a,h)acridine ($C_{13}H_9N$)

Dibenz(a,j)acridine ($C_{13}H_9N$)

7H-dibenzo(c,g)carbazole ($C_{12}H_9N$)

Furan ($C_4H_4O$)

Benzo(b)furan ($C_8H_6O$)

AROMATIC AMINES

Aniline ($C_6H_5NH_2$)

2-Toluidine ($CH_3C_6H_4NH_2$)

2-Naphthylamine ($C_{10}H_7NH_2$)

4-Aminobiphenyl ($C_6H_5C_6H_4NH_2$)

N-HETEROCYCLIC AMINES

2-Amino-9H-pyrido(2,3-b)indole

2-Amino-3-methyl-9H-pyrido(2,3-b)indole

2-Amino-3-methylimidazo(4,5-b)quinoline

3-Amino-1,4-dimethyl-5H-pyrido(4,3-b)indole

3-Amino-1-methyl-5H-pyrido(4,3-b)indole

2-Amino-6-methyl(1,2-a:3,2-d)imidazole

2-Aminodipyrido(1,2-a:3,2-d)imidazole

2-Amino-1-methyl-6-phenylimidazo(4,5-1)pyridine

N-NITROSAMINES

N-Nitrosodimethylamine ($(CH_3)_2NNO$)

N-Nitrosoethylmethylamine ($(CH_3CH_2)(CH_3)NNO$)

N Nitrosodiethylamine ($(CH_3CH_2)_2NNO$)

N-Nitroso-di-n-propylamine ($(CH_3(CH_2)_2)_2NNO$)

N-Nitroso-di-n-butylamine ($(CH_3(CH_2)_3)_2NNO$)

N-Nitrosopyrrolidine ($(C_4H_8NNO)$)

N-Nitrosopiperidine ($(C_5H_{10}NNO)$)

N-Nitroso-diethanolamine

N-Nitrosonornicotine

N-Nitrosoanabasine

4-(Methylnitrosamino) -1-(3-pyridyl)-1-butanone

MISCELLANEOUS ORGANIC

Methanol ($CH_3OH$)

Acetamide ($CH_3CONH_2$)

Acrylamide ($CH_2=CHC(CH_3)=CH_2$)

Acrylonitrile ($CH_2=CHCN$)

Acetonitrile ($CH_3CN$)

Vinyl Chloride ($CH_2=CHCl$)

Ethylene Oxide ($CH_2CH_2O$)

Ethyl Carbamate ($C_2H_5CO_2NH_2$)

1,1-Dimethylhydrazine ($(CH_3)_2NNH_2$)

Maleic Hydrazide ($C_4H_4O_2N_2$)

Methyl ioscyanate ($C_2H_3NO$)
2-Nitropropane ($(CH)_3CHNO_2$)
Nitrobenzene ($C_6H_5NO_2$)
Phenol ($C_6H_5OH$)
Catechol ($C_6H_4$-1,2-$(OH)_2$)
Dioctylphthalate
DDT ($(ClC_6H_4)_2CHCCl_3$)
DDE ($(ClC_6H_4)_2C=CCl_2$)

The present invention is concerned with the incorporation of one or more additives into filter tow during the manufacturing stage which may remove components of main-stream cigarette smoke, and in particular to remove Hoffmann analytes from cigarette smoke. By "remove" it is meant that the level of the component in cigarette smoke may be reduced or completely removed by a filter of the present invention in comparison to an equivalent filter which does not contain any such additives.

Preferred additives which may be used in the present invention are set out below:

Malic acid
Potassium carbonate
Citric acid
Tartaric acid
Lactic acid
Ascorbic acid
Polyethyleneimine
Cyclodextrin
Sodium hydroxide
Sulphamic acid
Sodium sulphamate
Polyvinyl acetate
Carboxylated acrylate
Carbon

Silica
Zeolite
Clay
Alumina
Metal
Molecular sieves
Ion exchange resins
Activated carbon
Acetate fibrils
Antioxidants
Proanthocyanidin
Impregnated carbon
Impregnated zeolites
Sodium carbonate
Sodium bicarbonate
Ammonium carbonate
Glycerol
Sodium silicate
Amino acids
Nitrogen-containing heterocycles
Polyamide
Aminopropylsilyl derivatised silica gel
Tributyl phosphate
Triethyl citrate
Encapsulated liquids
Sodium chloride + base
Plasticisers
Meltable waxes
Trimethyl octadecylammonium stearate
Quaternary compounds
Petroleum jelly
Sugar esters
Vegetable oils

Low boiling alkyl or hydroxy alkyl amine or double amine salts with inorganic salt of iron group and a colloidal metal hydroxide

Halogen-containing compounds

Vermiculite

Ferrous ferrite

Zirconium-containing solids

Polymeric hydrazides

Oxidative porphyrin

Slightly polymerised furfural

Desoxycholic acid

Polymeric amine salts

Collagen

Calcium silicate

Calcium alginate

Glutathione

Hydrate of double salt of ferroso-ferric chloride

Vitamin E

Hydroxycinnamic acids

Sodium percarbonate

Magnesium silicate

Quaternary ammonium acetate

Proteins (casein, gelatin, zein, soy bean, wheat gluten)

Activated silica gel

Amino acid derivatives

Polymeric amines

Sugars

Water soluble resins (PEO etc)

Expanded pearlite

Polyurethanes

Aromatic resins

Dextrans

Polyolefins

Tourmaline

Sodium pyroglutamate

Polyvalent metal salt of an acid

Platinum

Fullerene derivatives

Poly(arylene thioether)

Saturated cyclic secondary amine

Manganese oxide/ dihydroxide

Gold

Silver

Metal co-ordination complex

Metal phthalocyanine

Ferrous sulphate

Hydrotalcite

Fatty acid

Fatty acid ester

Iron aluminide

Iron aluminum carbide

Titanium aluminide

Ammonium bicarbonate

Copper ceria nano particles

Tetrasodium salt of ethylenediaminetetraacetic acid

Palladium

Polyphenols

Enediols

H-S-X-$SO_3H$

Humic acid

Ellagic acid

p-Aminobenzoic acid

Sorbic acid

Undecylenic acid

Silicic acid

Oil of anise, star anise oil, fennel oil, anethole, methyl chavicol, anisic acid and mixtures

Copper zinc alloy

Metal oxide oxidation catalyst

Spinel ferrite catalyst

Nitrided transition metal oxide nanoscale particles

Transition metal ethylene diamine complex

Magnesium chloride

Zinc oxide + carbonate

Thiol-functionalized sorbents

Chitosan

Nanoparticles -clay - or organically modified

Volcanic ash

Polycarboxylic acids

OUTLAST capsules with higher melting waxes

Isinglass

Sodium hydrogen carbonate

Clathrates

Starches

Poly hydroxy alkanoates

Nano titanium dioxide

Coated nano titanium dioxide

Polyvinylalcohol

Polyacrylamide

Quat-ammonium salts

Haemoglobin

Porphyrin ring compounds

Alumino zinc compounds

Mica

DNA

Water absorbent polymers

Silica gel

Meerschaum

Aluminum oxide

Triacetin

Calcium carbonate
Low melting polyethylene
Poly ethylene ethylacrylic acid
Nanosponges
Copper based cage structures
Propyl gallate
Copper included zeolites
Monoclonal antibodies
Diatom shells
Alpha-tocopherol
Dendrimer catalysts
Protein nanotubes
Layered double hydroxides
Molecularly imprinted polymers
Fluorinated mesoporous silica
Diatomaceous earth
Non-graphite nano-tubes
Prussian blue analogue
Selective nanocapsule
Nanometric metals, oxides, carbides and nitrides
Alumina
TAHT - colourless dye chemistry
Oligosaccharides of cellulose diacetate
Ruthenium + cerium oxide ($CeO_2$)
Poly (ethylene glycol) PEG
Amine salts
Chlorella algae
Sodium or potassium phosphite
Ammonium sulphate
Silver permanganate
Magnesium trisilicate
Sepiolite
Molecular sieves

With reference to Figure 2 a preferred aspect of the present invention is illustrated with reference to a spinning cell 20. The spinning cell 20 comprises a spinnerette 21 positioned above a drying chamber 22. As shown, dope is extruded through the spinneret head 21 to produce an array of filaments 23. The filaments 23 are passed through the elongated drying chamber 22 against a counter current of heated air. The heated air serves to remove the majority of the acetone from the extruded array of filaments 23. The array of filaments is gathered together at the bottom of the chamber 22 to give a gathered array of filaments 24, which is passed over a roller 25 which applies spin finish and then passed onto further manufacturing processes.

An additive may be incorporated into the array of filaments 23 at this stage as shown. A dispersion of a particulate material may be incorporated into the filament at this stage by spraying an aerosol at the array of filaments. Figure 2 shows the addition of particulate calcium carbonate to the filaments 23. A spray nozzle 26 is provided having an inlet 27 for compressed air and an inlet 28 for particulate calcium carbonate. The particulate calcium carbonate is blown into the drying chamber 22 to impact upon the filaments 23. This results in effective incorporation of the particulate material into the filaments. This technique is applicable to other forms of additive, including solutions, liquids, and emulsions.

Figure 3 shows a variation of this aspect of the invention. A spinning cell 30 is shown having a spinnerette 31 above a drying chamber 32. Dope is pumped through the spinneret 31 to form an array of filaments 33. After passing through the drying chamber, the gathered filaments 34 pass over a roller 35 which applies spin finish. Positioned in the drying chamber 32 is a metered stream application system (MSA) 36. The MSA 36 effectively incorporates an additive into the filaments 33 as they pass through the drying chamber 32. MSA comprises a metering pump that pumps a fluid to a guide having an aperture that allows the fluid to be applied directly onto the fibres surface. The fluid could be a dispersion, liquid, emulsion or solution.

An alternative method of introducing additional components into the filtered tow is shown in Figure 4. A spinning cell 40 is shown producing gathered filaments 41. The filaments 41 pass through an applicator system 42 which applies an additive to the filaments. The treated filaments 43 then pass over a spin finish roller 44 before continuing on the manufacture process. The applicator system 42 may comprises a roller, a spray, a MSA system or other suitable systems known in the art. A preferred applicator system is a MSA such as that shown in Figure ~~5~~ 3

Figure 5 shows an applicator 50 for use in the present invention. The applicator 50 has a generally tubular shape, comprising a cylindrical side wall 51 surrounding an inner plenum chamber 52. A series of apertures 53 are provided in the side wall 51 along the length of the applicator 50. The length of the series of apertures 53 is substantially equal to the width of a banded tow of filaments. One end of the applicator 50 is provided with an additive inlet 54 and the other end is closed off by an end wall 55. Thus, an additive may be introduced via the inlet 54 into the interior 52 of the applicator 50 in the form of a solution, liquid, emulsion or dispersion. The additive may then pass through the apertures 53 and be applied to the banded tow.

Figure 6 shows how the applicator 50 may be used in practice to apply an additive to both sides of a banded tow of acetate. As mentioned above, the output from a number of spinnerets is typically gathered together and arranged to provide a wide flat ribbon comprising several thousand individual filaments. Although the output from a wide range of numbers of spinnerets may be gathered together, for example 25 to 100, typically the output of around 50 to 70 spinneret heads is used to produce a banded tow 57. The banded tow 57 passes through a pair of applicators, with a first applicator 50 in contact with the upper face of the banded tow 57, and a second applicator 60 in contact with the lower face of the banded tow 57. The second applicator 60 is of similar construction to the first applicator 50. The first and second applicators 50 and 60 are arranged with offset apertures to ensure the even application of additive across the full width of the banded tow 57.

As the banded tow 57 passes against the first applicator 50, the additive is applied across its upper face to give a partially treated tow 58. The partially treated tow 58 then passes against the second applicator 60 which applies additive across its lower face to give the final treated tow 59. Thus, a solution, emulsion, liquid or dispersion of additive or additives may be applied to both sides of the banded tow. Solvents, liquids, dispersants, adhesives and or shed suppressors may be used during the application of additives. An "adhesive" is generally a solid and a "shed suppressor" is generally a liquid.

Preferred adhesives which may be used in the present invention are set out below:

PVP
Methyl cellulose
Propyl cellulose
Poly(vinyl aclohol)
Poly(vinyl acetate)
Poly(ethyleneimine)
Poly(ethylene oxide)
Dextrin
Polyethylene glycols (PEGs)
Carboxymethylcellulose
Poly acrylic acids (PAA)
Acrylic resins
Triacetin
Triethylene glycol diacrylate (TEGDA)
Diethylene glycol diacrylate (DEGDA)
Resins
Phenolic
Epoxides
Silicones
Cyanoacrylates
Polyurethanes
Polysulfides

Starch

Preferred shed suppressors which may be used in the present invention are set out below:

Glycerol
Sodium silicate
Low molecular weight polyethylene glycols (PEGs)
Low melting waxes
Ethylene glycol
Sorbitol
Propylene glycol
Sodium lactate
Calcium chloride
Potassium phosphate
Sodium pyrophosphate
Sodium polyphosphate
Calcium citrate
Calcium gluconate
Potassium citrate
Potassium gluconate
Sodium tartrate
Sodium potassium tartrate
Sodium glutamate
Vegetable oils
Mineral oils

The treated tow 59 may then be passed through a crimper in order to produce a crimped tow. The coated tow 59 may then be passed through dryers which are well known in the art. As mentioned above, the tow may undergo a stretching step. In particular, a stretching step may be necessary if the fibres have become partially bonded to each other in order to restore some of the openability of the treated banded tow. The crimped tow may then be plaited into bales for later use. This has the advantage that a conventional filter rod making process and machine may be

used with a bale of tow according to the present invention which has been previously treated with additives. The treated tow may be used in a conventional filter rod making machine with little or no modifications being required. The resulting cigarettes may then have the capability of selectively reducing the amount of certain components of cigarette smoke.

One advantage of the invention is that additives may be consistently applied to the filaments. In particular, a dispersion of particulate additive (such as activated carbon powder) may be applied to give a tow of filaments having a consistent amount of additive per unit length. This is to be contrasted with the prior art method of incorporating particulate material at the rod-maker stage which can lead to variable and inconsistent loading of the resultant filter rods.

Another particularly advantageous feature of the present invention is that a number of different components or additives may be incorporated into the tow during manufacture. For example, the list of Hoffmann analytes include acidic compounds and alkaline compounds. These may require different additives in order to reduce their concentration in main-stream smoke. For example, an acidic tow additive may remove an alkaline analyte whilst an alkaline tow additive may reduce an acidic analyte. However, the mixing of an acidic additive with an alkaline additive would simply lead to neutralisation and thus loss of activity and/or reactivity. It would therefore be beneficial to incorporate both acidic and alkaline additives into the tow whilst retaining their individual activity and reactivity. The present invention provides solutions to this particular problem which are also applicable to other additives which are not compatible with each other.

Another applicator 70 is shown in Figure 7 that has two separate applicator zones which allow for the separate and concurrent application of two different additives to tow. The applicator 70 corresponds to the applicator 50 shown in Figure 5 except that it has a barrier 71 positioned within the interior plenum chamber about midway along the length of the applicator 70, forming two separate applicator zones 72 and 73. One end of the applicator has a first additive inlet 74 leading to a

series of apertures 76 which form a first applicator zone 72. The other end of the applicator has a second additive inlet 75 leading to a series of apertures 77 which form a second applicator zone 73.

Figure 8 shows how the applicator 70 may be used in practice. A banded tow of filaments 81 passes against a pair of applicators comprising a first applicator 70 and a second applicator 80. The banded tow 81 passes through a pair of applicators, with a first applicator 70 in contact with the upper face of the banded tow 81, and a second applicator 80 in contact with the lower face of the banded tow 81. The second applicator 80 is of similar construction to the first applicator 70. The first and second applicators 70 and 80 are arranged with offset apertures to ensure the even application of additive across the full width of the banded tow 81.

As the banded tow 81 passes against the first applicator 80, the two additives are applied across its upper face by the two applicator zones to give a partially treated tow 82. The partially treated tow 82 then passes against the second applicator 80 which applies the two additives across its lower face to give the final treated tow 83. The treated tow has two stripes of additives along its length. This aspect allows an acidic additive to be applied to one half of the banded tow with an alkaline additive being added to the other half of the banded tow.

Figure 9 shows a plan view corresponding to Figure 8. The untreated banded tow 81 passes against the applicators 70 and 80 to become the treated tow 83. The first applicator zones of the applicators 70 and 80 coat one half of the width of the tow with an acidic additive to give treated stripe 84. The second applicator zones of the applicators 70 and 80 coat the other half of the width of the tow with an alkaline additive to give treated stripe 85.

The present invention also envisages the use of similar applicators to apply more than two additives to a banded tow. This could result in a banded tow having, for example, 3, 4 or 5 different types of additives across the width of the tow. Figure 10 shows an example of this aspect of the invention. A banded tow 90 passes

through a pair of applicators 91 and 92, which each have three applicators zones. As the tow 90 passes against the applicators 91 and 92, three different types of additives are applies to each face of the tow, giving a treated tow 93. The treated tow 93 has a first outer strip 94 of acidic material, a central strip 95 of particulate material, and a second outer strip 96 of alkaline material.

Thus, incompatible additives may be applied to the banded tow whilst being kept relatively isolated from other components. The treated banded tow may then be used in a conventional rod maker to produce filter rods having a mixture of different filaments with different additives thereon. The treated filter rod may then selectively reduce the presence of different types of components of main-stream-cigarette smoke.

It is also possible to minimise any unwanted interaction between different additives that are applied to the same tow of filaments by applying a barrier material between them. For example, a modified applicator may be used to apply a thin (eg 1 to 2 mm) strip of white oil between stripes of incompatible additives, such as an acidic compound and a basic compound, to prevent the additives from mixing together.

The concept of applying more than one additive is also applicable to other stages of the tow manufacture process. For example, different additives may be introduced to filaments during or after the spinning step but before being banded together. Thus, one set of spinning cells may produce filaments which incorporate acidic additive, sprayed thereon. A second set of spinning cells may produce filaments which incorporate an alkaline additive. The treated gathered arrays of filaments may be subsequently banded together to form the banded tow. This has the benefit that differently treated filaments may be more homogeneously distributed across the banded tow and in the resulting filter rod.

Figure 11 shows the output from four different spinning cells being banded together to form a banded tow. As mentioned above, although the output from a large number of spinning cells would be banded together in practice, only four

arrays of filaments are shown for clarity. A first array of filaments 100, incorporating an acidic additive, passes around a guide 101 to begin to form the banded tow. A second array of filaments 102, incorporating an adsorbent particulate additive, passes around a guide 103 to join the growing banded tow. A third array of filaments 104, incorporating an alkaline additive, passes around a guide 105 to join the banded tow. Finally, a fourth array of filaments 106, which does not incorporate an additional additive, passes around a guide 107 to complete the banded tow 108. The compete banded tow 108 thus comprises four stripes of filaments 109, 110, 111 and 112, each incorporating a different, or no, additive.

In practice, large numbers of arrays of filaments are arranged in overlapping arrangement to form banded tows, which could lead to more homogenous distribution of treated filaments in the complete treated banded tow and in the resulting filter rod.

Another aspect of the present invention concerns the combination of additives at different stages in the manufacturing process. In particular, it is possible to include one or more additives into the cellulose acetate dope itself. The additive-containing dope may then be used to form filaments which are treated with one or more further additives in accordance with the invention. For example, a compound such as sodium sulphamate may be dissolved in the dope and used to form filaments. The sodium sulphamate-containing filaments may then be treated with a dispersion of carbon powder before being crimped and formed into a bale. Numerous other combination of treatments are possible. Thus, the terms "cellulose acetate dope" or "dope" as used herein encompass a solution of cellulose acetate which includes one or more additives.

It is also to be appreciated that the different aspects of the present invention may be used in combination with themselves or with known techniques in the art. For example, the present invention may produce treated crimped tow which may then be used in a rod maker which incorporates particulate material. In this way a cigarette filter rod may be produced having enhanced functionality and the ability to selectively reduce different components of cigarette smoke.

Also, different aspects of the present invention may be used in combination with each other. For example a first additive may be incorporated as an aerosol of particulates blown into the drying chamber following spinning of an array of filaments. The resulting tow of filaments may then be treated by the application of an emulsion of a different additive at a downstream step.

Another aspect of the invention concerns the formation of a filter rod which contains a number of different additives. In particular, a filter rod may be formed by combining a number of filter rod segments together to form the final filter rod. For example, three filter rod segments each having a length of 10 mm may be joined together to form a complete filter rod having a length of 30 mm. Each of the filter rod segments may be made in accordance with the present invention and so contain different additives. The first segment may comprises filaments treated with an acidic compound, the second segment may comprise filaments treated with a basic compound and the third segment may comprises filaments treated with sodium sulphamate. In this way, the complete filter rod may remove basic compounds (first segment), acidic compounds (second segment) and formaldehyde (third segment), whilst keeping incompatible additives separate. This has the advantage that a filter rod having enhanced functionality may be readily prepared from separately prepared bales of tow, each being treated with different additives. This aspect of the invention encompasses a wide range of possible variations and combination of additives.

Other possible combinations of features may be apparent to a person skilled in the art. The present invention will now be exemplified with reference to the following experimental data. All the reagents and additives are commercially available and are used without additional purification, unless otherwise indicated.

## Examples

The examples below illustrate the application of liquids, solutions, emulsions and dispersions (comprising particles preferably having $<100 m^2/g$ surface area) at

various points in the tow manufacturing process to yield crimped tow product that contains additives. The bales of tows containing the additives were converted into filter rods using a standard Hauni KDF3/AF3 rodmaker. The resultant filter rods containing the treated tow have the effect of reducing the levels of selected components, such as Hoffmann analytes, in main-stream cigarette smoke.

Example 1 – The Application of a Solution of DL-Malic Acid to the Towband before Crimping

The application system consisted of a pressurised tank, (10 psi), containing a 50% aqueous solution of malic acid that supplied the inlet to a metering gear pump. The output from this pump was split into two separate streams with each outlet conduit feeding an applicator over which a tow comprising 3 denier filaments having a "Y-shaped" cross-section and 11,677 filaments in total (known as 3Y/35,000) with an oil level of ~0.3% ran prior to crimping. The conduits to each applicator were of equal length and internal bore to ensure equal flow to each applicator. The applicators consisted of a plenum chamber and a series of eleven or twelve 1 mm diameter holes through which the pumped 50% malic acid solution was uniformly applied to the uncrimped towband about 1 m before the crimper. The applicators were placed so that the positions of the holes relative to the towband were offset to ensure an uniform application to the towband with eleven apertures on one side and twelve apertures on the other side of the tow. The application process of the malic acid solution was performed after the towband had been assembled from the individual spinning ends, but prior to the crimping process.

The crimping process comprised a pair of driven rollers that drive the tow into a box. The box, well known as a stuffer box, had a hinged top knife. The rollers were forced together by a hydraulic ram. The pressure on this ram, (the roller pressure), was about 7 psi. The pump speed was adjusted until a slight excess of solution was observed to be dripping from the crimper. The individual filaments buckled and formed a stable crimped towband. The resultant crimped towband was dried, stretched as required in order to partially loosen the towband and plaited into a box in order to form a bale.

The malic acid loading on the tow in the bale was determined by measuring the linear density, (the total denier), of the tow and comparing with a control with no acid applied. The level of malic acid on the tow was found to be 16% by weight.

The distribution of the malic acid on the treated filament was investigated using a scanning electron microscope. For comparison, an untreated control filament was also investigated and the resulting electron micrograph is shown in Figure 12 (1000x magnification, 3 kV, 10 mm). The control filament was prepared according to the method of Example 1 except that malic acid solution was not applied to the filaments.

Figure 13 shows an electron micrograph for a filament prepared by the method of Example 1 (1000x magnification, 3 kV, 10 mm). It can be seen that the malic acid has formed a relatively smooth thin smeared layer over the surface of the filament.

Figure 14 shows the treated filament in more detail (10000x magnification, 3 kV, 10 mm). Again, at this greater magnification it can be seen that the malic acid has formed a relatively smooth layer over the surface of the filament.

A bale of the tow treated with malic acid was processed into filter rods using a standard Hauni KDF3/AF3 rod maker. A gravimetric analysis comparing the tow and rods indicated that there was surprisingly no significant loss of malic acid during the rod making process. The rods were cut into ~20 mm tips and attached to tobacco columns to produce cigarettes. A smoking analysis was carried out on these cigarettes, specifically evaluating the level of the compounds pyridine and quinoline in mainstream smoke. Quinoline and pyridine form part of the Hoffmann analyte list.

The results in Table 1 below compare the malic acid tow/filters with standard 3Y/35,000 acetate tow/filters with no additive applied.

Table 1

| Parameter | Sample | Control |
|---|---|---|
| Additive | DL-malic acid (16% by weight) | None |
| Rod Diameter | 7.73 | 7.72 |
| 20 mm Tip PD mm | 88 | 88 |
| Retention % TR | 53.5 | 49.9 |
| Retention % NR | 49.1 | 47.2 |
| Tar mg/cigarette | 8.4 | 8.4 |
| Nicotine mg/cigarette | 0.66 | 0.66 |
| CO mg/cigarette | 12.4 | 11.3 |
| Pyridine µg/cigarette | <0.2 | 10.2 |
| Quinoline µg/cigarette | 0.07 | 0.26 |

The abbreviation PD stands for pressure drop and is representative of the resistance to air flow through the filter. It is traditionally measured in mm of water in this technical field. The PD was measured using the method of a QTM, Filtrona rod tester well known in the field. TR and NR stand for tar retention and nicotine retention by the filter and were measured by standard methods well known in the field.

The results show that the volatile basic materials pyridine and quinoline were significantly reduced, by the amounts of 93% and 73% respectively in the main-stream smoke.

Example 2 - The Application of a Solution of Potassium Carbonate to the Towband before Crimping using Glycerol as a Shed Suppressor

In order to reduce loss of potassium carbonate when producing filter rods it was beneficial to use glycerol as a liquid shed suppressor.

The application system consisted of a pressurised tank (10 psi) containing a 50% aqueous solution of potassium carbonate and 10% glycerol that supplied the inlet

to a metering gear pump. The output from this pump was split into two streams with each outlet conduit feeding an applicator over which a 3Y/35,000 low oil (~0.3% oil) tow ran prior to crimping. It was found to be advantageous to reduce the oil level of the tow from typical values of 0.8 to 1.4% in order to enable better adhesion of the additive. The conduits to each applicator were of equal length and internal bore to ensure equal flow to each applicator. The applicators consisted of a plenum chamber and a series of eleven or twelve 1 mm diameter holes through which the pumped 50% potassium carbonate solution was uniformly applied to the uncrimped tow band about 1 m before the crimper. The applicators were placed so that the positions of the holes relative to the towband were offset to ensure an uniform application to the towband. The application process of the potassium carbonate solution was performed after the towband had been assembled from the individual spinning ends, but prior to the crimping process.

The crimping process comprised a pair of driven rollers that drive the tow into a box. The box (also known as a stuffer box) had a hinged top knife. The rollers were forced together by a hydraulic ram. The pressure on this ram (the roller pressure) was 7 psi. The pump speed was adjusted until a slight excess of solution was observed to be dripping from the crimper. The individual filaments buckled and formed a stable crimped towband. The resultant crimped towband was dried, stretched as required in order to partially loosen the towband and plaited into a box in order to form a bale.

The potassium carbonate loading on the tow in the bale was determined by measuring the linear density (the total denier) of the tow and comparing with a control tow with nothing applied. The level of potassium carbonate on the tow was found to be 8% by weight.

A bale of the tow treated with potassium carbonate tow was processed into filter rods using a standard Hauni KDF3/AF3 rod maker. A gravimetric analysis comparing the tow and rods indicated that there was surprisingly no significant loss of potassium carbonate during the rod making process. The rods were cut into 20 mm tips and attached to tobacco columns to produce cigarettes. A smoking

analysis was carried out on these cigarettes, specifically evaluating the level of the compounds hydrogen cyanide and phenol in mainstream smoke. Hydrogen cyanide and phenol form part of the Hoffmann analyte list.

The results in Table 2 below compare the potassium carbonate tow/filters with standard 3Y/35,000 acetate tow/filters with no additive applied.

Table 2

| **Parameter** | **Sample** | **Control** |
|---|---|---|
| Additive | Potassium carbonate/glycerol. (8% potassium carbonate) | None |
| Rod Diameter | 7.72 | 7.72 |
| Rod PD mm | 514 | 516 |
| 20 mm Tip PD mm | 91 | 88 |
| Retention % TR | 51.9 | 49.9 |
| Retention % NR | 38.4 | 47.2 |
| Tar mg/cigarette | 8.4 | 8.4 |
| Nicotine mg/cigarette | 0.80 | 0.66 |
| CO mg/cigarette | 11.9 | 11.3 |
| Phenol µg/cigarette | 12.6 | 14.6 |
| Hydrogen cyanide µg/cigarette | 63 | 124 |

The results show that the volatile acidic materials hydrogen cyanide and phenol were significantly reduced by 49% and 14% respectively from mainstream cigarette smoke.

Example 3 - The application of a Solution of Potassium Carbonate to the Towband before Crimping using Polyacrylic Acid as an Adhesive

In order to reduce loss of potassium carbonate when producing filter rods it was beneficial in this example to use polyacrylic acid as an adhesive shed suppressor.

The application system consisted of a pressurised tank (10 psi) containing a 50% aqueous solution of potassium carbonate and 1% polyacrylic acid that supplied the inlet to a metering gear pump. The output from this pump was split into two streams with each outlet conduit feeding an applicator over which a 3Y/35,000 low oil (~0.3% oil) tow ran prior to crimping. The conduits to each applicator were of equal length and internal bore to ensure equal flow to each applicator. The applicators consisted of a plenum chamber and a series of eleven or twelve 1 mm diameter holes through which the pumped the solution was uniformly applied to the uncrimped tow band about 1 m before the crimper. The applicators were placed so that the positions of the holes relative to the towband were offset to ensure an uniform application to the towband. The application process of the solution was performed after the towband had been assembled from the individual spinning ends, but prior to the crimping process.

The crimping process comprised a pair of driven rollers that drive the tow into a box. The box (also known as a stuffer box) had a hinged top knife. The rollers were forced together by a hydraulic ram. The pressure on this ram, (the roller pressure), was 7 psi. The pump speed was adjusted until a slight excess of solution was observed to be dripping from the crimper. The individual filaments buckled and formed a stable crimped towband. The resultant crimped towband was dried, stretched as required in order to partially loosen the towband and plaited into a box in order to form a bale.

The potassium carbonate loading on the tow in the bale was determined by measuring the linear density (the total denier) of the tow and comparing with a control tow with nothing applied. The level of potassium carbonate on the tow was found to be 8% by weight.

A bale of tow treated with potassium carbonate was processed into filter rods using a standard Hauni KDF3/AF3 rod maker. A gravimetric analysis comparing the tow and rods indicated that there was surprisingly no significant loss of potassium carbonate during the rod making process. The rods were cut into 20 mm tips and attached to tobacco columns to produce cigarettes. A smoking analysis was carried

out on these cigarettes, specifically evaluating the level of the acidic compounds hydrogen cyanide and phenol in mainstream smoke. Hydrogen cyanide and phenol form part of the Hoffmann analyte list.

The results in Table 3 below compare the potassium carbonate tow/filters with standard 3Y/35,000 acetate tow/filters with no additive applied.

Table 3

| **Parameter** | **Sample** | **Control** |
|---|---|---|
| Additive | Potassium carbonate/polyacrylic acid (8% by weight) | None |
| Rod Diameter mm | 7.73 | 7.72 |
| Rod PD mm | 498 | 516 |
| 20 mm Tip PD mm | 91 | 88 |
| Retention % TR | 47.5 | 49.9 |
| Retention % NR | 39.2 | 47.2 |
| Tar mg/cigarette | 8.3 | 8.4 |
| Nicotine mg/cigarette | 0.80 | 0.66 |
| CO mg/cigarette | 11.7 | 11.3 |
| Phenol µg/cigarette | 11.4 | 14.6 |
| Hydrogen cyanide µg/cigarette | 58 | 124 |

The results show that the volatile acidic materials hydrogen cyanide and phenol were significantly reduced by 53% and 11% respectively from mainstream cigarette smoke.

Example 4 - The Application of Various Solutions of Acids to the Towband before Crimping.

Following the work of Example 1, a range of other acids were investigated. These included citric, L-tartaric, lactic (a liquid at room temperature) and ascorbic acids. In each case an aqueous solution was made up and placed in the pressurised tank

previously described. The roller nip pressure was set to 6 psi and the loadings on the tow determined by a gravimetric method. The results are shown in Table 4 below.

Table 4

| | Citric acid | L-Tartaric acid | Lactic acid | Ascorbic acid |
|---|---|---|---|---|
| Solution Conc (%) | 50 | 50 | 50 | 17 |
| Level of acid on tow (% by weight) | 9.2 | 11.8 | 5.7 | 3.8 |

This work demonstrates the flexibility of this invention to apply a range of solutions, in this example acids, to the uncrimped towband and surprisingly produce a satisfactory crimped towband with satisfactory tow opening and tow strength properties.

Example 5 – The Application of Poly(Ethyleneimine) (PEI) Solution to the Towband before Crimping

A sample of a branched poly(ethyleneimine) (Mn 60,000, Mw 750,000) was obtained from Sigma Aldrich as a 50% aqueous solution. 25 and 35% solutions of the PEI were made up and applied to the tow using the method of Example 1. Surprisingly a satisfactory tow was produced. The loading of PEI on tow using a crimper roller pressure of 6psi is shown in Table 5 below.

Table 5

| Solution Conc (%) | 25% solution | 35% solution |
|---|---|---|
| Loading (% by weight) | 6.5 | 8.4 |

A bale of this tow was processed into filter rods using a standard Hauni KDF3/AF3 opener and rod maker. There was minimal loss of the additive on processing.

This tow is expected to reduce the level of Formaldehyde in mainstream smoke. Formaldehyde is on the Hoffmann analyte list.

Example 6 – The Application of Cyclodextrin Solution to the Towband before Crimping

A sample of Cavasol W7 M (a methylated cyclodextrin from Wacker Chemie) was made into a 25% aqueous solution and applied to the uncrimped tow using the method of Example 1. It was desirable to use the derivatised cyclodextrins in order to make use of the increased solubility as this leads to higher potential loadings on the tow. Surprisingly a satisfactory tow was produced. The resultant loadings on the tow are given below. The loading of the methylated cyclodextrin on tow using a crimper roller pressure of 6 psi is shown in Table 6 below.

Table 6

| Roller Pressure (psi) | Loading on tow (% by weight) |
|---|---|
| 6 | 6.5 |

A bale of the material was processed into filter rods using a standard Hauni KDF3/AF3 opener and rod maker. There was minimal loss of the additive on processing.

It is believed this tow has the potential to reduce the level of small organic aromatic molecules in main-stream smoke.

Example 7 –The Application of Sodium Sulphamate Solution to the Towband before Crimping

A 40% aqueous solution of sodium sulphamate was produced by carefully adding an equimolar amount of sodium hydroxide to a solution of sulphamic acid. The solution was applied to the uncrimped tow using the method of Example 1. Surprisingly a satisfactory tow was produced. The loading of Sodium Sulphamate on tow using a crimper roller pressure of 6 psi is shown in Table 7 below.

Table 7

| Roller Pressure (psi) | Loading on Tow (% by weight) |
|---|---|
| 6 | 5.9 |

The addition of sodium sulphamate is expected to remove or reduce formaldehyde in main-stream smoke

Example 8 – The Spraying of a Calcium Carbonate Dispersion onto Filaments in the Spinning Cell

The spinning cell used consisted of a 30cm square, 5 m long rectangular chamber through which air at about 100°C was forced in a direction counter to that of the filament extrusion. At the top of the spinning cell dope was fed to a spinneret. This jet had 200 triangular holes. The side of each triangle was 56 μm in length. A spinning dope was extruded through the spinneret holes. The dope concentration was 26% cellulose acetate in a solvent comprising 97% acetone 3% water. The dope extrusion rate was adjusted to give a filament denier per filament (dpf) of 3.

A 30% aqueous dispersion of finely divided calcium carbonate powder (70% <1-2 μm, 97%<5 μm supplied by Longcliffe) having a surface area of <5$m^2$/g was placed in a bottle equipped with an aerosol fitting. The vessel was connected to a compressed air supply and the dispersion was sprayed onto the cellulose diacetate

filaments in the first part of the extrusion zone. Typically this was within a distance of 15 cm from the face of the spinneret. Surprisingly the spinning stability was not affected and the particles were attached to the nascent filaments. A loading of 1.5% by weight of calcium carbonate was applied to the filaments.

This work demonstrates the potential for applying particles that preferably have a surface area less than $100m^2/g$ that are potentially capable of reducing substances in mainstream smoke that are on the Hoffmann analyte list.

Example 9 – The Addition of a Carboxylated Acrylic Emulsions to Fibres Exiting the Spinning Cell

A carboxylated acrylate emulsion (Glascol C20 supplied by Ciba Specialities as a 46% polymer in water emulsion) was added as a 20% solids emulsion below the spinning cell but prior to spin finish application via an MSA system.

A satisfactory fibre was produced. This work demonstrates the potential for adding emulsions to the fibre that are potentially capable of reducing substances in mainstream smoke that are on the Hoffmann analyte list.

Example 10 – The Application of Two Different Additives to the Towband before Crimping – Citric Acid and Potassium Carbonate

Following the work principles of Example 1, two different aqueous solutions were applied to the towband, namely citric acid and potassium carbonate/glycerol. In each case an aqueous solution was made up and placed in two separate pressurised tanks previously described. Each tank was connected to a separate pump that pumped the solution to an applicator. In this example the applicator had a plate that divided the plenum chamber into two. One solution was fed to one side of the applicator the other solution to the other side. This resulted in one half of the towband being treated with citric acid solution and the other half of the towband being treated with potassium carbonate solution. The feed rate of the solutions was carefully regulated in order to ensure no excess solutions were being applied

in order to reduce any potential for the solutions to mix together. Surprisingly a satifactory towband was produced with good opening and strength properties. There was only a small amount of mixing of the two solutions at the centre of the towband. The roller nip pressure was 6 psi and the total loading on the tow was determined to be 15% by weight by a gravimetric method

This work demonstrates one method of applying two different additives to the towband before crimping with each additive capable of reducing different classes of compounds in mainstream smoke that are on the Hoffmann analyte list e.g. in the example described here, both basic and acidic compounds can be reduced.

Example 11 – Combination of Application Methods to apply multiple additives

This example illustrates the potential to combine the addition methods described above in order to get a combined effect.

The method of example 8 is used to apply a loading of calcium carbonate to the filaments in the cell. In addition the method of example 6 is used to apply a cyclodextrin solution to the already treated filaments. This gives a resulting tow that possesses the functionality of both species.

CLAIMS

1. A method of preparing a crimped tow of cellulose acetate filaments comprising the steps of:

a) providing cellulose acetate dope

b) forming filaments from the dope

c) applying at least one additive to the filaments

d) crimping the filaments to form a crimped tow

wherein the at least one additive is capable of removing a component from cigarette smoke.

2. A method according to claim 1 wherein the at least one additive comprises a solution, emulsion, liquid, or particulate material or combinations thereof.

3. A method according to claim 1 or 2 wherein the at least one additive comprises an acidic compound or an alkaline compound.

4. A method according to any preceding claim wherein the at least one additive comprises malic acid, potassium carbonate, citric acid, tartaric acid, lactic acid, ascorbic acid, polyethyleneimine, cyclodextrin, sodium hydroxide, sulphamic acid, sodium sulphamate, polyvinyl acetate and carboxylated acrylate.

5. A method according to any preceding claim wherein the at least one additive comprises particles of carbon, silica, zeolite, clay, alumina, metal, molecular sieves or an ion exchange resin.

6. A method according to claim 5 wherein the carbon comprises activated carbon.

7. A method according to claim 6 wherein the particles comprise a material capable of generating a gaseous emission.

8. A method according to claim 7 wherein the material is a liquid which can volatilized to generate a gas or vapour by the action of heat and/or reduced pressure.

9. A method according to claim 7 or 8 wherein the material is water.

10. A method according to any of claims 5 to 9 further comprising the step of steeping the particles in water before application to the filaments.

11. A method according to any preceding claim wherein the at least one additive is applied to the filaments using an adhesive.

12. A method according to claim 11 wherein the adhesive comprises a cellulose ether.

13. A method according to claim 11 or 12 wherein the adhesive comprises methyl cellulose.

14. A method according to any preceding claim further comprising the step of applying a shed suppressor to the filaments.

15. A method according to claim 14 wherein the shed suppressor is glycerol.

16. A method according to any preceding claim wherein the filaments have a non-circular cross-section.

17. A method according to any preceding claim wherein the filaments have a multi-lobal cross-section.

18. A method according to any preceding claim wherein the component is a Hoffmann analyte.

19. A method according to any preceding claim wherein the component comprises hydrogen cyanide, formaldehyde, pyridine, quinoline or phenol.

20. A method according to any preceding claim wherein the step of forming filaments from the dope comprises extruding the dope through a spinneret to form an array of filaments, and drying the filaments to remove a dope solvent.

21. A method according to claim 20 wherein the at least one additive is applied to the filaments during the drying step.

22. A method according to claim 20 wherein the at least one additive is applied to the filaments after the drying step.

23. A method according to claim 20 comprising the step of combining the filaments produced by a plurality of spinnerets to produce a banded tow of filaments.

24. A method according to claim 23 wherein the at least one additive is applied to the filaments before formation of the banded tow.

25. A method according to claim 23 wherein the at least one additive is applied to the filaments after formation of the banded tow.

26. A method according to claim 23 wherein the at least one additive is applied to the filaments immediately before the step of crimping to form the crimped tow.

27. A method according to any preceding claim wherein the at least one additive comprises a plurality of additives.

28. A method according to claim 27 wherein the plurality of additives comprises two additives.

29. A method according to claim 27 wherein the plurality of additives comprises three additives.

30. A method according to any of claims 27 to 29 wherein the plurality of additives are applied separately to the filaments.

31. A method according to claims 27 to 30 wherein the plurality of additives are applied concurrently to the filaments.

32. A method according to claims 27 to 30 wherein the plurality of additives are applied sequentially to the filaments.

33. A method according to any of claims 27 to 32 wherein each of the plurality of additives is incorporated into a substantially separate portion of the filaments.

34. A method according to any of claims 27 to 33 comprising the step of applying the plurality of additives to the banded tow in stripes.

35. A method according to claim 34 wherein the step of applying the plurality of additives to the banded tow in stripes further comprises the application of a barrier material between adjacent stripes.

36. A method according to claim 35 wherein the barrier material comprises white oil.

37. A method according to any of claims 27 to 36 wherein the step of forming filaments from the dope comprises extruding the dope through a spinneret to form an array of filaments, and drying the filaments to remove a dope solvent.

38. A method according to claim 37 wherein one of the plurality of additives is applied to the filaments during the drying step and another of the plurality of additives is applied to the filaments after the drying step.

39. A method according to claim 37 wherein one of the plurality of additives is applied to the filaments formed by a first spinnerette and another of the plurality of additives is applied to the filaments formed by a second spinnerette.

40. A method according to any preceding claim wherein the step of providing cellulose acetate dope comprises incorporating at least one additive into the dope.

41. A method according to any preceding claim further comprising the step of plaiting the crimped tow of filaments into a bale.

42. A method according to any preceding claim further comprising the step of forming a filter rod from the crimped tow of filaments.

43. A method according to claim 42 wherein the step of forming a filter rod further comprises incorporating at least one additive into the filter rod.

44. A method according to claim 43 wherein a particulate additive is incorporated into the tow of filaments.

45. A method according to claim 43 wherein a particulate additive is incorporated into a cavity in the filter rod.

46. A method according to claim 42 wherein the step of forming a filter rod comprises combining a plurality of filter rod segments together to form the filter rod.

47. A method according to claim 46 wherein each of the plurality of filter rod segments comprises filaments that incorporate a different additive.

48. A method according to claim 46 or 47 wherein the filter rod comprises three filter rod segments.

49. A method according to any of claims 42 to 48 further comprising the step of forming a cigarette from the filter rod.

50. A crimped tow of cellulose acetate filaments obtainable by a method according to any of claims 1 to 40.

51. A bale of tow obtainable by a method according to claim 41.

52. A bale of tow according to claim 51 which is suitable for use on a conventional rod-maker with little or no modification being necessary.

53. A filter rod obtainable by a method according to any of claims 42 to 48.

54. A cigarette obtainable by a method according to claim 49.

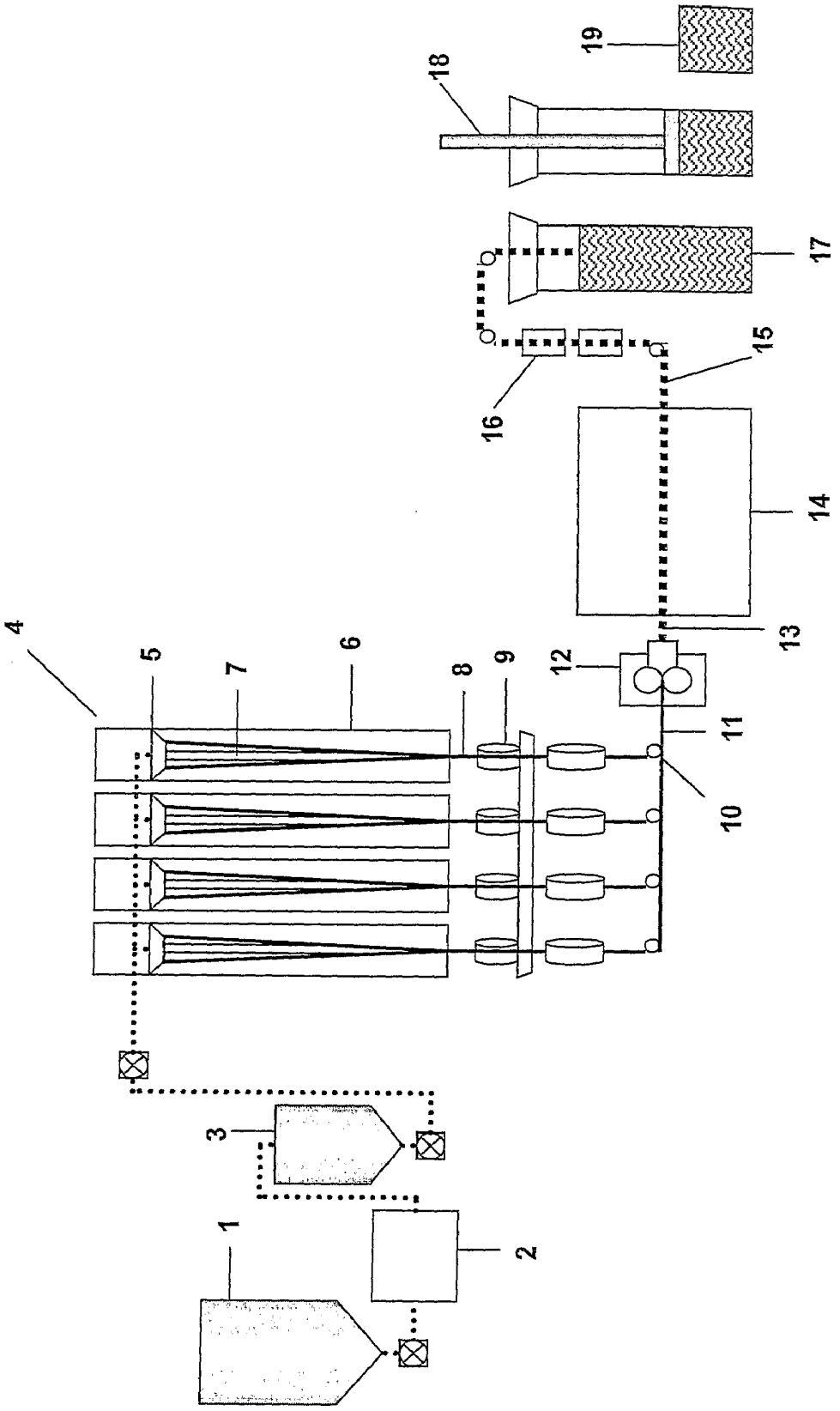



Figure 1

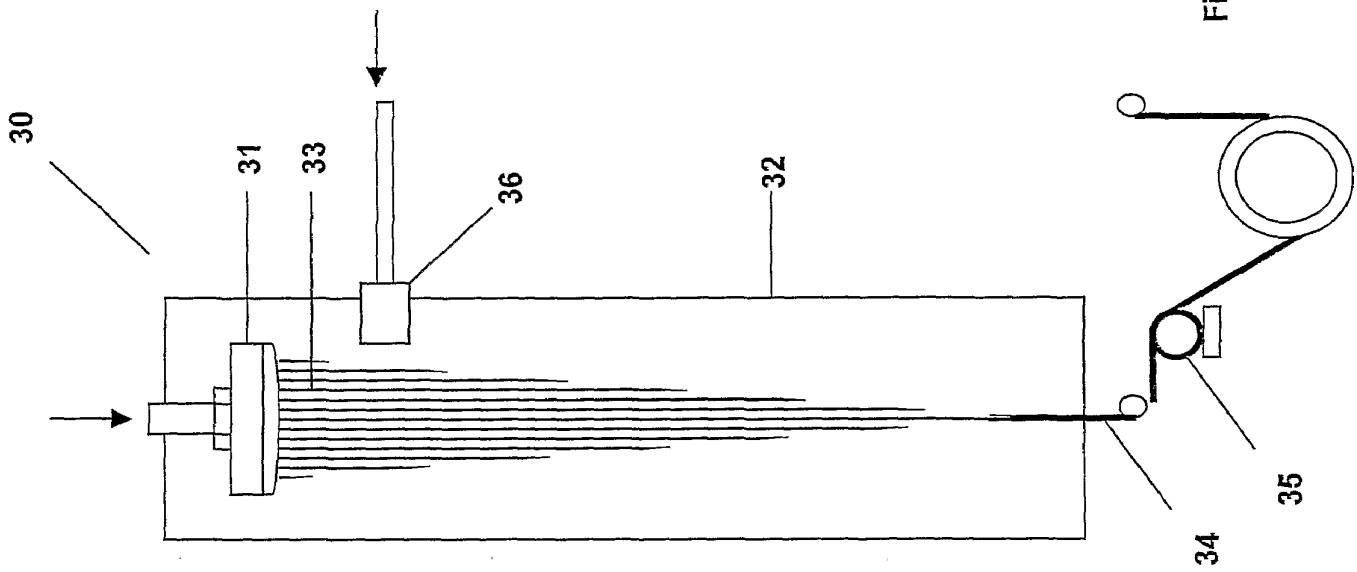



Figure 3

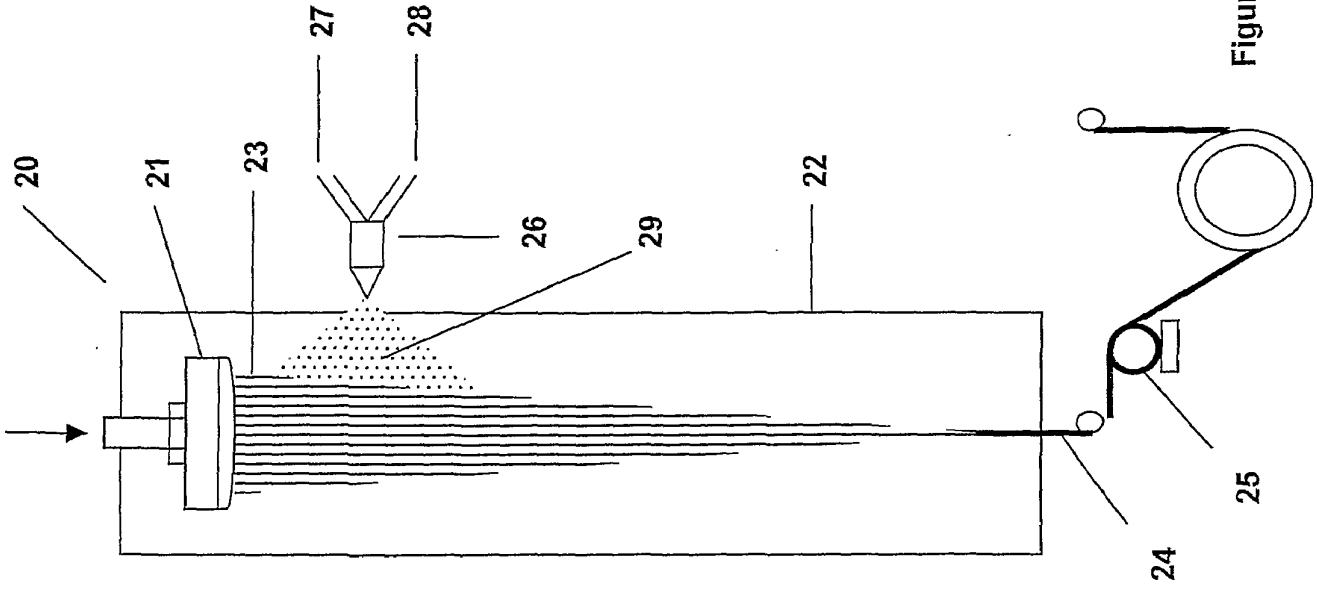



Figure 2

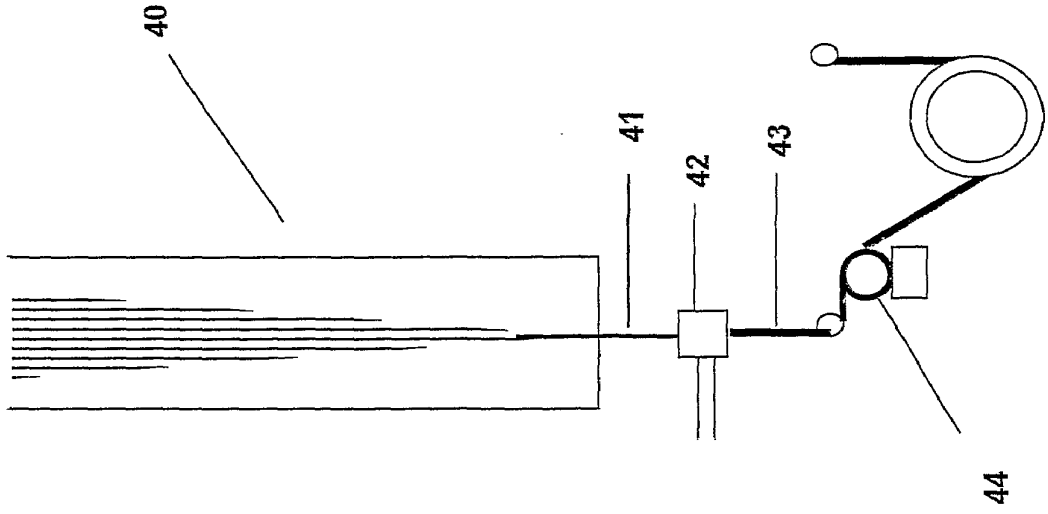



Figure 4

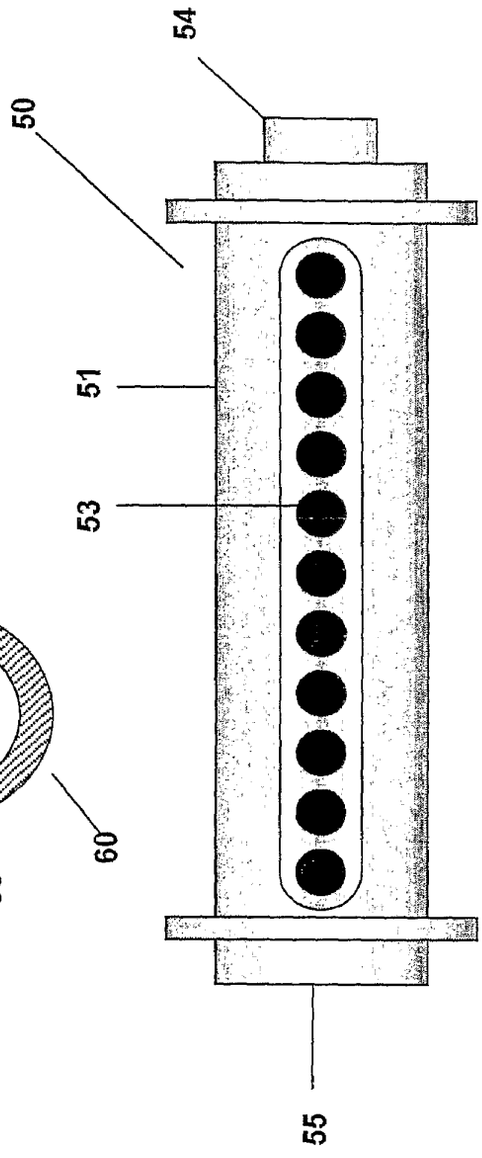



Figure 5

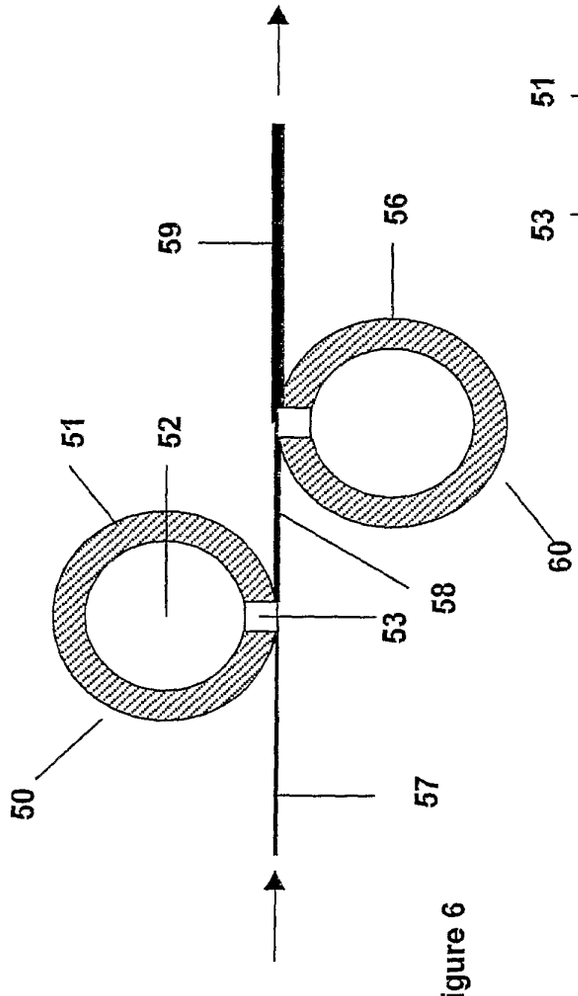



Figure 6

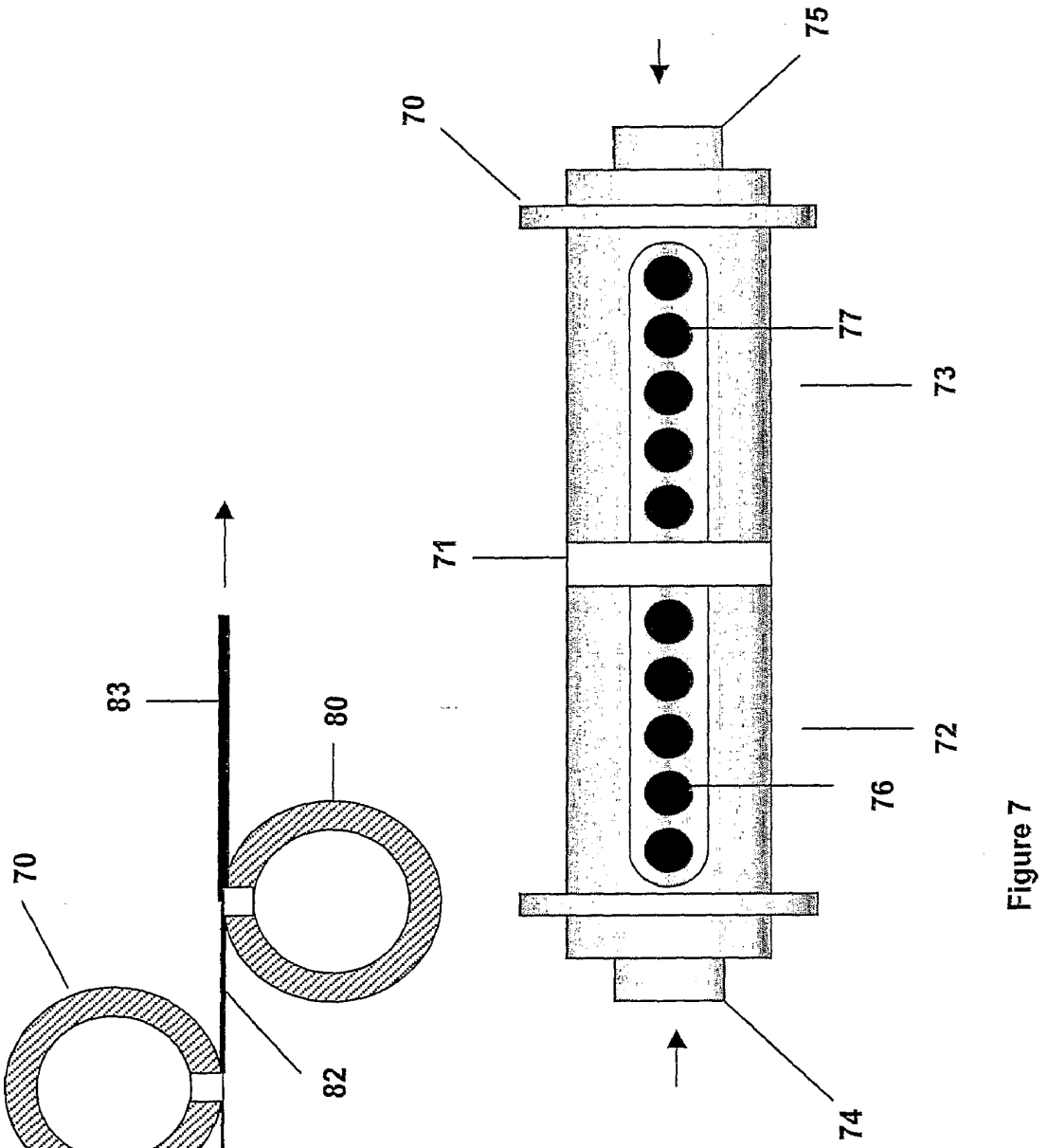



Figure 7

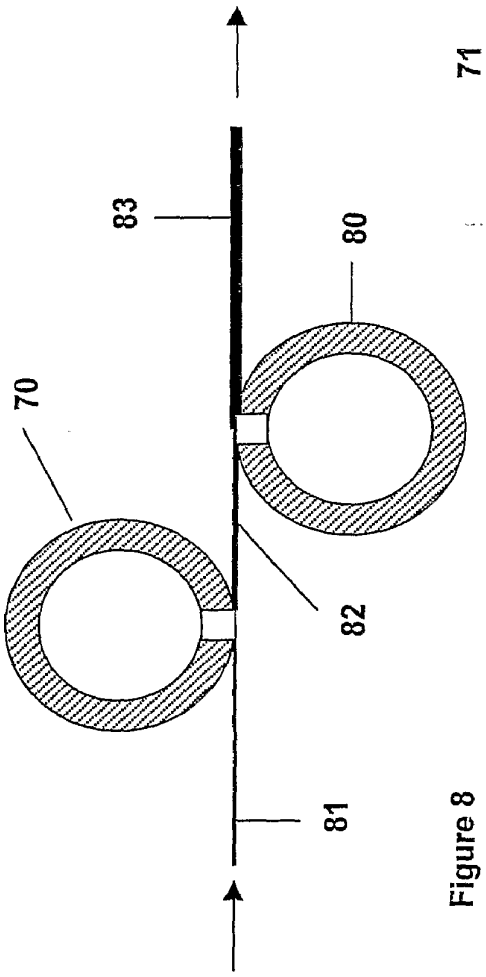



Figure 8

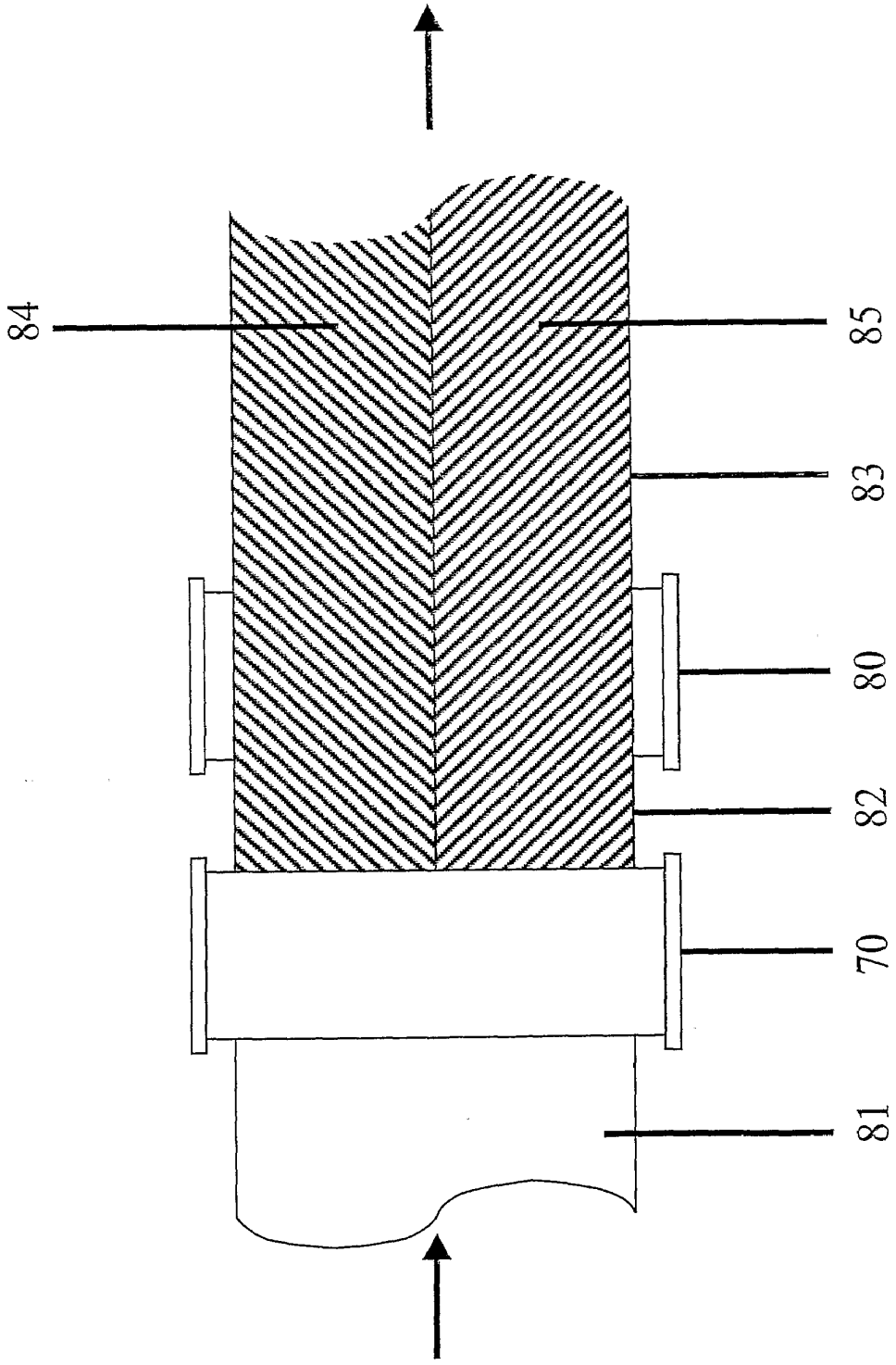



Figure 9

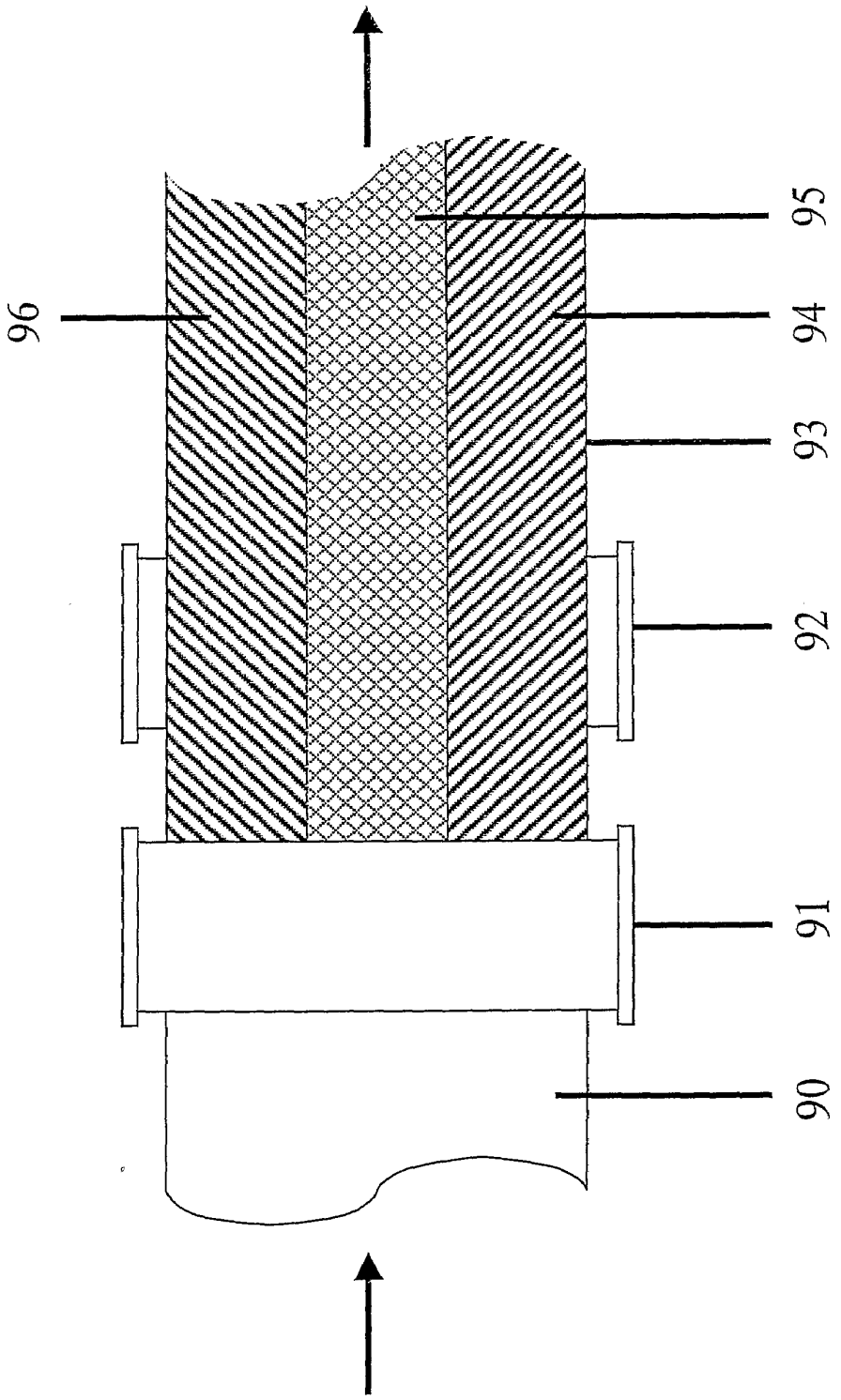



Figure 10

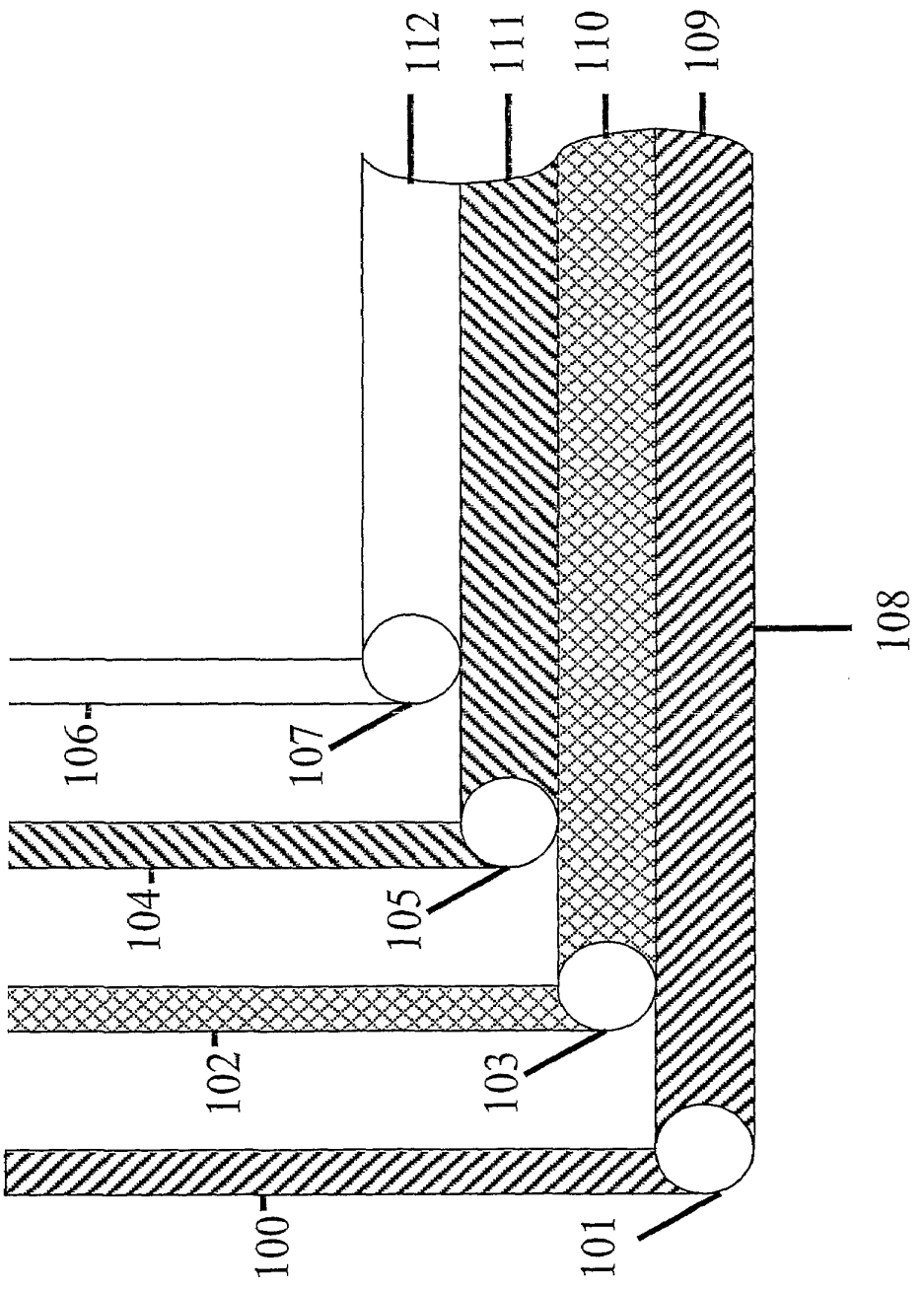



Figure 11

1252

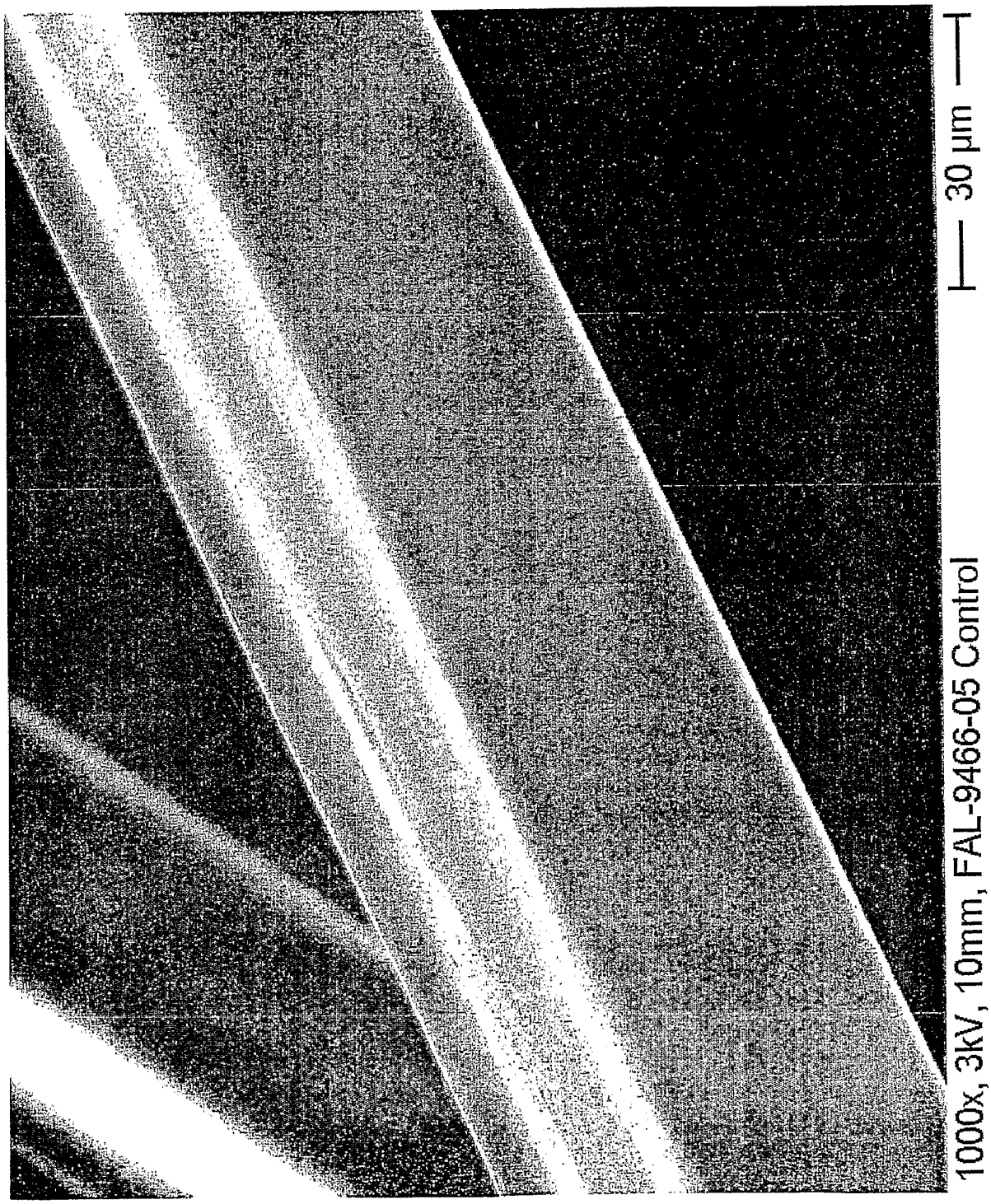



Figure 12

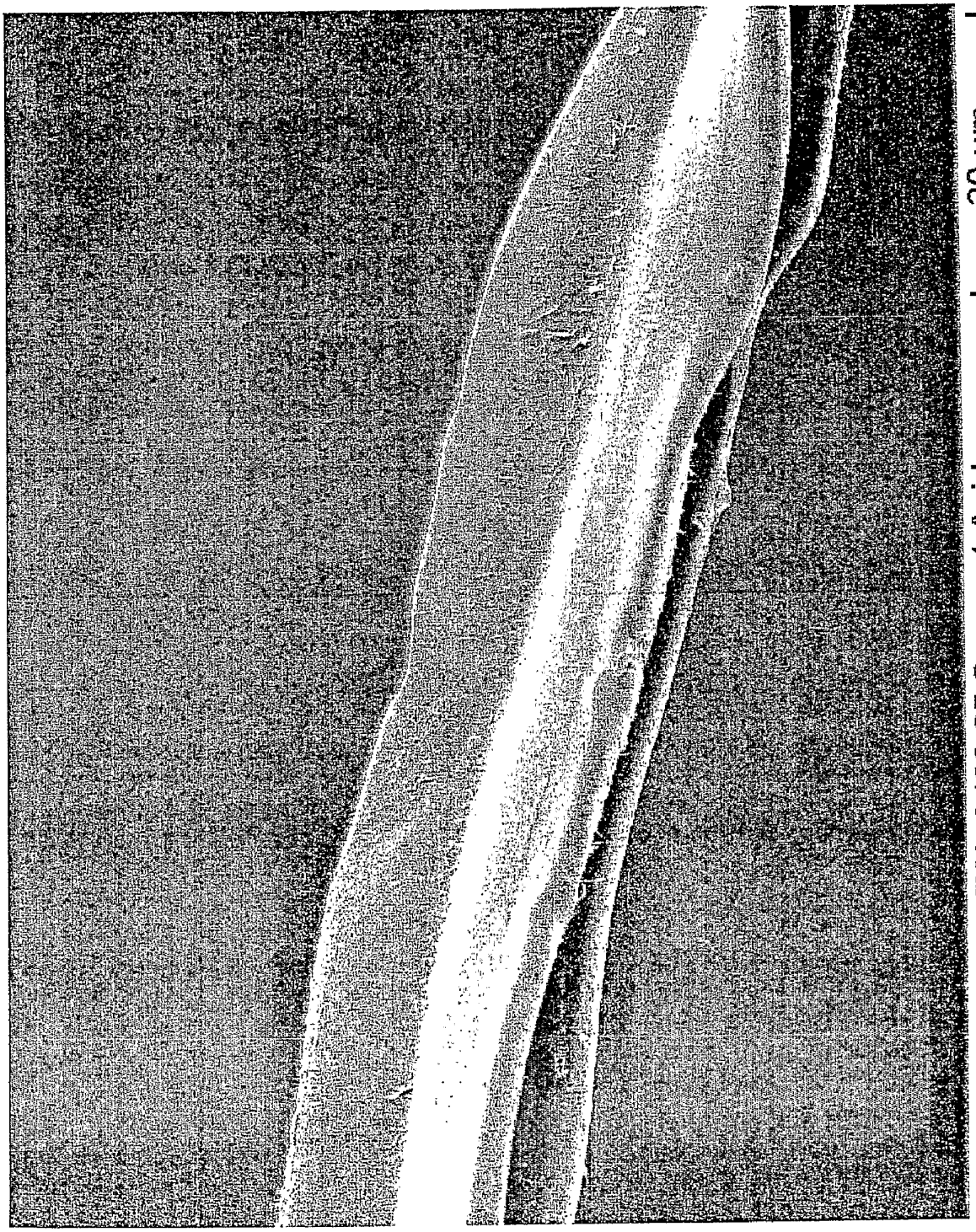



Figure 13

1254

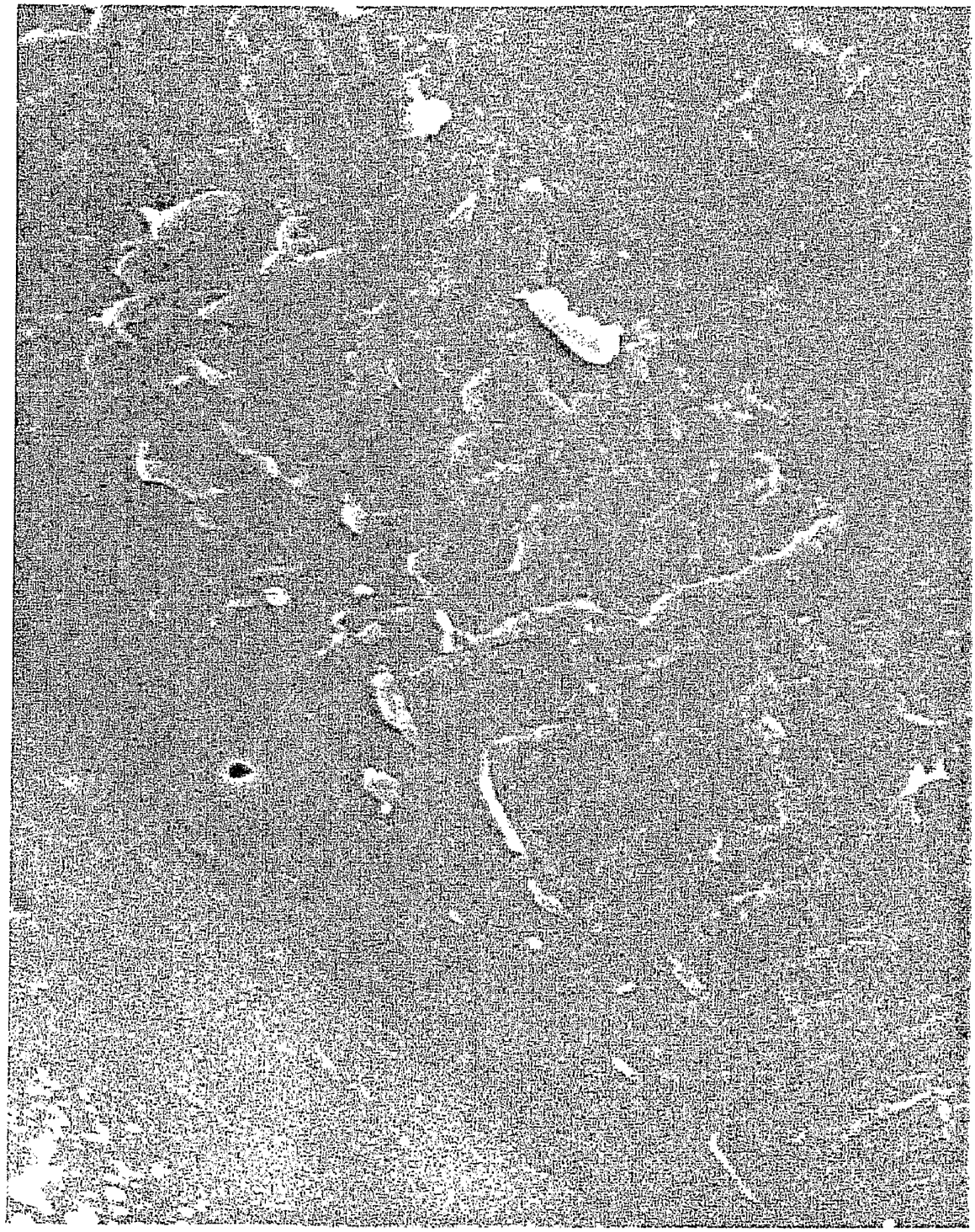



Figure 14

1255

# INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003179

A. CLASSIFICATION OF SUBJECT MATTER
INV. A24D3/02 A24D3/10 A24D3/14 A24D3/16

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)
A24D

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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2004/007687 A1 (DOBBELSTEIN HUBERT [DE] ET AL) 15 January 2004 (2004-01-15) | 1,2,7-9, 14,16, 20-24, 27-29, 37,41, 42,49-54 |
| Y | paragraphs [0007], [0026]; claims | 3-6, 10-13, 17-19, 25,26, 31, 33-35, 38,39, 43-48 |
| | ----- -/-- | |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 3 November 2006 | 14/11/2006 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Lepretre, François |

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | column 3, line 1 - column 4, line 41;<br>examples | 3-6,<br>10-13,<br>17-19,<br>25,26,<br>31,<br>33-35,<br>38,39,<br>43-48 |
| Y | WO 91/12737 A (EASTMAN KODAK CO [US])<br>5 September 1991 (1991-09-05)<br>cited in the application<br><br>claims | 3-6,<br>10-13,<br>17-19,<br>25,26,<br>31,<br>33-35,<br>38,39,<br>43-48 |

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Information on patent family members

International application No
PCT/GB2006/003179

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**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: PROCESS FOR PREPARING VARENICLINE, VARENICLINE INTERMEDIATES, AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) Abstract: Provided herein is an improved, convenient, commercially viable and environmentally friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof comprising reacting l-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-trien- 10-yl)-2,2,2-trifluoro-ethanone with chloroacetaldehyde in the pressence of an oxygen source. Provided further herein is an improved and industrially advantageous process for the preparation of l-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2- trifluoro-ethanone.

WO 2010/023561 A1

# PROCESS FOR PREPARING VARENICLINE, VARENICLINE INTERMEDIATES, AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

## CROSS REFERENCE TO RELATED APPLICATION

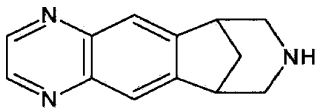
This application claims the benefit of priority to Indian provisional application No. 2133/CHE/2008, filed on September 1, 2008, which is incorporated herein by reference in its entirety.

## FIELD OF THE DISCLOSURE

Disclosed herein is a convenient, commercially viable and environmentally friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof. Disclosed further herein is an improved and industrially advantageous process for the preparation of a varenicline intermediate.

## BACKGROUND OF THE INVENTION

Varenicline, 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, is known to bind to neuronal nicotinic acetylcholine specific receptor sites and is useful in modulating cholinergic function. This compound is useful in the treatment of inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, vasoconstriction, anxiety, panic disorder, depression, cognitive dysfunction, drug/toxin-induced cognitive impairment (e.g., from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), particularly, nicotine dependency, addiction and withdrawal; including use in smoking cessation therapy. Varenicline is represented by the following structural formula:



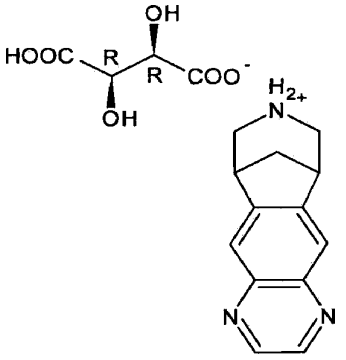

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and its first synthesis was disclosed in U.S. Patent No. 6,410,550 (hereinafter referred to as the '550 patent). Varenicline is sold by Pfizer under the brand name CHANTIX™ to help adults quit smoking by blocking $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes. It is orally administered as tablets containing 0.85 mg or 1.71 mg of varenicline tartrate equivalent to 0.5 mg or 1 mg of varenicline.

The '550 patent describes various processes for the preparation of aryl fused azapolycyclic compounds, including varenicline, and their pharmaceutically acceptable salts, combinations with other therapeutic agents, and methods of using such combinations in the treatment of neurogical and psychological disorders. Varenicline has been exemplified as a free base and a hydrochloride salt in the '550 patent.

U.S. Patent No. 6,890,927 (hereinafter referred to as the '927 patent) discloses tartrate salts, including L-tartrate, D-tartrate, D,L-tartrate and meso-tartrate, of varenicline and their polymorphs, processes for their preparation, and pharmaceutical compositions thereof. The '927 patent further discloses various polymorphs of the varenicline L-tartrate salt, including two anhydrous polymorphs (Forms A & B) and a hydrate polymorph (Form C), and characterizes them by powder X-ray diffraction (P-XRD), X-ray crystal structure, solid state $^{13}C$ NMR spectroscopy, and Differential Scanning Calorimetry (DSC).

Varenicline tartrate, 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3] benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1), has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3.C_4H_6O_6$. Varenicline tartrate is represented by the following structural formula:




US patent Nos. 6,897,310 and 6,951,938 describe a process for the preparation of aryl fused azapolycyclic compounds and their pharmaceutically acceptable salts in combination with another therapeutic agents and methods of using such combinations in the treatment of neurogical and psychological disorder. The '938 patent discloses the ring closure for making quinoxalines by reacting diamine compound with glyoxal or glyoxal derivatives in water or other polar solvents such as tetrahydrofuran, dimethylformamide or dimethylsulfoxide at a temperature of about 40°C to about 100°C.

PCT publication WO2004/108725 describes a process for the preparation of substituted quinoxalines by cyclization of the corresponding diamine compound with 2,3-dihydroxy-1,4-dioxane.

PCT Publication WO 2008/060487 (hereinafter referred to as the '487 application) discloses crystal forms of intermediates used in the process for the preparation of varenicline tartrate including the varenicline free base. According to the '487 application, the varenicline free base exists in four crystalline forms (Form A, Form C, Form D and Form E).

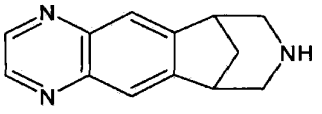
The synthetic routes described in the above mentioned prior art suffers from disadvantages such as high cost of reagents, the use of pyrophoric and hazardous reagents, the use of additional reagents and low yields of product. Hence, these routes are not advisable for scale up operations.

A need remains for an improved and commercially viable process of preparing a substantially pure varenicline or a pharmaceutically acceptable salt thereof, to resolve the problems associated with the processes described in the prior art, and that will be suitable for large-scale preparation, in a shorter reaction time. Desirable process properties include less hazardous and environmentally friendly reagents, reduced cost, greater simplicity, increased product purity and increased yield of the product.

## SUMMARY

The present inventors have surprisingly found that varenicline can be prepared in high purity and with high yield by condensing a protected diamino-10-aza-tricyclo compoud with haloacetaldehyde in the presence or absence of an oxygen source in a suitable solvent to produce a protected triazatetracyclo compound, followed by deprotection. The novel process solves the drawbacks associated with the prior processes and is commercially viable for preparing varenicline.

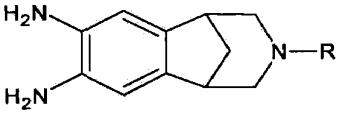
In one embodiment, a process for the preparation of varenicline of formula I:



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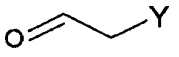
or a pharmaceutically acceptable salt thereof comprises:

a) reacting a protected diaminoazatricyclo compound of formula III:



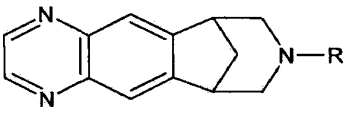
---------- III

wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



---------- IV

wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



---------- II

wherein R is as defined in formula III; and

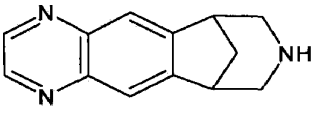
b) deprotecting the compound of formula II to provide pure varenicline of formula I, and optionally converting the varenicline obtained into a pharmaceutically acceptable salt thereof.

In one aspect, provided herein is an efficient, convenient, commercially viable and environment friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof. Advantageously, the reagents used for the present invention are less hazardous and easier to handle at a commercial scale, and are also less expensive reagents than those used previously.

In another aspect, provided also herein is an improved, convenient, commercially viable process for the preparation of the protected diamino-10-aza-tricyclo intermediate.

## DETAILED DESCRIPTION

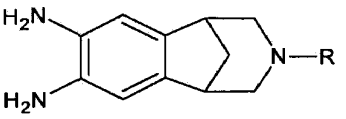
According to one aspect, there is provided a process for the preparation of varenicline of formula I:



---------- I

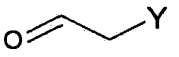
or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a protected diaminoazatricyclo compound of formula III:



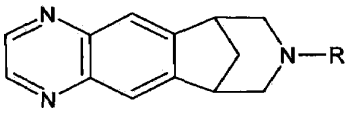
---------- III

wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



---------- IV

wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



---------- II

wherein R is as defined in formula III; and

b) deprotecting the compound of formula II to provide pure varenicline of formula I and optionally converting the varenicline obtained in to a pharmaceutically acceptable salt thereof.

In one embodiment, the reaction in step-(a) is carried out in the presence of a solvent. The term solvent also includes mixtures of solvents.

Exemplary solvents employed in step-(a) include, but are not limited to, water, an alcohol, a chlorinated hydrocarbon, a ketone, a polar aprotic solvent, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, ethyl acetate, isopropyl acetate, and mixtures thereof. More specifically, the solvent is selected from the group consisting of water, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and mixtures thereof.

In one embodiment, the amount of solvent employed in the coupling reaction is about 5 volumes to about 25 volumes, and specifically about 7 volumes to about 15 volumes with respect to the diaminoazatricyclo compound of formula III.

Exemplary oxygen sources employed in step-(a) include, but are not limited to, lead monoxide, manganese dioxide, mercuric iodide, ceric ammonium nitrate, and the like, and combinations thereof. A specific oxygen source is lead monoxide.

The condensation reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 25°C to the reflux temperature of the solvent used for at least 1 hour, and most specifically at the reflux

temperature of the solvent used for about 2 hours to about 10 hours. The reaction mass may be quenched with water after completion of the reaction.

As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

Exemplary nitrogen protecting groups 'R' include, but are not limited to, acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl. Specific nitrogen protecting groups are trifluoroacetyl, trichloroacetyl, trichloroethxoycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl and pivaloyl. A most specific nitrogen protecting group is trifluoroacetyl.

In one embodiment, the halogen atom 'Y' in the compound of formula IV is Cl.

The reaction mass containing the protected triazatetracyclo compound of formula II obtained in step-(a) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce varenicline of formula I, or the compound of formula II may be isolated and then used in the next step.

The removal of protecting groups in step-(b) can be achieved by conventional methods used in peptide chemistry and are described e.g. in the relevant chapters of standard reference works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T.W.Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981.

In one embodiment, the deprotection in step-(b) is carried out by treating the protected triazatetracyclo compound of formula II with a base in a reaction inert solvent.

The base used for deprotection is an organic or inorganic base. Specific organic bases are triethyl amine, trimethylamine, N,N-diisopropylethylamine, N-methylmorpholine and N-methylpiperidine. Specific inorganic bases are ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium tert-butoxide, sodium

isopropoxide and potassium tert-butoxide. A most specific base is sodium hydroxide or potassium hydroxide.

Exemplary solvents used for deprotection in step-(b) include, but are not limited to, water, an alcohol, a chlorinated hydrocarbon, a ketone, a polar aprotic solvent, a nitrile, an ester, and mixtures thereof. In one embodiment, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, acetone, and mixtures thereof.

The reaction mass containing the varenicline of formula I obtained in step-(b) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof, followed by isolation as solid from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure varenicline is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof. A most specific solvent is diisopropyl ether.

In another embodiment, the isolation is carried out by cooling the solution at a temperature of below 30°C for at least 30 minutes, specifically at about 0°C to about 30°C for about 1 hour to about 20 hours, and more specifically at about 0°C to about 25°C for about 2 hours to about 10 hours. The solid obtained is then recovered by techniques such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the solid is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

The pure varenicline obtained by the process disclosed herein may be further dried in, for example, a Vacuum Tray Dryer, a Rotocon Vacuum Dryer, a Vacuum Paddle Dryer or a pilot plant Rota vapor, to further lower residual solvents. Drying can be carried out under reduced pressure until the residual solvent content reduces to the desired amount such as an amount that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines.

In one embodiment, the drying is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm Hg, or below about 50 mm Hg, at temperatures such as about 35°C to about 70°C. The drying can be carried out for any desired time period that achieves the desired result, such as about 1 to 20 hours. Drying may also be carried out for

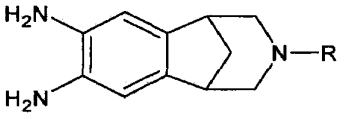
shorter or longer periods of time depending on the product specifications. Temperatures and pressures will be chosen based on the volatility of the solvent being used and the foregoing should be considered as only a general guidance. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, or using a fluidized bed drier, spin flash dryer, flash dryer and the like. Drying equipment selection is well within the ordinary skill in the art.

The varenicline of formula I obtained by the process disclosed herein has a purity (measured by High Performance Liquid Chromatography, hereinafter referred to as 'HPLC') greater than about 98%, specifically greater than about 99%, more specifically greater than about 99.5%, and still more specifically greater than about 99.9%. For example, the purity of the varenicline can be about 99% to about 99.95%, or about 99.5% to about 99.99%.

Pharmaceutically acceptable salts of varenicline can be prepared in high purity by using the substantially pure varenicline obtained by the methods disclosed herein, by known methods.

Exemplary pharmaceutically acceptable salts of varenicline are obtained from organic and inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, tartaric acid, derivatives of tartaric acid, fumaric acid, maleic acid, oxalic acid, acetic acid, propionic acid, succinic acid, mandelic acid, citric acid, and more preferable salt being varenicline tartrate.

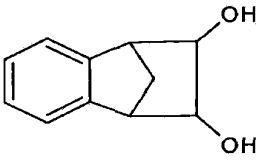
According to another aspect, there is provided a process for the preparation of the protected diaminoazatricyclo compound of formula III:




---------- III

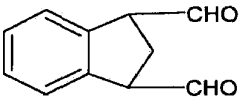
wherein 'R' represents a nitrogen protecting group, comprising:

a) oxidizing 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X:



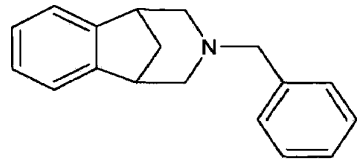

---------- X

in the presence of an oxidizing agent in a solvent, optionally in the presence of a phase transfer catalyst, to provide indane-1,3-dicarbaldehyde of formula IX:



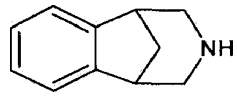

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b) reacting the compound of formula IX with benzyl amine in the presence of a reducing agent, optionally in the presence of a Lewis acid, in a solvent to provide 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII:



---------- VIII

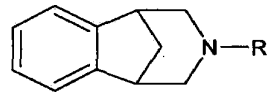
c) hydrogenating the compound of formula VIII using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide 10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VII:



---------- VII

or an acid addition salt thereof, preferably hydrochloride salt, wherein the hydrogen source is a formate salt;

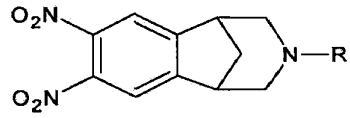
d) protecting the compound of formula VII with a nitrogen protecting group 'R' to provide a protected compound of formula VI:



---------- VI

wherein 'R' represents a nitrogen protecting group;

e) nitrating the compound of formula VI in the presence of a mixture of nitric acid and sulfuric acid in a solvent, to provide a dinitro compound of formula V:



---------- V

wherein R is as defined in formula VI; and

f) hydrogenating the compound of formula V using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide the protected diaminoazatricyclo compound of formula III, wherein the hydrogen source is a formate salt.

Exemplary nitrogen protecting group 'R' used in the compounds of formulae III, V and VI are selected from the group as described above. A most specific nitrogen protecting group is trifluoroacetyl.

These groups may be added or removed by conventional methods used in peptide chemistry as described above.

Exemplary solvents used in step-(a) include, but are not limited to, water, an alcohol, a ketone, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; more specifically, the solvent is selected from the group consisting of water, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, and mixtures thereof; and a most specific solvent is a mixture of water and methylene chloride.

Exemplary oxidizing agents used in step-(a) include, but are not limited to, sodium periodate, sodium chlorate, sodium hypochlorite, collins reagent, barium permanganate, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), iodine/$K_2CO_3$, N-chlorosuccinimide/ dimethylsulfide, ceric ammonium nitrate, and the like. A specific oxidizing agent is sodium periodate. Collins reagent is the complex of chromium(VI) oxide with pyridine in dichloromethane. It is used to selectively oxidize primary alcohols to the aldehyde, and will tolerate many other functional groups within the molecule. It can be used as an alternative to the Jones reagent and pyridinium chlorochromate when oxidising secondary alcohols to ketones. Moreover, the Collins reagent is especially useful for oxidations of acid sensitive compounds.

In one embodiment, the oxidizing agent is used in a molar ratio of about 1 to 5 moles, specifically about 1 to 2 moles, per 1 mole of the 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X in order to ensure a proper course of the reaction.

The reaction in step-(a) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 40°C for at least 30 minutes, and more specifically at about 10°C to about 40°C from about 1 hour to about 5 hours.

In one embodiment, the oxidation in step-(a) is carried out in the presence of a phase transfer catalyst. A "phase transfer catalyst" refers to a catalyst or agent which is added to a reaction mixture of components, to transfer one or more of the reacting components to a location where it can conveniently and rapidly react with another reacting component.

Exemplary phase transfer catalysts for use herein include, but are not limited to, quaternary ammonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, phenyl lower alkyl group including a straight or branched alkyl group having 1 to 6 carbon atoms which is substituted by an aryl group and phenyl group, e.g., tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexyl ammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexylammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanylammonium chloride, benzyltripropylammonium chloride, benzyltriethyl ammonium chloride, phenyltriethylammonium chloride and the like; phosphonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., 1-dodecanylpyridinium chloride and the like.

Specific phase transfer catalysts are tetrabutylammonium bromide, tetrabutylphosphonium bromide, tetrabutylammonium chloride, tetrabutylphosphonium chloride, benzyltriethylammonium chloride, tetrabutylammonium hydrogen sulfate; and more specifically benzyltriethylammonium chloride or tetrabutylammonium bromide.

In one embodiment, the amount of the phase transfer catalyst employed is 0.5% w/w to about 10% w/w, and specifically from about 5% w/w to about 10% w/w.

The reaction mass containing the indane-1,3-dicarbaldehyde of formula IX obtained in step-(a) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII, or the compound of formula IX may be isolated and then used in the next step.

Exemplary solvents used in step-(b) include, but are not limited to, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester and the like, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate,

isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and more specifically, the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

The reducing agent used in step-(b) is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, diisobutyl aluminium hydride, borane and its derivatives. A specific reducing agent is sodium cyanoborohydride.

The Lewis acid used in step-(b) is selected from the group consisting of aluminium chloride, calcium chloride, boron triflouride and zinc chloride. A specific Lewis acid is aluminium chloride.

In one embodiment, the reducing agent is used in a molar ratio of about 1 to 5 moles, specifically about 2.5 to 3.5 moles, per 1 mole of the compound of formula IX in order to ensure a proper course of the reaction.

The reaction in step-(b) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 40°C for at least 30 minutes, and more specifically at about 10°C to about 40°C from about 1 hour to about 5 hours.

The reaction mass containing the 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VIII obtained in step-(b) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce 10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VII, or the compound of formula VIII may be isolated and then used in the next step.

Exemplary solvents used in step-(c) include, but are not limited to, water, an alcohol, a ketone, a nitrile, an ester, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof; and a most specific solvent is methanol.

Exemplary hydrogenation catalysts used in step-(c) include, but are not limited to, platinum catalysts such as platinum plate, platinum sponge, platinum black, colloidal platinum, platinum oxide, platinum wire and the like; palladium catalysts such as palladium sponge, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on

carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate and the like; and nickel catalysts such as reduced nickel, nickel oxide, Raney nickel and the like. A specific hydrogenation catalyst is palladium hydroxide.

Exemplary formate salts used in step-(c) include, but are not limited to, ammonium formate, and an alkali metal salt of formic acid such as sodium formate and potassium formate. A specific formate salt is ammonium formate.

The reaction in step-(c) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, more specifically at a temperature of about 40°C to the reflux temperature of the solvent used for at least 20 minutes, and most specifically at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

The reaction mass containing the 10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VII obtained in step-(c) is optionally subjected to usual work up as described above. The reaction mass may be used directly in the next step to produce compound of formula VI, or the compound of formula VII may be isolated and then used in the next step, or the compound of formula VII may be converted into its acid addition salt followed by isolation and then used in the next step. In one embodiment, the compound of formula VII is converted into its acid addition salt by reaction with an acid in a solvent followed by isolation of an acid addition salt of the compound of formula VII as solid.

The acid addition salts are derived from a therapeutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid and, phosphoric acid, succinic acid, maleic acid, fumaric acid, citric acid, glutaric acid, citraconic acid, glutaconic acid, tartaric acid, di-p-toluoyl-L-(+)-tartrate, malic acid, and ascorbic acid. A specific acid addition salt of the compound of formula VII is hydrochloride.

The treatment of the compound of formula VII with acid is carried out in a solvent selected from the group consisting of a chlorinated solvent, a hydrocarbon solvent, an ether solvent, an alcoholic solvent, a ketonic solvent, an ester solvents, and mixtures thereof.

Nitrogen protecting groups 'R' as used in step-(d) are described above.

Exemplary solvents used in step-(e) include, but are not limited to, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate,

isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and more specifically, the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

In one embodiment, the sulfuric acid employed in step-(e) is in the form of concentrated sulfuric acid.

In another embodiment, the nitric acid employed in step-(e) is in the form of concentrated nitric acid, specifically 95% concentrated nitric acid and more specifically 100% concentrated nitric acid. In one embodiment, the nitric acid is fuming nitric acid.

The nitration reaction in step-(e) is carried out at a temperature below 40°C for about 3 hours to about 20 hours, and specifically at about 0°C to about 30°C for about 4 hours to about 10 hours.

The reaction mass containing the dinitro compound of formula V obtained in step-(e)is optionally subjected to usual work as described above. The reaction mass may be used directly in the next step to produce diamine compound of formula III, or the compound of formula V may be isolated and then used in the next step.

The isolation of the compound of formula V is performed from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure compound of formula V is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, methylene chloride, and mixtures thereof. Most specific solvents are water, methanol and mixtures thereof.

Exemplary solvents used in step-(f) include, but are not limited to, water, an alcohol, a ketone, a nitrile, an ester, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof; and a most specific solvent is methanol.

The hydrogenation catalyst used in step-(f) is selected from the group as described above. A specific hydrogenation catalyst is palladium hydroxide.

The formate salt used in step-(f) is selected from the group as described above. A specific formate salt is ammonium formate.

The reaction in step-(f) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, more specifically at a temperature of about 40°C to the reflux temperature of the solvent used for at least 20 minutes, and most specifically at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

The reaction mass containing the diaminoazatricyclo compound of formula III obtained in step-(f) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof, followed by isolation as solid from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure diaminoazatricyclo compound of formula III is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof. A most specific solvent is diisopropyl ether.

The total purity of the diaminoazatricyclo compound of formula III obtained by the process disclosed herein is greater than about 98%, specifically greater than about 99%, and more specifically greater than about 99.5% as measured by HPLC.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

## EXAMPLES

### Example 1

**Preparation of 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene**

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2,3-diol (100 g) was stirred in a mixture of water (2600 ml) and methylene chloride (1040 ml) under nitrogen at 10°C. This step was followed by the addition of sodium periodate (127.6 g) and triethylbenzyl ammonium chloride (10 g). The resulting mixture was stirred for 1 hour followed by aqueous/organic layer separation. The aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with water (4 x 1000 ml, or until no reaction to starch iodide was observed in the

aqueous wash) and then dried over sodium sulfate. Benzyl amine (63.86 g) was added to the resulting organic layer, the mixture was stirred for 1 minute at 25-30°C, and then immediately added to the suspension of sodiumcyanoborohydride (114.25 g) in methylene chloride (2000 ml) at 0°C in another reaction flask. The resulting orange mixture was warmed to 25-30°C and stirred for 30 minutes to 1 hour. The reaction mass was quenched by adding saturated sodium carbonate solution (1000 ml) and stirred for 1 hour (pH: 9). The layers were separated and the aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with saturated aqueous sodium chloride solution (2 x 600 ml) and dried over sodium sulfate followed by evaporation to afford a red oil. This oil was dissolved in a minimum of diethyl ether and filtered through a silica pad (3 x 4 inch) eluting with a mixture of 1000 ml of 15% ethyl acetate and 75% hexane solution to remove baseline red color. The resulting mass was concentrated under vacuum at 40-45°C to yield 95 g of 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$] dodeca-2(7),3,5-triene as yellow oil (Purity by HPLC: 99%).

**Example 2**

**Preparation of 10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt**

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene (94 g), ammonium formate (357 g) and 20% palladium hydroxide ( 7.5 g) were combined in methanol (1175 ml) and refluxed under nitrogen atmosphere for 30 minutes. The reaction mixture was cooled to 25°C and filtered through a celite pad which was rinsed with methanol. The filtrate was concentrated and the resulted residue was treated with a saturated aqueous sodium carbonate solution (940 ml) and the resulting mass was extracted with methylene chloride (940 ml). The two layers were separated and the aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with saturated aqueous sodium chloride solution (940 ml), dried over sodium sulfate and concentrated. The residue was treated with ethyl acetate (94 ml) and cooled to 0-5°C. Cooling was followed by the addition of hydrochloride in ethyl acetate (150 ml) at 0-5°C and adjusting the pH to 1-2. The suspension was stirred at 0-5°C for 1 hour and the resulting white crystals were collected by filtration to produce 64 g of 10-aza-tricyclo [6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt (Purity by HPLC: 99.68%).

**Example 3**

**Preparation of 1-(10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone**

10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (60 g) was stirred in methylene chloride (600 ml) at 25-30°C, the mixture was cooled to 0°C, and then treated with pyridine (61.68 g), followed by the addition of trifluoroacetic anhydride (TFAA) (81.39 g) over 10 minutes. Aqueous hydrochloric acid solution (600 ml) was added to the resulting mass followed by the separation of layers. The aqueous layer was extracted with methylene chloride (2 x 300 ml) and the combined organic layer was washed with aqueous hydrochloric acid solution (300 ml), water (2 x 600 ml) and saturated aqueous sodium bicarbonate solution (600 ml). The resulting solution was dried over sodium sulfate followed by concentration under vacuum at below 40°C to afford a clear oil which was then crystallized to give 66 g of 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as white needles (Purity by HPLC: 99.33%).

**Example 4**

**Preparation of 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone**

Fuming nitric acid (39 g) was slowly added to a solution concentrated sulfuric acid (126.17 g) in methylene chloride (450 ml) followed by stirring at 0°C to generate a white precipitate. This step was followed by drop wise addition of a solution of 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (65 g) in methylene chloride (100 ml) through an addition funnel over 30 minutes. The reaction mixture was stirred for 2 hours 30 minutes at 0°C and then stirred for 4 hours at 25-30°C. The resulting mass was poured into a vigorously stirred mixture of water (650 ml) at 15-20°C. The resulting layers were separated and the aqueous layer was extracted with methylene chloride (1 x 325 ml). The organic layers were combined and washed with water (3 x 650 ml) and then dried over sodium sulfate and concentrated to afford a solid. The resulting solid was slurried with methanol (325 ml), filtered and dried to yield 60 g of 1-(4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as off-white solid (Purity by HPLC: 99.5%).

**Example 5**

**Preparation of 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-y1)-2,2,2-trifluoro-ethanone**

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (40 g), ammonium formate (114.28 g) and 20% palladium hydroxide (4 g) were combined in

methanol (400 ml) and refluxed for 30 minutes under a nitrogen atmosphere. The reaction mixture was cooled to 25°C and filtered through a celite pad which was rinsed with methanol. The filtrate was concentrated and the product was extracted with methylene chloride (200 ml) and water (200 ml). The resulting two layers were extracted with methylene chloride (200 ml). The organic layer was washed with saturated aqueous sodium chloride solution (200 ml), dried over sodium sulfate and then concentrated. The residue was crystallized with diisopropyl ether (400 ml) followed by filtration to yield 13 g of 1-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as pink crystals (Purity by HPLC: 99%).

**Example 6**

**Preparation of 1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone**

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1 g), 50% solution of chloroacetaldehyde (0.27 g) in water and lead monoxide (0.39 g) were heated in 20% aqueous dimethyl sulfoxide (80: 20, dimethyl sulfoxide : water) (17 ml) at 60°C. The reaction mixture was stirred at 60°C for 30 minutes. A 50% solution of chloroacetaldehyde (0.13 g) in water was added to the reaction mixture and then heated to 90°C. The reaction mixture was stirred for 30 minutes at 90°C and followed by the addition of 50% solution of chloroacetaldehyde (0.15 g) in water at 90°C. The reaction mixture was stirred for 4-5 hours at 90-95°C. The resulting mass was cooled to 25-30°C followed by the addition of water (34 ml). The unreacted lead monoxide was filtered and washed with water (34 ml). The filtrate was extracted with methylene chloride (5 x 25 ml) at 25-30°C. All the organic layers were combined and washed with 1N hydrochloric acid (3 x 25 ml). The organic layer was dried over sodium sulfate and charcoalized. The methylene chloride layer was concentrated under vacuum at below 45°C followed by recrystallization in isopropyl alcohol to yield 0.6 g of 1-(5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (Purity by HPLC: 99.88%).

**Example 7**

**Preparation of 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine (Varenicline)**

1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (100 g) was slurried in methanol (1000 ml) followed by treatment with sodium

hydroxide (26 g) in water (50 ml). The mixture was heated for 1 hour at 40-45°C, the resulting mass concentrated under vacuum at below 45°C followed by treatment with water (500 ml) and then extracted with methylene chloride (2 x 1000 ml). The organic layer was washed with water (1000 ml) and then dried over anhydrous sodium sulfate. Methylene dichloride was distilled out under vacuum followed by crystallization in diisopropyl ether. The brownish color solid obtained was dried at 50-55°C to give 60 g of varenicline free base (Purity by HPLC: 99.8%).

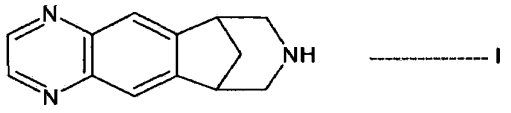
**Example 8**

**Preparation of 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (Varenicline tartrate)**

7,8,9,10-Tetrahydro-6,10-methano-6*H*-pyrazino-[2,3-h][3]benzazepine (50 g) was dissolved in methanol (375 ml) and the solution was added to a solution of tartaric acid (39.31 g) dissolved in methanol (375 ml) at 20-25°C. The suspension was stirred for 1 hour 30 minutes at 20-25°C followed by filtration of the solid and then drying to yield 82 g of varenicline tartrate (Purity by HPLC: 99.9%).

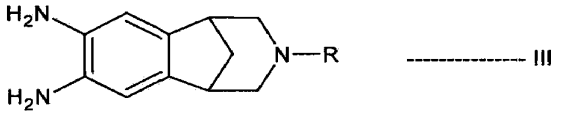
We claim:

1. A process for the preparation of varenicline of formula I:



or a pharmaceutically acceptable salt thereof; comprising:

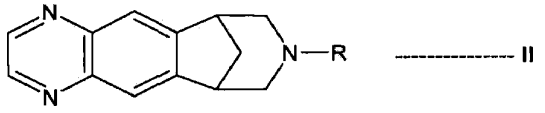
a) reacting a protected diaminoazatricyclo compound of formula III:



wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



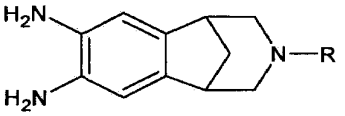
wherein R is as defined in formula III; and

b) deprotecting the compound of formula II to provide pure varenicline of formula I, and optionally converting the varenicline obtained into a pharmaceutically acceptable salt thereof.

2. The process of claim 1, wherein the reaction in step-(a) is carried out in the presence of a solvent selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, ethyl acetate, isopropyl acetate, and mixtures thereof.

3. The process of claim 2, wherein the solvent is selected from the group consisting of water, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and mixtures thereof.

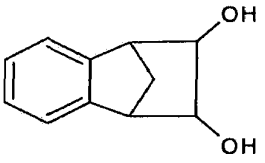
4. The process of claim 1, wherein the oxygen source employed in step-(a) is selected from the group consisting of lead monoxide, manganese dioxide, mercuric iodide and ceric ammonium nitrate.
5. The process of claim 1, wherein the condensation reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used.
6. The process of claim 5, wherein the reaction is carried out at the reflux temperature of the solvent used for about 2 hours to about 10 hours.
7. The process of claim 1, wherein the nitrogen protecting group 'R' is selected from the group consisting of acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl.
8. The process of claim 7, wherein the nitrogen protecting group 'R' is trifluoroacetyl or t-butoxycarbonyl.
9. The process of claim 1, wherein the halogen atom 'Y' in the compound of formula IV is Cl.
10. The process of claim 1, wherein the varenicline of formula I obtained in step-(b) is isolated from a solvent by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof; wherein the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof.
11. The process of claim 1, wherein the pharmaceutically acceptable salt of varenicline is a hydrochloride salt, a hydrobromide salt, a sulfate salt, a phosphate salt, a tartrate salt, a fumarate salt, a maleate salt, an oxalate salt, an acetate, a propionate salt, a succinate salt, a citrate salt, or a mandelate salt.
12. The process of claim 1, wherein the varenicline of formula I or a pharmaceutically acceptable salt obtained has a purity of about 99% to about 99.95% as measured by HPLC.
13. A process for the preparation of a protected diaminoazatricyclo compound of formula III:




---------- III

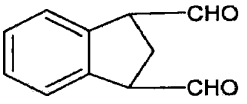
wherein 'R' represents a nitrogen protecting group, comprising:

a) oxidizing 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X:



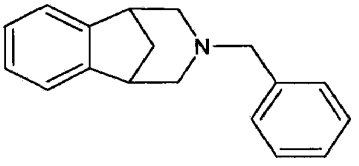

---------- X

in the presence of an oxidizing agent in a solvent, optionally in the presence of a phase transfer catalyst, to provide indane-1,3-dicarbaldehyde of formula IX:



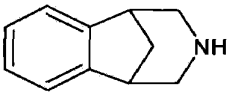

---------- IX

b) reacting the compound of formula IX with benzyl amine in the presence of a reducing agent, optionally in the presence of a Lewis acid, in a solvent to provide 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII:



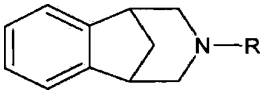

---------- VIII

c) hydrogenating the compound of formula VIII using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide 10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VII:

or an acid 


---------- VII addition salt thereof, wherein the hydrogen source is a formate salt;

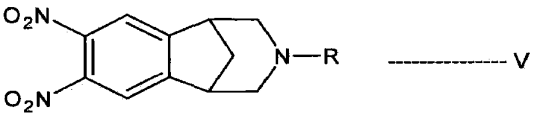
d) protecting the compound of formula VII with a nitrogen protecting group 'R' to provide a protected compound of formula VI:




---------- VI

wherein 'R' represents a nitrogen protecting group;

e) nitrating the compound of formula VI in the presence of a mixture of nitric acid and sulfuric acid in a solvent, to provide a dinitro compound of formula V:



wherein R is as defined in formula VI; and

f) hydrogenating the compound of formula V using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide the protected diaminoazatricyclo compound of formula III, wherein the hydrogen source is a formate salt.

14. The process of claim 13, wherein the nitrogen protecting group 'R' in the compounds of formulae III, V and VI is selected from the group consisting of acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl.

15. The process of claim 14, wherein the nitrogen protecting group 'R' is trifluoroacetyl.

16. The process of claim 13, wherein the solvent used in step-(a) is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof.

17. The process of claim 16, wherein the solvent is a mixture of water and methylene chloride.

18. The process of claim 13, wherein the oxidizing agent used in step-(a) is selected from the group consisting of sodium periodate, sodium chlorate, sodium hypochlorite, collins reagent, barium permanganate, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), iodine/$K_2CO_3$, N-chlorosuccinimide/ dimethylsulfide and ceric ammonium nitrate.

19. The process of claim 13, wherein the reaction in step-(a) is carried out at a temperature of about 0°C to about 40°C for at least 30 minutes.

20. The process of claim 13, wherein the oxidation in step-(a) is carried out in the presence of a phase transfer catalyst, wherein the phase transfer catalyst is selected from the group consisting of tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutyl ammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzyl ammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexyl ammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanyl ammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethyl ammonium chloride, tetrabutylphosphonium chloride and 1-dodecanylpyridinium chloride.

21. The process of claim 20, wherein the phase transfer catalyst is benzyltriethylammonium chloride or tetrabutylammonium bromide.

22. The process of claim 13, wherein the solvent used in steps-(b) and (e) is, each independently, selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof.

23. The process of claim 22, wherein the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

24. The process of claim 13, wherein the reducing agent used in step-(b) is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, diisobutyl aluminium hydride, borane and its derivatives; and wherein the Lewis acid is selected from the group consisting of aluminium chloride, calcium chloride, boron triflouride and zinc chloride.

25. The process of claim 24, wherein the reducing agent is sodium cyanoborohydride; and wherein the Lewis acid is aluminium chloride.

26. The process of claim 13, wherein the solvent used in steps-(c) and (f) is, each independently, selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

27. The process of claim 26, wherein the solvent is methanol.

28. The process of claim 13, wherein the hydrogenation catalyst used in steps-(c) and (f) is, each independently, selected from the group consisting of platinum plate, platinum sponge, platinum black, colloidal platinum, platinum oxide, platinum wire, palladium sponge, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, reduced nickel, nickel oxide and Raney nickel.
29. The process of claim 28, wherein the hydrogenation catalyst is palladium hydroxide.
30. The process of claim 13, wherein the formate salt used in steps-(c) and (f) is, each independently, selected from the group consisting of ammonium formate, sodium formate and potassium formate.
31. The process of claim 13, wherein the reaction in steps-(c) and (f) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used.
32. The process of claim 31, wherein the reaction is carried out at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.
33. The process of claim 13, wherein the reaction in step-(e) is carried out at a temperature of about 0°C to about 30°C for about 3 hours to about 20 hours.
34. The process of claim 13, wherein the diaminoazatricyclo compound of formula III obtained in step-(f) is isolated from a solvent by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof; wherein the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/007081

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08

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)
C07D

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)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | US 2002/072524 A1 (WADSWORTH JOTHAM [US] ET AL) 13 June 2002 (2002-06-13)<br>scheme 4 and p. 9 paragraphs 0075-0080;<br>scheme 8 and scheme 1<br>----- | 13-34<br>1-12 |
| Y | DAS ET AL: "An efficient and convenient protocol for the synthesis of quinoxalines and dihydropyrazines via cyclization-oxidation processes using HClO4.SiO2 as a heterogeneous recyclable catalyst"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL,<br>vol. 48, no. 31, 4 July 2007 (2007-07-04), pages 5371-5374, XP022141736<br>ISSN: 0040-4039<br>Scheme 1<br>-----<br>-/-- | 1-12 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 December 2009 | 21/01/2010 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Wolf, Claudia |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/007081

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 2004/108725 A1 (PFIZER PROD INC [US]; RAINVILLE JOSEPH PHILIP [US]; TABER GERALDINE PA)<br>16 December 2004 (2004-12-16)<br>cited in the application<br>claim 1;<br>----- | 1-34 |

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/007081

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2002072524 A1 | 13-06-2002 | US 2002072525 A1 | 13-06-2002 |
| | | US 2002111350 A1 | 15-08-2002 |
| | | US 2002132824 A1 | 19-09-2002 |
| | | US 6410550 B1 | 25-06-2002 |
| WO 2004108725 A1 | 16-12-2004 | AT 405566 T | 15-09-2008 |
| | | BR PI0410613 A | 20-06-2006 |
| | | CA 2527337 A1 | 16-12-2004 |
| | | CL 12712004 A1 | 22-04-2005 |
| | | DK 1638971 T3 | 27-10-2008 |
| | | EP 1638971 A1 | 29-03-2006 |
| | | ES 2310730 T3 | 16-01-2009 |
| | | JP 2006526607 T | 24-11-2006 |
| | | MX PA05013084 A | 02-03-2006 |
| | | PT 1638971 E | 23-10-2008 |
| | | SI 1638971 T1 | 31-12-2008 |
| | | TW 251594 B | 21-03-2006 |
| | | US 2007185327 A1 | 09-08-2007 |

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(72) Inventors; and

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(74) Agent: **LECUYER, Karen, A.**; Cantor Colburn Llp, 20 Church Street, 22nd Floor, Hartford, CT 06103 (US).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published**:

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(48) Date of publication of this corrected version:
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(15) Information about Correction:
see Notice of 4 August 2011

(54) Title: PROCESS FOR PREPARING VARENICLINE, VARENICLINE INTERMEDIATES, AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) Abstract: Provided herein is an improved, convenient, commercially viable and environmentally friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof comprising reacting l-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-trien- 10-yl)-2,2,2-trifluoro-ethanone with chloroacetaldehyde in the pressence of an oxygen source. Provided further herein is an improved and industrially advantageous process for the preparation of l-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2\ 7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2- trifluoro-ethanone.

WO 2010/023561 A9

# PROCESS FOR PREPARING VARENICLINE, VARENICLINE INTERMEDIATES, AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

## CROSS REFERENCE TO RELATED APPLICATION

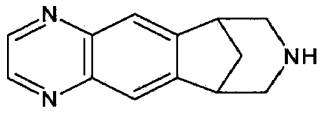
This application claims the benefit of priority to Indian provisional application No. 2133/CHE/2008, filed on September 1, 2008, which is incorporated herein by reference in its entirety.

## FIELD OF THE DISCLOSURE

Disclosed herein is a convenient, commercially viable and environmentally friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof. Disclosed further herein is an improved and industrially advantageous process for the preparation of a varenicline intermediate.

## BACKGROUND OF THE INVENTION

Varenicline, 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, is known to bind to neuronal nicotinic acetylcholine specific receptor sites and is useful in modulating cholinergic function. This compound is useful in the treatment of inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, vasoconstriction, anxiety, panic disorder, depression, cognitive dysfunction, drug/toxin-induced cognitive impairment (e.g., from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), particularly, nicotine dependency, addiction and withdrawal; including use in smoking cessation therapy. Varenicline is represented by the following structural formula:



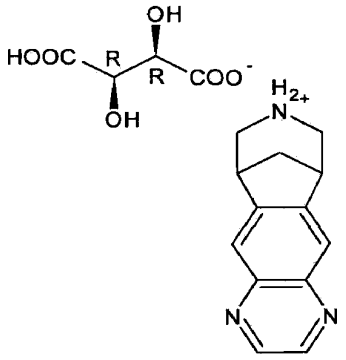

---------- I

and its first synthesis was disclosed in U.S. Patent No. 6,410,550 (hereinafter referred to as the '550 patent). Varenicline is sold by Pfizer under the brand name CHANTIX™ to help adults quit smoking by blocking $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes. It is orally administered as tablets containing 0.85 mg or 1.71 mg of varenicline tartrate equivalent to 0.5 mg or 1 mg of varenicline.

The '550 patent describes various processes for the preparation of aryl fused azapolycyclic compounds, including varenicline, and their pharmaceutically acceptable salts, combinations with other therapeutic agents, and methods of using such combinations in the treatment of neurogical and psychological disorders. Varenicline has been exemplified as a free base and a hydrochloride salt in the '550 patent.

U.S. Patent No. 6,890,927 (hereinafter referred to as the '927 patent) discloses tartrate salts, including L-tartrate, D-tartrate, D,L-tartrate and meso-tartrate, of varenicline and their polymorphs, processes for their preparation, and pharmaceutical compositions thereof. The '927 patent further discloses various polymorphs of the varenicline L-tartrate salt, including two anhydrous polymorphs (Forms A & B) and a hydrate polymorph (Form C), and characterizes them by powder X-ray diffraction (P-XRD), X-ray crystal structure, solid state $^{13}C$ NMR spectroscopy, and Differential Scanning Calorimetry (DSC).

Varenicline tartrate, 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3] benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1), has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3.C_4H_6O_6$. Varenicline tartrate is represented by the following structural formula:




US patent Nos. 6,897,310 and 6,951,938 describe a process for the preparation of aryl fused azapolycyclic compounds and their pharmaceutically acceptable salts in combination with another therapeutic agents and methods of using such combinations in the treatment of neurogical and psychological disorder. The '938 patent discloses the ring closure for making quinoxalines by reacting diamine compound with glyoxal or glyoxal derivatives in water or other polar solvents such as tetrahydrofuran, dimethylformamide or dimethylsulfoxide at a temperature of about 40°C to about 100°C.

PCT publication WO2004/108725 describes a process for the preparation of substituted quinoxalines by cyclization of the corresponding diamine compound with 2,3-dihydroxy-1,4-dioxane.

PCT Publication WO 2008/060487 (hereinafter referred to as the '487 application) discloses crystal forms of intermediates used in the process for the preparation of varenicline tartrate including the varenicline free base. According to the '487 application, the varenicline free base exists in four crystalline forms (Form A, Form C, Form D and Form E).

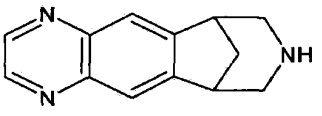
The synthetic routes described in the above mentioned prior art suffers from disadvantages such as high cost of reagents, the use of pyrophoric and hazardous reagents, the use of additional reagents and low yields of product. Hence, these routes are not advisable for scale up operations.

A need remains for an improved and commercially viable process of preparing a substantially pure varenicline or a pharmaceutically acceptable salt thereof, to resolve the problems associated with the processes described in the prior art, and that will be suitable for large-scale preparation, in a shorter reaction time. Desirable process properties include less hazardous and environmentally friendly reagents, reduced cost, greater simplicity, increased product purity and increased yield of the product.

## SUMMARY

The present inventors have surprisingly found that varenicline can be prepared in high purity and with high yield by condensing a protected diamino-10-aza-tricyclo compoud with haloacetaldehyde in the presence or absence of an oxygen source in a suitable solvent to produce a protected triazatetracyclo compound, followed by deprotection. The novel process solves the drawbacks associated with the prior processes and is commercially viable for preparing varenicline.

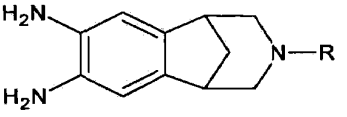
In one embodiment, a process for the preparation of varenicline of formula I:




---------- I

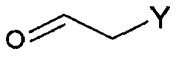
or a pharmaceutically acceptable salt thereof comprises:

a) reacting a protected diaminoazatricyclo compound of formula III:



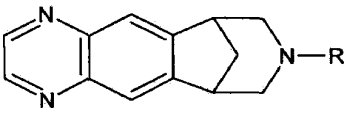

---------- III

wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:




---------- IV

wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:




---------- II

wherein R is as defined in formula III; and

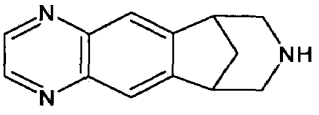
b) deprotecting the compound of formula II to provide pure varenicline of formula I, and optionally converting the varenicline obtained into a pharmaceutically acceptable salt thereof.

In one aspect, provided herein is an efficient, convenient, commercially viable and environment friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof. Advantageously, the reagents used for the present invention are less hazardous and easier to handle at a commercial scale, and are also less expensive reagents than those used previously.

In another aspect, provided also herein is an improved, convenient, commercially viable process for the preparation of the protected diamino-10-aza-tricyclo intermediate.

## DETAILED DESCRIPTION

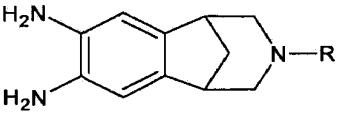
According to one aspect, there is provided a process for the preparation of varenicline of formula I:




---------- I

or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a protected diaminoazatricyclo compound of formula III:

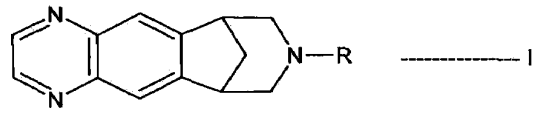



---------- III

wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



wherein R is as defined in formula III; and

b) deprotecting the compound of formula II to provide pure varenicline of formula I and optionally converting the varenicline obtained in to a pharmaceutically acceptable salt thereof.

In one embodiment, the reaction in step-(a) is carried out in the presence of a solvent. The term solvent also includes mixtures of solvents.

Exemplary solvents employed in step-(a) include, but are not limited to, water, an alcohol, a chlorinated hydrocarbon, a ketone, a polar aprotic solvent, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, ethyl acetate, isopropyl acetate, and mixtures thereof. More specifically, the solvent is selected from the group consisting of water, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and mixtures thereof.

In one embodiment, the amount of solvent employed in the coupling reaction is about 5 volumes to about 25 volumes, and specifically about 7 volumes to about 15 volumes with respect to the diaminoazatricyclo compound of formula III.

Exemplary oxygen sources employed in step-(a) include, but are not limited to, lead monoxide, manganese dioxide, mercuric iodide, ceric ammonium nitrate, and the like, and combinations thereof. A specific oxygen source is lead monoxide.

The condensation reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 25°C to the reflux temperature of the solvent used for at least 1 hour, and most specifically at the reflux

temperature of the solvent used for about 2 hours to about 10 hours. The reaction mass may be quenched with water after completion of the reaction.

As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

Exemplary nitrogen protecting groups 'R' include, but are not limited to, acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl. Specific nitrogen protecting groups are trifluoroacetyl, trichloroacetyl, trichloroethxoycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl and pivaloyl. A most specific nitrogen protecting group is trifluoroacetyl.

In one embodiment, the halogen atom 'Y' in the compound of formula IV is Cl.

The reaction mass containing the protected triazatetracyclo compound of formula II obtained in step-(a) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce varenicline of formula I, or the compound of formula II may be isolated and then used in the next step.

The removal of protecting groups in step-(b) can be achieved by conventional methods used in peptide chemistry and are described e.g. in the relevant chapters of standard reference works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T.W.Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981.

In one embodiment, the deprotection in step-(b) is carried out by treating the protected triazatetracyclo compound of formula II with a base in a reaction inert solvent.

The base used for deprotection is an organic or inorganic base. Specific organic bases are triethyl amine, trimethylamine, N,N-diisopropylethylamine, N-methylmorpholine and N-methylpiperidine. Specific inorganic bases are ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium tert-butoxide, sodium

isopropoxide and potassium tert-butoxide. A most specific base is sodium hydroxide or potassium hydroxide.

Exemplary solvents used for deprotection in step-(b) include, but are not limited to, water, an alcohol, a chlorinated hydrocarbon, a ketone, a polar aprotic solvent, a nitrile, an ester, and mixtures thereof. In one embodiment, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, acetone, and mixtures thereof.

The reaction mass containing the varenicline of formula I obtained in step-(b) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof, followed by isolation as solid from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure varenicline is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof. A most specific solvent is diisopropyl ether.

In another embodiment, the isolation is carried out by cooling the solution at a temperature of below 30°C for at least 30 minutes, specifically at about 0°C to about 30°C for about 1 hour to about 20 hours, and more specifically at about 0°C to about 25°C for about 2 hours to about 10 hours. The solid obtained is then recovered by techniques such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the solid is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

The pure varenicline obtained by the process disclosed herein may be further dried in, for example, a Vacuum Tray Dryer, a Rotocon Vacuum Dryer, a Vacuum Paddle Dryer or a pilot plant Rota vapor, to further lower residual solvents. Drying can be carried out under reduced pressure until the residual solvent content reduces to the desired amount such as an amount that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines.

In one embodiment, the drying is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm Hg, or below about 50 mm Hg, at temperatures such as about 35°C to about 70°C. The drying can be carried out for any desired time period that achieves the desired result, such as about 1 to 20 hours. Drying may also be carried out for

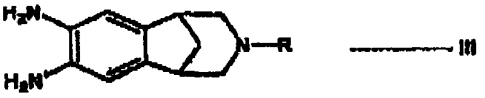
shorter or longer periods of time depending on the product specifications. Temperatures and pressures will be chosen based on the volatility of the solvent being used and the foregoing should be considered as only a general guidance. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, or using a fluidized bed drier, spin flash dryer, flash dryer and the like. Drying equipment selection is well within the ordinary skill in the art.

The varenicline of formula I obtained by the process disclosed herein has a purity (measured by High Performance Liquid Chromatography, hereinafter referred to as 'HPLC') greater than about 98%, specifically greater than about 99%, more specifically greater than about 99.5%, and still more specifically greater than about 99.9%. For example, the purity of the varenicline can be about 99% to about 99.95%, or about 99.5% to about 99.99%.

Pharmaceutically acceptable salts of varenicline can be prepared in high purity by using the substantially pure varenicline obtained by the methods disclosed herein, by known methods.

Exemplary pharmaceutically acceptable salts of varenicline are obtained from organic and inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, tartaric acid, derivatives of tartaric acid, fumaric acid, maleic acid, oxalic acid, acetic acid, propionic acid, succinic acid, mandelic acid, citric acid, and more preferable salt being varenicline tartrate.

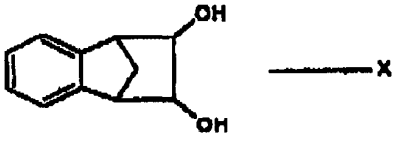
According to another aspect, there is provided a process for the preparation of the protected diaminoazatricyclo compound of formula III:




——— III

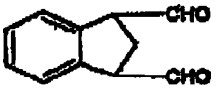
wherein 'R' represents a nitrogen protecting group, comprising:

a) oxidizing 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X:




——— X

in the presence of an oxidizing agent in a solvent, optionally in the presence of a phase transfer catalyst, to provide indane-1,3-dicarbaldehyde of formula IX:

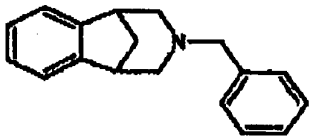



——— IX



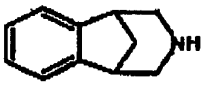
RECTIFIED SHEET (RULE 91) ISA/EP

b) reacting the compound of formula IX with benzyl amine in the presence of a reducing agent, optionally in the presence of a Lewis acid, in a solvent to provide 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII:



——— VIII

c) hydrogenating the compound of formula VIII using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide 10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VII:



——— VII

or an acid addition salt thereof, preferably hydrochloride salt, wherein the hydrogen source is a formate salt;

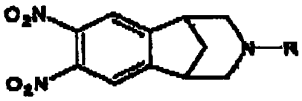
d) protecting the compound of formula VII with a nitrogen protecting group 'R' to provide a protected compound of formula VI:



——— VI

wherein 'R' represents a nitrogen protecting group;

e) nitrating the compound of formula VI in the presence of a mixture of nitric acid and sulfuric acid in a solvent, to provide a dinitro compound of formula V:



——— V

wherein R is as defined in formula VI; and

f) hydrogenating the compound of formula V using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide the protected diaminoazatricyclo compound of formula III, wherein the hydrogen source is a formate salt.

Exemplary nitrogen protecting group 'R' used in the compounds of formulae III, V and VI are selected from the group as described above. A most specific nitrogen protecting group is trifluoroacetyl.



RECTIFIED SHEET (RULE 91) ISA/EP

These groups may be added or removed by conventional methods used in peptide chemistry as described above.

Exemplary solvents used in step-(a) include, but are not limited to, water, an alcohol, a ketone, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; more specifically, the solvent is selected from the group consisting of water, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, and mixtures thereof; and a most specific solvent is a mixture of water and methylene chloride.

Exemplary oxidizing agents used in step-(a) include, but are not limited to, sodium periodate, sodium chlorate, sodium hypochlorite, collins reagent, barium permanganate, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), iodine/$K_2CO_3$, N-chlorosuccinimide/ dimethylsulfide, ceric ammonium nitrate, and the like. A specific oxidizing agent is sodium periodate. Collins reagent is the complex of chromium(VI) oxide with pyridine in dichloromethane. It is used to selectively oxidize primary alcohols to the aldehyde, and will tolerate many other functional groups within the molecule. It can be used as an alternative to the Jones reagent and pyridinium chlorochromate when oxidising secondary alcohols to ketones. Moreover, the Collins reagent is especially useful for oxidations of acid sensitive compounds.

In one embodiment, the oxidizing agent is used in a molar ratio of about 1 to 5 moles, specifically about 1 to 2 moles, per 1 mole of the 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X in order to ensure a proper course of the reaction.

The reaction in step-(a) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 40°C for at least 30 minutes, and more specifically at about 10°C to about 40°C from about 1 hour to about 5 hours.

In one embodiment, the oxidation in step-(a) is carried out in the presence of a phase transfer catalyst. A "phase transfer catalyst" refers to a catalyst or agent which is added to a reaction mixture of components, to transfer one or more of the reacting components to a location where it can conveniently and rapidly react with another reacting component.

Exemplary phase transfer catalysts for use herein include, but are not limited to, quaternary ammonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, phenyl lower alkyl group including a straight or branched alkyl group having 1 to 6 carbon atoms which is substituted by an aryl group and phenyl group, e.g., tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexyl ammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexylammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanylammonium chloride, benzyltripropylammonium chloride, benzyltriethyl ammonium chloride, phenyltriethylammonium chloride and the like; phosphonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., 1-dodecanylpyridinium chloride and the like.

Specific phase transfer catalysts are tetrabutylammonium bromide, tetrabutylphosphonium bromide, tetrabutylammonium chloride, tetrabutylphosphonium chloride, benzyltriethylammonium chloride, tetrabutylammonium hydrogen sulfate; and more specifically benzyltriethylammonium chloride or tetrabutylammonium bromide.

In one embodiment, the amount of the phase transfer catalyst employed is 0.5% w/w to about 10% w/w, and specifically from about 5% w/w to about 10% w/w.

The reaction mass containing the indane-1,3-dicarbaldehyde of formula IX obtained in step-(a) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII, or the compound of formula IX may be isolated and then used in the next step.

Exemplary solvents used in step-(b) include, but are not limited to, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester and the like, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate,

isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and more specifically, the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

The reducing agent used in step-(b) is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, diisobutyl aluminium hydride, borane and its derivatives. A specific reducing agent is sodium cyanoborohydride.

The Lewis acid used in step-(b) is selected from the group consisting of aluminium chloride, calcium chloride, boron triflouride and zinc chloride. A specific Lewis acid is aluminium chloride.

In one embodiment, the reducing agent is used in a molar ratio of about 1 to 5 moles, specifically about 2.5 to 3.5 moles, per 1 mole of the compound of formula IX in order to ensure a proper course of the reaction.

The reaction in step-(b) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 40°C for at least 30 minutes, and more specifically at about 10°C to about 40°C from about 1 hour to about 5 hours.

The reaction mass containing the 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VIII obtained in step-(b) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce 10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VII, or the compound of formula VIII may be isolated and then used in the next step.

Exemplary solvents used in step-(c) include, but are not limited to, water, an alcohol, a ketone, a nitrile, an ester, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof; and a most specific solvent is methanol.

Exemplary hydrogenation catalysts used in step-(c) include, but are not limited to, platinum catalysts such as platinum plate, platinum sponge, platinum black, colloidal platinum, platinum oxide, platinum wire and the like; palladium catalysts such as palladium sponge, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on

carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate and the like; and nickel catalysts such as reduced nickel, nickel oxide, Raney nickel and the like. A specific hydrogenation catalyst is palladium hydroxide.

Exemplary formate salts used in step-(c) include, but are not limited to, ammonium formate, and an alkali metal salt of formic acid such as sodium formate and potassium formate. A specific formate salt is ammonium formate.

The reaction in step-(c) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, more specifically at a temperature of about 40°C to the reflux temperature of the solvent used for at least 20 minutes, and most specifically at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

The reaction mass containing the 10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VII obtained in step-(c) is optionally subjected to usual work up as described above. The reaction mass may be used directly in the next step to produce compound of formula VI, or the compound of formula VII may be isolated and then used in the next step, or the compound of formula VII may be converted into its acid addition salt followed by isolation and then used in the next step. In one embodiment, the compound of formula VII is converted into its acid addition salt by reaction with an acid in a solvent followed by isolation of an acid addition salt of the compound of formula VII as solid.

The acid addition salts are derived from a therapeutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid and, phosphoric acid, succinic acid, maleic acid, fumaric acid, citric acid, glutaric acid, citraconic acid, glutaconic acid, tartaric acid, di-p-toluoyl-L-(+)-tartrate, malic acid, and ascorbic acid. A specific acid addition salt of the compound of formula VII is hydrochloride.

The treatment of the compound of formula VII with acid is carried out in a solvent selected from the group consisting of a chlorinated solvent, a hydrocarbon solvent, an ether solvent, an alcoholic solvent, a ketonic solvent, an ester solvents, and mixtures thereof.

Nitrogen protecting groups 'R' as used in step-(d) are described above.

Exemplary solvents used in step-(e) include, but are not limited to, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate,

isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and more specifically, the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

In one embodiment, the sulfuric acid employed in step-(e) is in the form of concentrated sulfuric acid.

In another embodiment, the nitric acid employed in step-(e) is in the form of concentrated nitric acid, specifically 95% concentrated nitric acid and more specifically 100% concentrated nitric acid. In one embodiment, the nitric acid is fuming nitric acid.

The nitration reaction in step-(e) is carried out at a temperature below 40°C for about 3 hours to about 20 hours, and specifically at about 0°C to about 30°C for about 4 hours to about 10 hours.

The reaction mass containing the dinitro compound of formula V obtained in step-(e)is optionally subjected to usual work as described above. The reaction mass may be used directly in the next step to produce diamine compound of formula III, or the compound of formula V may be isolated and then used in the next step.

The isolation of the compound of formula V is performed from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure compound of formula V is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, methylene chloride, and mixtures thereof. Most specific solvents are water, methanol and mixtures thereof.

Exemplary solvents used in step-(f) include, but are not limited to, water, an alcohol, a ketone, a nitrile, an ester, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof; and a most specific solvent is methanol.

The hydrogenation catalyst used in step-(f) is selected from the group as described above. A specific hydrogenation catalyst is palladium hydroxide.

The formate salt used in step-(f) is selected from the group as described above. A specific formate salt is ammonium formate.

The reaction in step-(f) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, more specifically at a temperature of about 40°C to the reflux temperature of the solvent used for at least 20 minutes, and most specifically at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

The reaction mass containing the diaminoazatricyclo compound of formula III obtained in step-(f) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof, followed by isolation as solid from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure diaminoazatricyclo compound of formula III is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof. A most specific solvent is diisopropyl ether.

The total purity of the diaminoazatricyclo compound of formula III obtained by the process disclosed herein is greater than about 98%, specifically greater than about 99%, and more specifically greater than about 99.5% as measured by HPLC.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

## EXAMPLES

### Example 1

**Preparation of 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene**

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2,3-diol (100 g) was stirred in a mixture of water (2600 ml) and methylene chloride (1040 ml) under nitrogen at 10°C. This step was followed by the addition of sodium periodate (127.6 g) and triethylbenzyl ammonium chloride (10 g). The resulting mixture was stirred for 1 hour followed by aqueous/organic layer separation. The aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with water (4 x 1000 ml, or until no reaction to starch iodide was observed in the

aqueous wash) and then dried over sodium sulfate. Benzyl amine (63.86 g) was added to the resulting organic layer, the mixture was stirred for 1 minute at 25-30°C, and then immediately added to the suspension of sodiumcyanoborohydride (114.25 g) in methylene chloride (2000 ml) at 0°C in another reaction flask. The resulting orange mixture was warmed to 25-30°C and stirred for 30 minutes to 1 hour. The reaction mass was quenched by adding saturated sodium carbonate solution (1000 ml) and stirred for 1 hour (pH: 9). The layers were separated and the aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with saturated aqueous sodium chloride solution (2 x 600 ml) and dried over sodium sulfate followed by evaporation to afford a red oil. This oil was dissolved in a minimum of diethyl ether and filtered through a silica pad (3 x 4 inch) eluting with a mixture of 1000 ml of 15% ethyl acetate and 75% hexane solution to remove baseline red color. The resulting mass was concentrated under vacuum at 40-45°C to yield 95 g of 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$] dodeca-2(7),3,5-triene as yellow oil (Purity by HPLC: 99%).

**Example 2**

**Preparation of 10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt**

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene (94 g), ammonium formate (357 g) and 20% palladium hydroxide ( 7.5 g) were combined in methanol (1175 ml) and refluxed under nitrogen atmosphere for 30 minutes. The reaction mixture was cooled to 25°C and filtered through a celite pad which was rinsed with methanol. The filtrate was concentrated and the resulted residue was treated with a saturated aqueous sodium carbonate solution (940 ml) and the resulting mass was extracted with methylene chloride (940 ml). The two layers were separated and the aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with saturated aqueous sodium chloride solution (940 ml), dried over sodium sulfate and concentrated. The residue was treated with ethyl acetate (94 ml) and cooled to 0-5°C. Cooling was followed by the addition of hydrochloride in ethyl acetate (150 ml) at 0-5°C and adjusting the pH to 1-2. The suspension was stirred at 0-5°C for 1 hour and the resulting white crystals were collected by filtration to produce 64 g of 10-aza-tricyclo [6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt (Purity by HPLC: 99.68%).

**Example 3**

**Preparation of 1-(10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone**

10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (60 g) was stirred in methylene chloride (600 ml) at 25-30°C, the mixture was cooled to 0°C, and then treated with pyridine (61.68 g), followed by the addition of trifluoroacetic anhydride (TFAA) (81.39 g) over 10 minutes. Aqueous hydrochloric acid solution (600 ml) was added to the resulting mass followed by the separation of layers. The aqueous layer was extracted with methylene chloride (2 x 300 ml) and the combined organic layer was washed with aqueous hydrochloric acid solution (300 ml), water (2 x 600 ml) and saturated aqueous sodium bicarbonate solution (600 ml). The resulting solution was dried over sodium sulfate followed by concentration under vacuum at below 40°C to afford a clear oil which was then crystallized to give 66 g of 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as white needles (Purity by HPLC: 99.33%).

**Example 4**

**Preparation of 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone**

Fuming nitric acid (39 g) was slowly added to a solution concentrated sulfuric acid (126.17 g) in methylene chloride (450 ml) followed by stirring at 0°C to generate a white precipitate. This step was followed by drop wise addition of a solution of 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (65 g) in methylene chloride (100 ml) through an addition funnel over 30 minutes. The reaction mixture was stirred for 2 hours 30 minutes at 0°C and then stirred for 4 hours at 25-30°C. The resulting mass was poured into a vigorously stirred mixture of water (650 ml) at 15-20°C. The resulting layers were separated and the aqueous layer was extracted with methylene chloride (1 x 325 ml). The organic layers were combined and washed with water (3 x 650 ml) and then dried over sodium sulfate and concentrated to afford a solid. The resulting solid was slurried with methanol (325 ml), filtered and dried to yield 60 g of 1-(4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as off-white solid (Purity by HPLC: 99.5%).

**Example 5**

**Preparation of 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-y1)-2,2,2-trifluoro-ethanone**

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (40 g), ammonium formate (114.28 g) and 20% palladium hydroxide (4 g) were combined in

methanol (400 ml) and refluxed for 30 minutes under a nitrogen atmosphere. The reaction mixture was cooled to 25°C and filtered through a celite pad which was rinsed with methanol. The filtrate was concentrated and the product was extracted with methylene chloride (200 ml) and water (200 ml). The resulting two layers were extracted with methylene chloride (200 ml). The organic layer was washed with saturated aqueous sodium chloride solution (200 ml), dried over sodium sulfate and then concentrated. The residue was crystallized with diisopropyl ether (400 ml) followed by filtration to yield 13 g of 1-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-y1)-2,2,2-trifluoro-ethanone as pink crystals (Purity by HPLC: 99%).

**Example 6**

**Preparation of 1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone**

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-y1)-2,2,2-trifluoro-ethanone (1 g), 50% solution of chloroacetaldehyde (0.27 g) in water and lead monoxide (0.39 g) were heated in 20% aqueous dimethyl sulfoxide (80: 20, dimethyl sulfoxide : water) (17 ml) at 60°C. The reaction mixture was stirred at 60°C for 30 minutes. A 50% solution of chloroacetaldehyde (0.13 g) in water was added to the reaction mixture and then heated to 90°C. The reaction mixture was stirred for 30 minutes at 90°C and followed by the addition of 50% solution of chloroacetaldehyde (0.15 g) in water at 90°C. The reaction mixture was stirred for 4-5 hours at 90-95°C. The resulting mass was cooled to 25-30°C followed by the addition of water (34 ml). The unreacted lead monoxide was filtered and washed with water (34 ml). The filtrate was extracted with methylene chloride (5 x 25 ml) at 25-30°C. All the organic layers were combined and washed with 1N hydrochloric acid (3 x 25 ml). The organic layer was dried over sodium sulfate and charcoalized. The methylene chloride layer was concentrated under vacuum at below 45°C followed by recrystallization in isopropyl alcohol to yield 0.6 g of 1-(5,8,14-triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (Purity by HPLC: 99.88%).

**Example 7**

**Preparation of 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine (Varenicline)**

1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2.11}$.$0^{4.9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (100 g) was slurried in methanol (1000 ml) followed by treatment with sodium

hydroxide (26 g) in water (50 ml). The mixture was heated for 1 hour at 40-45°C, the resulting mass concentrated under vacuum at below 45°C followed by treatment with water (500 ml) and then extracted with methylene chloride (2 x 1000 ml). The organic layer was washed with water (1000 ml) and then dried over anhydrous sodium sulfate. Methylene dichloride was distilled out under vacuum followed by crystallization in diisopropyl ether. The brownish color solid obtained was dried at 50-55°C to give 60 g of varenicline free base (Purity by HPLC: 99.8%).

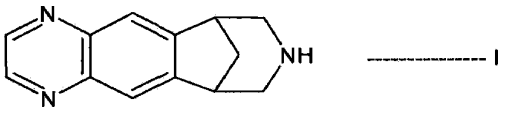
**Example 8**

**Preparation of 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (Varenicline tartrate)**

7,8,9,10-Tetrahydro-6,10-methano-6*H*-pyrazino-[2,3-h][3]benzazepine (50 g) was dissolved in methanol (375 ml) and the solution was added to a solution of tartaric acid (39.31 g) dissolved in methanol (375 ml) at 20-25°C. The suspension was stirred for 1 hour 30 minutes at 20-25°C followed by filtration of the solid and then drying to yield 82 g of varenicline tartrate (Purity by HPLC: 99.9%).

We claim:

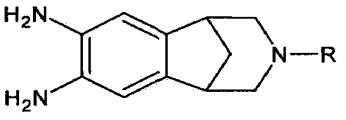
1. A process for the preparation of varenicline of formula I:



---------- I

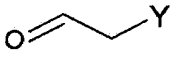
or a pharmaceutically acceptable salt thereof; comprising:

a) reacting a protected diaminoazatricyclo compound of formula III:



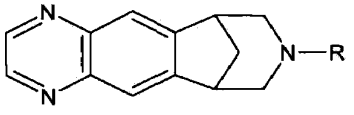
---------- III

wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



---------- IV

wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



---------- II

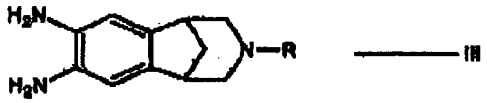
wherein R is as defined in formula III; and

b) deprotecting the compound of formula II to provide pure varenicline of formula I, and optionally converting the varenicline obtained into a pharmaceutically acceptable salt thereof.

2. The process of claim 1, wherein the reaction in step-(a) is carried out in the presence of a solvent selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, ethyl acetate, isopropyl acetate, and mixtures thereof.

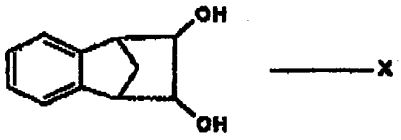
3. The process of claim 2, wherein the solvent is selected from the group consisting of water, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and mixtures thereof.

4. The process of claim 1, wherein the oxygen source employed in step-(a) is selected from the group consisting of lead monoxide, manganese dioxide, mercuric iodide and ceric ammonium nitrate.
5. The process of claim 1, wherein the condensation reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used.
6. The process of claim 5, wherein the reaction is carried out at the reflux temperature of the solvent used for about 2 hours to about 10 hours.
7. The process of claim 1, wherein the nitrogen protecting group 'R' is selected from the group consisting of acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl.
8. The process of claim 7, wherein the nitrogen protecting group 'R' is trifluoroacetyl or t-butoxycarbonyl.
9. The process of claim 1, wherein the halogen atom 'Y' in the compound of formula IV is Cl.
10. The process of claim 1, wherein the varenicline of formula I obtained in step-(b) is isolated from a solvent by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof; wherein the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof.
11. The process of claim 1, wherein the pharmaceutically acceptable salt of varenicline is a hydrochloride salt, a hydrobromide salt, a sulfate salt, a phosphate salt, a tartrate salt, a fumarate salt, a maleate salt, an oxalate salt, an acetate, a propionate salt, a succinate salt, a citrate salt, or a mandelate salt.
12. The process of claim 1, wherein the varenicline of formula I or a pharmaceutically acceptable salt obtained has a purity of about 99% to about 99.95% as measured by HPLC.
13. A process for the preparation of a protected diaminoazatricyclo compound of formula III:

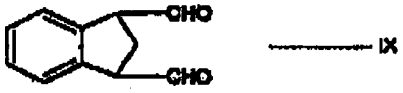


wherein 'R' represents a nitrogen protecting group, comprising:

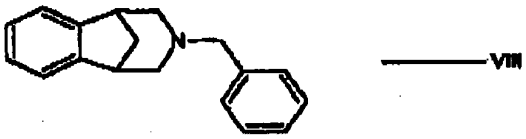
a) oxidizing 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X:



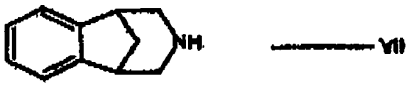
in the presence of an oxidizing agent in a solvent, optionally in the presence of a phase transfer catalyst, to provide indane-1,3-dicarbaldehyde of formula IX:



b) reacting the compound of formula IX with benzyl amine in the presence of a reducing agent, optionally in the presence of a Lewis acid, in a solvent to provide 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII:

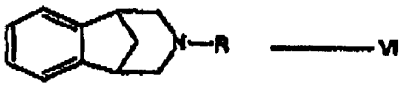


c) hydrogenating the compound of formula VIII using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide 10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VII:



or an acid addition salt thereof, wherein the hydrogen source is a formate salt;

d) protecting the compound of formula VII with a nitrogen protecting group 'R' to provide a protected compound of formula VI:

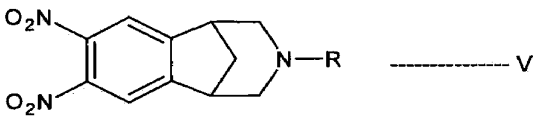


wherein 'R' represents a nitrogen protecting group;



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e) nitrating the compound of formula VI in the presence of a mixture of nitric acid and sulfuric acid in a solvent, to provide a dinitro compound of formula V:




V

wherein R is as defined in formula VI; and

f) hydrogenating the compound of formula V using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide the protected diaminoazatricyclo compound of formula III, wherein the hydrogen source is a formate salt.

14. The process of claim 13, wherein the nitrogen protecting group 'R' in the compounds of formulae III, V and VI is selected from the group consisting of acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl.

15. The process of claim 14, wherein the nitrogen protecting group 'R' is trifluoroacetyl.

16. The process of claim 13, wherein the solvent used in step-(a) is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof.

17. The process of claim 16, wherein the solvent is a mixture of water and methylene chloride.

18. The process of claim 13, wherein the oxidizing agent used in step-(a) is selected from the group consisting of sodium periodate, sodium chlorate, sodium hypochlorite, collins reagent, barium permanganate, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), iodine/$K_2CO_3$, N-chlorosuccinimide/ dimethylsulfide and ceric ammonium nitrate.

19. The process of claim 13, wherein the reaction in step-(a) is carried out at a temperature of about 0°C to about 40°C for at least 30 minutes.

20. The process of claim 13, wherein the oxidation in step-(a) is carried out in the presence of a phase transfer catalyst, wherein the phase transfer catalyst is selected from the group consisting of tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutyl ammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzyl ammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexyl ammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanyl ammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethyl ammonium chloride, tetrabutylphosphonium chloride and 1-dodecanylpyridinium chloride.

21. The process of claim 20, wherein the phase transfer catalyst is benzyltriethylammonium chloride or tetrabutylammonium bromide.

22. The process of claim 13, wherein the solvent used in steps-(b) and (e) is, each independently, selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof.

23. The process of claim 22, wherein the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

24. The process of claim 13, wherein the reducing agent used in step-(b) is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, diisobutyl aluminium hydride, borane and its derivatives; and wherein the Lewis acid is selected from the group consisting of aluminium chloride, calcium chloride, boron triflouride and zinc chloride.

25. The process of claim 24, wherein the reducing agent is sodium cyanoborohydride; and wherein the Lewis acid is aluminium chloride.

26. The process of claim 13, wherein the solvent used in steps-(c) and (f) is, each independently, selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

27. The process of claim 26, wherein the solvent is methanol.

28. The process of claim 13, wherein the hydrogenation catalyst used in steps-(c) and (f) is, each independently, selected from the group consisting of platinum plate, platinum sponge, platinum black, colloidal platinum, platinum oxide, platinum wire, palladium sponge, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, reduced nickel, nickel oxide and Raney nickel.

29. The process of claim 28, wherein the hydrogenation catalyst is palladium hydroxide.

30. The process of claim 13, wherein the formate salt used in steps-(c) and (f) is, each independently, selected from the group consisting of ammonium formate, sodium formate and potassium formate.

31. The process of claim 13, wherein the reaction in steps-(c) and (f) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used.

32. The process of claim 31, wherein the reaction is carried out at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

33. The process of claim 13, wherein the reaction in step-(e) is carried out at a temperature of about 0°C to about 30°C for about 3 hours to about 20 hours.

34. The process of claim 13, wherein the diaminoazatricyclo compound of formula III obtained in step-(f) is isolated from a solvent by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof; wherein the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/007081

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08

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)
C07D

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)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | US 2002/072524 A1 (WADSWORTH JOTHAM [US] ET AL) 13 June 2002 (2002-06-13)<br>scheme 4 and p. 9 paragraphs 0075-0080;<br>scheme 8 and scheme 1 | 13-34<br>1-12 |
| Y | DAS ET AL: "An efficient and convenient protocol for the synthesis of quinoxalines and dihydropyrazines via cyclization-oxidation processes using HClO4.SiO2 as a heterogeneous recyclable catalyst"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL,<br>vol. 48, no. 31, 4 July 2007 (2007-07-04), pages 5371-5374, XP022141736<br>ISSN: 0040-4039<br>Scheme 1 | 1-12 |

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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 |
|---|---|
| 14 December 2009 | 21/01/2010 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Wolf, Claudia |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/007081

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 2004/108725 A1 (PFIZER PROD INC [US]; RAINVILLE JOSEPH PHILIP [US]; TABER GERALDINE PA)<br>16 December 2004 (2004-12-16)<br>cited in the application<br>claim 1;<br>----- | 1-34 |

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/007081

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | US 2002111350 A1 | 15-08-2002 |
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**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: PROCESS FOR PREPARING VARENICLINE, VARENICLINE INTERMEDIATES, AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) Abstract: Provided herein is an improved, convenient, commercially viable and environmentally friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof comprising reacting 1-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien- 10-yl)-2,2,2-trifluoro-ethanone with chloroacetaldehyde in the pressence of an oxygen source. Provided further herein is an improved and industrially advantageous process for the preparation of 1-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2- trifluoro-ethanone.

WO 2010/023561 A9

# PROCESS FOR PREPARING VARENICLINE, VARENICLINE INTERMEDIATES, AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

## CROSS REFERENCE TO RELATED APPLICATION

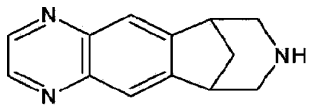
This application claims the benefit of priority to Indian provisional application No. 2133/CHE/2008, filed on September 1, 2008, which is incorporated herein by reference in its entirety.

## FIELD OF THE DISCLOSURE

Disclosed herein is a convenient, commercially viable and environmentally friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof. Disclosed further herein is an improved and industrially advantageous process for the preparation of a varenicline intermediate.

## BACKGROUND OF THE INVENTION

Varenicline, 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, is known to bind to neuronal nicotinic acetylcholine specific receptor sites and is useful in modulating cholinergic function. This compound is useful in the treatment of inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, vasoconstriction, anxiety, panic disorder, depression, cognitive dysfunction, drug/toxin-induced cognitive impairment (e.g., from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), particularly, nicotine dependency, addiction and withdrawal; including use in smoking cessation therapy. Varenicline is represented by the following structural formula:



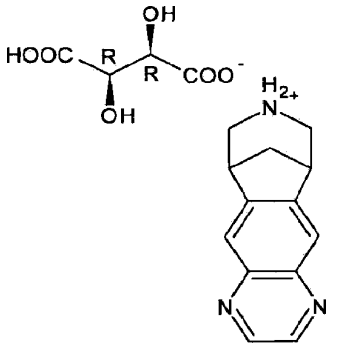

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and its first synthesis was disclosed in U.S. Patent No. 6,410,550 (hereinafter referred to as the '550 patent). Varenicline is sold by Pfizer under the brand name CHANTIX™ to help adults quit smoking by blocking $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes. It is orally administered as tablets containing 0.85 mg or 1.71 mg of varenicline tartrate equivalent to 0.5 mg or 1 mg of varenicline.

The '550 patent describes various processes for the preparation of aryl fused azapolycyclic compounds, including varenicline, and their pharmaceutically acceptable salts, combinations with other therapeutic agents, and methods of using such combinations in the treatment of neurogical and psychological disorders. Varenicline has been exemplified as a free base and a hydrochloride salt in the '550 patent.

U.S. Patent No. 6,890,927 (hereinafter referred to as the '927 patent) discloses tartrate salts, including L-tartrate, D-tartrate, D,L-tartrate and meso-tartrate, of varenicline and their polymorphs, processes for their preparation, and pharmaceutical compositions thereof. The '927 patent further discloses various polymorphs of the varenicline L-tartrate salt, including two anhydrous polymorphs (Forms A & B) and a hydrate polymorph (Form C), and characterizes them by powder X-ray diffraction (P-XRD), X-ray crystal structure, solid state $^{13}C$ NMR spectroscopy, and Differential Scanning Calorimetry (DSC).

Varenicline tartrate, 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3] benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1), has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3.C_4H_6O_6$. Varenicline tartrate is represented by the following structural formula:




US patent Nos. 6,897,310 and 6,951,938 describe a process for the preparation of aryl fused azapolycyclic compounds and their pharmaceutically acceptable salts in combination with another therapeutic agents and methods of using such combinations in the treatment of neurogical and psychological disorder. The '938 patent discloses the ring closure for making quinoxalines by reacting diamine compound with glyoxal or glyoxal derivatives in water or other polar solvents such as tetrahydrofuran, dimethylformamide or dimethylsulfoxide at a temperature of about 40°C to about 100°C.

PCT publication WO2004/108725 describes a process for the preparation of substituted quinoxalines by cyclization of the corresponding diamine compound with 2,3-dihydroxy-1,4-dioxane.

PCT Publication WO 2008/060487 (hereinafter referred to as the '487 application) discloses crystal forms of intermediates used in the process for the preparation of varenicline tartrate including the varenicline free base. According to the '487 application, the varenicline free base exists in four crystalline forms (Form A, Form C, Form D and Form E).

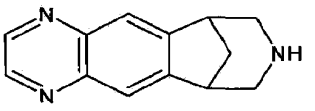
The synthetic routes described in the above mentioned prior art suffers from disadvantages such as high cost of reagents, the use of pyrophoric and hazardous reagents, the use of additional reagents and low yields of product. Hence, these routes are not advisable for scale up operations.

A need remains for an improved and commercially viable process of preparing a substantially pure varenicline or a pharmaceutically acceptable salt thereof, to resolve the problems associated with the processes described in the prior art, and that will be suitable for large-scale preparation, in a shorter reaction time. Desirable process properties include less hazardous and environmentally friendly reagents, reduced cost, greater simplicity, increased product purity and increased yield of the product.

## SUMMARY

The present inventors have surprisingly found that varenicline can be prepared in high purity and with high yield by condensing a protected diamino-10-aza-tricyclo compoud with haloacetaldehyde in the presence or absence of an oxygen source in a suitable solvent to produce a protected triazatetracyclo compound, followed by deprotection. The novel process solves the drawbacks associated with the prior processes and is commercially viable for preparing varenicline.

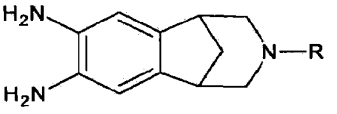
In one embodiment, a process for the preparation of varenicline of formula I:



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or a pharmaceutically acceptable salt thereof comprises:

a) reacting a protected diaminoazatricyclo compound of formula III:

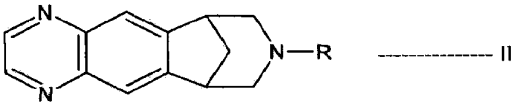


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wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



wherein R is as defined in formula III; and

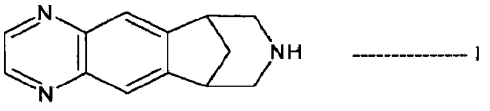
b) deprotecting the compound of formula II to provide pure varenicline of formula I, and optionally converting the varenicline obtained into a pharmaceutically acceptable salt thereof.

In one aspect, provided herein is an efficient, convenient, commercially viable and environment friendly process for the preparation of varenicline or a pharmaceutically acceptable salt thereof. Advantageously, the reagents used for the present invention are less hazardous and easier to handle at a commercial scale, and are also less expensive reagents than those used previously.

In another aspect, provided also herein is an improved, convenient, commercially viable process for the preparation of the protected diamino-10-aza-tricyclo intermediate.

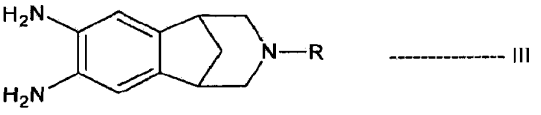
## DETAILED DESCRIPTION

According to one aspect, there is provided a process for the preparation of varenicline of formula I:

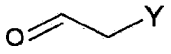


or a pharmaceutically acceptable salt thereof, comprising:

a) reacting a protected diaminoazatricyclo compound of formula III:

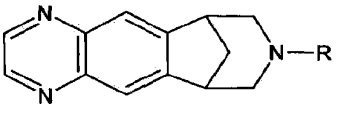


wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:




---------- IV

wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:




---------- II

wherein R is as defined in formula III; and

b) deprotecting the compound of formula II to provide pure varenicline of formula I and optionally converting the varenicline obtained in to a pharmaceutically acceptable salt thereof.

In one embodiment, the reaction in step-(a) is carried out in the presence of a solvent. The term solvent also includes mixtures of solvents.

Exemplary solvents employed in step-(a) include, but are not limited to, water, an alcohol, a chlorinated hydrocarbon, a ketone, a polar aprotic solvent, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, ethyl acetate, isopropyl acetate, and mixtures thereof. More specifically, the solvent is selected from the group consisting of water, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and mixtures thereof.

In one embodiment, the amount of solvent employed in the coupling reaction is about 5 volumes to about 25 volumes, and specifically about 7 volumes to about 15 volumes with respect to the diaminoazatricyclo compound of formula III.

Exemplary oxygen sources employed in step-(a) include, but are not limited to, lead monoxide, manganese dioxide, mercuric iodide, ceric ammonium nitrate, and the like, and combinations thereof. A specific oxygen source is lead monoxide.

The condensation reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 25°C to the reflux temperature of the solvent used for at least 1 hour, and most specifically at the reflux

temperature of the solvent used for about 2 hours to about 10 hours. The reaction mass may be quenched with water after completion of the reaction.

As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

Exemplary nitrogen protecting groups 'R' include, but are not limited to, acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl. Specific nitrogen protecting groups are trifluoroacetyl, trichloroacetyl, trichloroethxoycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl and pivaloyl. A most specific nitrogen protecting group is trifluoroacetyl.

In one embodiment, the halogen atom 'Y' in the compound of formula IV is Cl.

The reaction mass containing the protected triazatetracyclo compound of formula II obtained in step-(a) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce varenicline of formula I, or the compound of formula II may be isolated and then used in the next step.

The removal of protecting groups in step-(b) can be achieved by conventional methods used in peptide chemistry and are described e.g. in the relevant chapters of standard reference works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T.W.Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981.

In one embodiment, the deprotection in step-(b) is carried out by treating the protected triazatetracyclo compound of formula II with a base in a reaction inert solvent.

The base used for deprotection is an organic or inorganic base. Specific organic bases are triethyl amine, trimethylamine, N,N-diisopropylethylamine, N-methylmorpholine and N-methylpiperidine. Specific inorganic bases are ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium tert-butoxide, sodium

isopropoxide and potassium tert-butoxide. A most specific base is sodium hydroxide or potassium hydroxide.

Exemplary solvents used for deprotection in step-(b) include, but are not limited to, water, an alcohol, a chlorinated hydrocarbon, a ketone, a polar aprotic solvent, a nitrile, an ester, and mixtures thereof. In one embodiment, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, acetone, and mixtures thereof.

The reaction mass containing the varenicline of formula I obtained in step-(b) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof, followed by isolation as solid from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure varenicline is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof. A most specific solvent is diisopropyl ether.

In another embodiment, the isolation is carried out by cooling the solution at a temperature of below 30°C for at least 30 minutes, specifically at about 0°C to about 30°C for about 1 hour to about 20 hours, and more specifically at about 0°C to about 25°C for about 2 hours to about 10 hours. The solid obtained is then recovered by techniques such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the solid is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

The pure varenicline obtained by the process disclosed herein may be further dried in, for example, a Vacuum Tray Dryer, a Rotocon Vacuum Dryer, a Vacuum Paddle Dryer or a pilot plant Rota vapor, to further lower residual solvents. Drying can be carried out under reduced pressure until the residual solvent content reduces to the desired amount such as an amount that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines.

In one embodiment, the drying is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm Hg, or below about 50 mm Hg, at temperatures such as about 35°C to about 70°C. The drying can be carried out for any desired time period that achieves the desired result, such as about 1 to 20 hours. Drying may also be carried out for

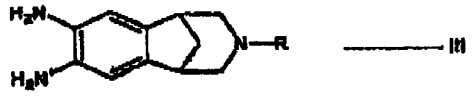
shorter or longer periods of time depending on the product specifications. Temperatures and pressures will be chosen based on the volatility of the solvent being used and the foregoing should be considered as only a general guidance. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, or using a fluidized bed drier, spin flash dryer, flash dryer and the like. Drying equipment selection is well within the ordinary skill in the art.

The varenicline of formula I obtained by the process disclosed herein has a purity (measured by High Performance Liquid Chromatography, hereinafter referred to as 'HPLC') greater than about 98%, specifically greater than about 99%, more specifically greater than about 99.5%, and still more specifically greater than about 99.9%. For example, the purity of the varenicline can be about 99% to about 99.95%, or about 99.5% to about 99.99%.

Pharmaceutically acceptable salts of varenicline can be prepared in high purity by using the substantially pure varenicline obtained by the methods disclosed herein, by known methods.

Exemplary pharmaceutically acceptable salts of varenicline are obtained from organic and inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, tartaric acid, derivatives of tartaric acid, fumaric acid, maleic acid, oxalic acid, acetic acid, propionic acid, succinic acid, mandelic acid, citric acid, and more preferable salt being varenicline tartrate.

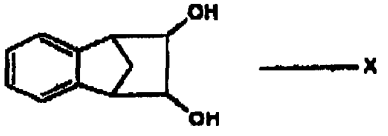
According to another aspect, there is provided a process for the preparation of the protected diaminoazatricyclo compound of formula III:



——— III

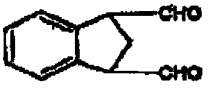
wherein 'R' represents a nitrogen protecting group, comprising:

a) oxidizing 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X:



——— X

in the presence of an oxidizing agent in a solvent, optionally in the presence of a phase transfer catalyst, to provide indane-1,3-dicarbaldehyde of formula IX:

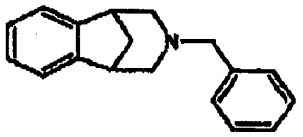


——— IX



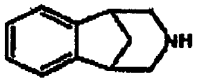
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b) reacting the compound of formula IX with benzyl amine in the presence of a reducing agent, optionally in the presence of a Lewis acid, in a solvent to provide 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII:



VIII

c) hydrogenating the compound of formula VIII using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide 10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VII:



VII

or an acid addition salt thereof, preferably hydrochloride salt, wherein the hydrogen source is a formate salt;

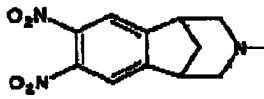
d) protecting the compound of formula VII with a nitrogen protecting group 'R' to provide a protected compound of formula VI:



VI

wherein 'R' represents a nitrogen protecting group;

e) nitrating the compound of formula VI in the presence of a mixture of nitric acid and sulfuric acid in a solvent, to provide a dinitro compound of formula V:



V

wherein R is as defined in formula VI; and

f) hydrogenating the compound of formula V using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide the protected diaminoazatricyclo compound of formula III, wherein the hydrogen source is a formate salt.

Exemplary nitrogen protecting group 'R' used in the compounds of formulae III, V and VI are selected from the group as described above. A most specific nitrogen protecting group is trifluoroacetyl.



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These groups may be added or removed by conventional methods used in peptide chemistry as described above.

Exemplary solvents used in step-(a) include, but are not limited to, water, an alcohol, a ketone, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; more specifically, the solvent is selected from the group consisting of water, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, and mixtures thereof; and a most specific solvent is a mixture of water and methylene chloride.

Exemplary oxidizing agents used in step-(a) include, but are not limited to, sodium periodate, sodium chlorate, sodium hypochlorite, collins reagent, barium permanganate, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), iodine/$K_2CO_3$, N-chlorosuccinimide/ dimethylsulfide, ceric ammonium nitrate, and the like. A specific oxidizing agent is sodium periodate. Collins reagent is the complex of chromium(VI) oxide with pyridine in dichloromethane. It is used to selectively oxidize primary alcohols to the aldehyde, and will tolerate many other functional groups within the molecule. It can be used as an alternative to the Jones reagent and pyridinium chlorochromate when oxidising secondary alcohols to ketones. Moreover, the Collins reagent is especially useful for oxidations of acid sensitive compounds.

In one embodiment, the oxidizing agent is used in a molar ratio of about 1 to 5 moles, specifically about 1 to 2 moles, per 1 mole of the 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X in order to ensure a proper course of the reaction.

The reaction in step-(a) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 40°C for at least 30 minutes, and more specifically at about 10°C to about 40°C from about 1 hour to about 5 hours.

In one embodiment, the oxidation in step-(a) is carried out in the presence of a phase transfer catalyst. A "phase transfer catalyst" refers to a catalyst or agent which is added to a reaction mixture of components, to transfer one or more of the reacting components to a location where it can conveniently and rapidly react with another reacting component.

Exemplary phase transfer catalysts for use herein include, but are not limited to, quaternary ammonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, phenyl lower alkyl group including a straight or branched alkyl group having 1 to 6 carbon atoms which is substituted by an aryl group and phenyl group, e.g., tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexyl ammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexylammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanylammonium chloride, benzyltripropylammonium chloride, benzyltriethyl ammonium chloride, phenyltriethylammonium chloride and the like; phosphonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., 1-dodecanylpyridinium chloride and the like.

Specific phase transfer catalysts are tetrabutylammonium bromide, tetrabutylphosphonium bromide, tetrabutylammonium chloride, tetrabutylphosphonium chloride, benzyltriethylammonium chloride, tetrabutylammonium hydrogen sulfate; and more specifically benzyltriethylammonium chloride or tetrabutylammonium bromide.

In one embodiment, the amount of the phase transfer catalyst employed is 0.5% w/w to about 10% w/w, and specifically from about 5% w/w to about 10% w/w.

The reaction mass containing the indane-1,3-dicarbaldehyde of formula IX obtained in step-(a) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII, or the compound of formula IX may be isolated and then used in the next step.

Exemplary solvents used in step-(b) include, but are not limited to, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester and the like, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate,

isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and more specifically, the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

The reducing agent used in step-(b) is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, diisobutyl aluminium hydride, borane and its derivatives. A specific reducing agent is sodium cyanoborohydride.

The Lewis acid used in step-(b) is selected from the group consisting of aluminium chloride, calcium chloride, boron triflouride and zinc chloride. A specific Lewis acid is aluminium chloride.

In one embodiment, the reducing agent is used in a molar ratio of about 1 to 5 moles, specifically about 2.5 to 3.5 moles, per 1 mole of the compound of formula IX in order to ensure a proper course of the reaction.

The reaction in step-(b) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 40°C for at least 30 minutes, and more specifically at about 10°C to about 40°C from about 1 hour to about 5 hours.

The reaction mass containing the 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VIII obtained in step-(b) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof. The reaction mass may be used directly in the next step to produce 10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VII, or the compound of formula VIII may be isolated and then used in the next step.

Exemplary solvents used in step-(c) include, but are not limited to, water, an alcohol, a ketone, a nitrile, an ester, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof; and a most specific solvent is methanol.

Exemplary hydrogenation catalysts used in step-(c) include, but are not limited to, platinum catalysts such as platinum plate, platinum sponge, platinum black, colloidal platinum, platinum oxide, platinum wire and the like; palladium catalysts such as palladium sponge, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on

carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate and the like; and nickel catalysts such as reduced nickel, nickel oxide, Raney nickel and the like. A specific hydrogenation catalyst is palladium hydroxide.

Exemplary formate salts used in step-(c) include, but are not limited to, ammonium formate, and an alkali metal salt of formic acid such as sodium formate and potassium formate. A specific formate salt is ammonium formate.

The reaction in step-(c) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, more specifically at a temperature of about 40°C to the reflux temperature of the solvent used for at least 20 minutes, and most specifically at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

The reaction mass containing the 10-aza-tricyclo[6.3.1.$0^{2.7}$]-dodeca-2(7),3,5-triene of formula VII obtained in step-(c) is optionally subjected to usual work up as described above. The reaction mass may be used directly in the next step to produce compound of formula VI, or the compound of formula VII may be isolated and then used in the next step, or the compound of formula VII may be converted into its acid addition salt followed by isolation and then used in the next step. In one embodiment, the compound of formula VII is converted into its acid addition salt by reaction with an acid in a solvent followed by isolation of an acid addition salt of the compound of formula VII as solid.

The acid addition salts are derived from a therapeutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid and, phosphoric acid, succinic acid, maleic acid, fumaric acid, citric acid, glutaric acid, citraconic acid, glutaconic acid, tartaric acid, di-p-toluoyl-L-(+)-tartrate, malic acid, and ascorbic acid. A specific acid addition salt of the compound of formula VII is hydrochloride.

The treatment of the compound of formula VII with acid is carried out in a solvent selected from the group consisting of a chlorinated solvent, a hydrocarbon solvent, an ether solvent, an alcoholic solvent, a ketonic solvent, an ester solvents, and mixtures thereof.

Nitrogen protecting groups 'R' as used in step-(d) are described above.

Exemplary solvents used in step-(e) include, but are not limited to, a cyclic ether, an aliphatic ether, a hydrocarbon, a chlorinated hydrocarbon, a nitrile, an ester, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate,

isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and more specifically, the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

In one embodiment, the sulfuric acid employed in step-(e) is in the form of concentrated sulfuric acid.

In another embodiment, the nitric acid employed in step-(e) is in the form of concentrated nitric acid, specifically 95% concentrated nitric acid and more specifically 100% concentrated nitric acid. In one embodiment, the nitric acid is fuming nitric acid.

The nitration reaction in step-(e) is carried out at a temperature below 40°C for about 3 hours to about 20 hours, and specifically at about 0°C to about 30°C for about 4 hours to about 10 hours.

The reaction mass containing the dinitro compound of formula V obtained in step-(e)is optionally subjected to usual work as described above. The reaction mass may be used directly in the next step to produce diamine compound of formula III, or the compound of formula V may be isolated and then used in the next step.

The isolation of the compound of formula V is performed from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure compound of formula V is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, methylene chloride, and mixtures thereof. Most specific solvents are water, methanol and mixtures thereof.

Exemplary solvents used in step-(f) include, but are not limited to, water, an alcohol, a ketone, a nitrile, an ester, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof; and a most specific solvent is methanol.

The hydrogenation catalyst used in step-(f) is selected from the group as described above. A specific hydrogenation catalyst is palladium hydroxide.

The formate salt used in step-(f) is selected from the group as described above. A specific formate salt is ammonium formate.

The reaction in step-(f) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, more specifically at a temperature of about 40°C to the reflux temperature of the solvent used for at least 20 minutes, and most specifically at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

The reaction mass containing the diaminoazatricyclo compound of formula III obtained in step-(f) is optionally subjected to usual work up such as a washing, an extraction, a layer separation, an evaporation, a filtration, a pH adjustment or a combination thereof, followed by isolation as solid from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof.

In one embodiment, the solvent used for isolating the pure diaminoazatricyclo compound of formula III is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof. A most specific solvent is diisopropyl ether.

The total purity of the diaminoazatricyclo compound of formula III obtained by the process disclosed herein is greater than about 98%, specifically greater than about 99%, and more specifically greater than about 99.5% as measured by HPLC.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

## EXAMPLES

### Example 1

**Preparation of 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene**

1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2,3-diol (100 g) was stirred in a mixture of water (2600 ml) and methylene chloride (1040 ml) under nitrogen at 10°C. This step was followed by the addition of sodium periodate (127.6 g) and triethylbenzyl ammonium chloride (10 g). The resulting mixture was stirred for 1 hour followed by aqueous/organic layer separation. The aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with water (4 x 1000 ml, or until no reaction to starch iodide was observed in the

aqueous wash) and then dried over sodium sulfate. Benzyl amine (63.86 g) was added to the resulting organic layer, the mixture was stirred for 1 minute at 25-30°C, and then immediately added to the suspension of sodiumcyanoborohydride (114.25 g) in methylene chloride (2000 ml) at 0°C in another reaction flask. The resulting orange mixture was warmed to 25-30°C and stirred for 30 minutes to 1 hour. The reaction mass was quenched by adding saturated sodium carbonate solution (1000 ml) and stirred for 1 hour (pH: 9). The layers were separated and the aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with saturated aqueous sodium chloride solution (2 x 600 ml) and dried over sodium sulfate followed by evaporation to afford a red oil. This oil was dissolved in a minimum of diethyl ether and filtered through a silica pad (3 x 4 inch) eluting with a mixture of 1000 ml of 15% ethyl acetate and 75% hexane solution to remove baseline red color. The resulting mass was concentrated under vacuum at 40-45°C to yield 95 g of 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$] dodeca-2(7),3,5-triene as yellow oil (Purity by HPLC: 99%).

**Example 2**

**Preparation of 10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt**

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene (94 g), ammonium formate (357 g) and 20% palladium hydroxide ( 7.5 g) were combined in methanol (1175 ml) and refluxed under nitrogen atmosphere for 30 minutes. The reaction mixture was cooled to 25°C and filtered through a celite pad which was rinsed with methanol. The filtrate was concentrated and the resulted residue was treated with a saturated aqueous sodium carbonate solution (940 ml) and the resulting mass was extracted with methylene chloride (940 ml). The two layers were separated and the aqueous layer was extracted with methylene chloride (500 ml). The organic layer was washed with saturated aqueous sodium chloride solution (940 ml), dried over sodium sulfate and concentrated. The residue was treated with ethyl acetate (94 ml) and cooled to 0-5°C. Cooling was followed by the addition of hydrochloride in ethyl acetate (150 ml) at 0-5°C and adjusting the pH to 1-2. The suspension was stirred at 0-5°C for 1 hour and the resulting white crystals were collected by filtration to produce 64 g of 10-aza-tricyclo [6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt (Purity by HPLC: 99.68%).

**Example 3**

**Preparation of 1-(10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone**

10-Aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-triene hydrochloride salt (60 g) was stirred in methylene chloride (600 ml) at 25-30°C, the mixture was cooled to 0°C, and then treated with pyridine (61.68 g), followed by the addition of trifluoroacetic anhydride (TFAA) (81.39 g) over 10 minutes. Aqueous hydrochloric acid solution (600 ml) was added to the resulting mass followed by the separation of layers. The aqueous layer was extracted with methylene chloride (2 x 300 ml) and the combined organic layer was washed with aqueous hydrochloric acid solution (300 ml), water (2 x 600 ml) and saturated aqueous sodium bicarbonate solution (600 ml). The resulting solution was dried over sodium sulfate followed by concentration under vacuum at below 40°C to afford a clear oil which was then crystallized to give 66 g of 1-(10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as white needles (Purity by HPLC: 99.33%).

**Example 4**

**Preparation of 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone**

Fuming nitric acid (39 g) was slowly added to a solution concentrated sulfuric acid (126.17 g) in methylene chloride (450 ml) followed by stirring at 0°C to generate a white precipitate. This step was followed by drop wise addition of a solution of 1-(10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (65 g) in methylene chloride (100 ml) through an addition funnel over 30 minutes. The reaction mixture was stirred for 2 hours 30 minutes at 0°C and then stirred for 4 hours at 25-30°C. The resulting mass was poured into a vigorously stirred mixture of water (650 ml) at 15-20°C. The resulting layers were separated and the aqueous layer was extracted with methylene chloride (1 x 325 ml). The organic layers were combined and washed with water (3 x 650 ml) and then dried over sodium sulfate and concentrated to afford a solid. The resulting solid was slurried with methanol (325 ml), filtered and dried to yield 60 g of 1-(4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as off-white solid (Purity by HPLC: 99.5%).

**Example 5**

**Preparation of 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-y1)-2,2,2-trifluoro-ethanone**

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2.7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (40 g), ammonium formate (114.28 g) and 20% palladium hydroxide (4 g) were combined in

methanol (400 ml) and refluxed for 30 minutes under a nitrogen atmosphere. The reaction mixture was cooled to 25°C and filtered through a celite pad which was rinsed with methanol. The filtrate was concentrated and the product was extracted with methylene chloride (200 ml) and water (200 ml). The resulting two layers were extracted with methylene chloride (200 ml). The organic layer was washed with saturated aqueous sodium chloride solution (200 ml), dried over sodium sulfate and then concentrated. The residue was crystallized with diisopropyl ether (400 ml) followed by filtration to yield 13 g of 1-(4,5-diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone as pink crystals (Purity by HPLC: 99%).

**Example 6**

**Preparation of 1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone**

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1 g), 50% solution of chloroacetaldehyde (0.27 g) in water and lead monoxide (0.39 g) were heated in 20% aqueous dimethyl sulfoxide (80: 20, dimethyl sulfoxide : water) (17 ml) at 60°C. The reaction mixture was stirred at 60°C for 30 minutes. A 50% solution of chloroacetaldehyde (0.13 g) in water was added to the reaction mixture and then heated to 90°C. The reaction mixture was stirred for 30 minutes at 90°C and followed by the addition of 50% solution of chloroacetaldehyde (0.15 g) in water at 90°C. The reaction mixture was stirred for 4-5 hours at 90-95°C. The resulting mass was cooled to 25-30°C followed by the addition of water (34 ml). The unreacted lead monoxide was filtered and washed with water (34 ml). The filtrate was extracted with methylene chloride (5 x 25 ml) at 25-30°C. All the organic layers were combined and washed with 1N hydrochloric acid (3 x 25 ml). The organic layer was dried over sodium sulfate and charcoalized. The methylene chloride layer was concentrated under vacuum at below 45°C followed by recrystallization in isopropyl alcohol to yield 0.6 g of 1-(5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (Purity by HPLC: 99.88%).

**Example 7**

**Preparation of 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine (Varenicline)**

1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (100 g) was slurried in methanol (1000 ml) followed by treatment with sodium

hydroxide (26 g) in water (50 ml). The mixture was heated for 1 hour at 40-45°C, the resulting mass concentrated under vacuum at below 45°C followed by treatment with water (500 ml) and then extracted with methylene chloride (2 x 1000 ml). The organic layer was washed with water (1000 ml) and then dried over anhydrous sodium sulfate. Methylene dichloride was distilled out under vacuum followed by crystallization in diisopropyl ether. The brownish color solid obtained was dried at 50-55°C to give 60 g of varenicline free base (Purity by HPLC: 99.8%).

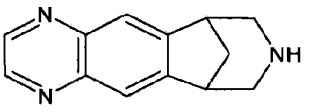
**Example 8**

**Preparation of 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (Varenicline tartrate)**

7,8,9,10-Tetrahydro-6,10-methano-6*H*-pyrazino-[2,3-h][3]benzazepine (50 g) was dissolved in methanol (375 ml) and the solution was added to a solution of tartaric acid (39.31 g) dissolved in methanol (375 ml) at 20-25°C. The suspension was stirred for 1 hour 30 minutes at 20-25°C followed by filtration of the solid and then drying to yield 82 g of varenicline tartrate (Purity by HPLC: 99.9%).

We claim:

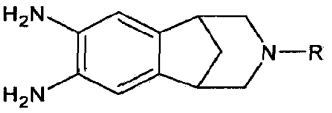
1. A process for the preparation of varenicline of formula I:



---------- I

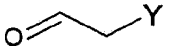
or a pharmaceutically acceptable salt thereof; comprising:

a) reacting a protected diaminoazatricyclo compound of formula III:



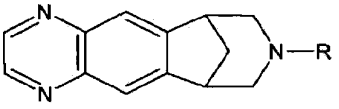
---------- III

wherein 'R' represents a nitrogen protecting group, with haloacetaldehyde compound of formula IV:



---------- IV

wherein 'Y' represents a halogen atom selected from the group consisting of F, Cl, Br and I; optionally in the presence of oxygen source, to provide a protected triazatetracyclo compound of formula II:



---------- II

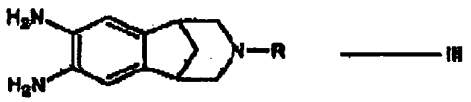
wherein R is as defined in formula III; and

b) deprotecting the compound of formula II to provide pure varenicline of formula I, and optionally converting the varenicline obtained into a pharmaceutically acceptable salt thereof.

2. The process of claim 1, wherein the reaction in step-(a) is carried out in the presence of a solvent selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, acetone, methyl isobutyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, acetonitrile, propionitrile, ethyl acetate, isopropyl acetate, and mixtures thereof.

3. The process of claim 2, wherein the solvent is selected from the group consisting of water, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and mixtures thereof.

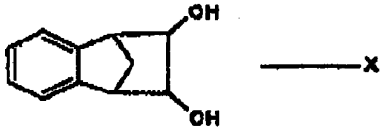
4. The process of claim 1, wherein the oxygen source employed in step-(a) is selected from the group consisting of lead monoxide, manganese dioxide, mercuric iodide and ceric ammonium nitrate.
5. The process of claim 1, wherein the condensation reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used.
6. The process of claim 5, wherein the reaction is carried out at the reflux temperature of the solvent used for about 2 hours to about 10 hours.
7. The process of claim 1, wherein the nitrogen protecting group 'R' is selected from the group consisting of acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl.
8. The process of claim 7, wherein the nitrogen protecting group 'R' is trifluoroacetyl or t-butoxycarbonyl.
9. The process of claim 1, wherein the halogen atom 'Y' in the compound of formula IV is Cl.
10. The process of claim 1, wherein the varenicline of formula I obtained in step-(b) is isolated from a solvent by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof; wherein the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof.
11. The process of claim 1, wherein the pharmaceutically acceptable salt of varenicline is a hydrochloride salt, a hydrobromide salt, a sulfate salt, a phosphate salt, a tartrate salt, a fumarate salt, a maleate salt, an oxalate salt, an acetate, a propionate salt, a succinate salt, a citrate salt, or a mandelate salt.
12. The process of claim 1, wherein the varenicline of formula I or a pharmaceutically acceptable salt obtained has a purity of about 99% to about 99.95% as measured by HPLC.
13. A process for the preparation of a protected diaminoazatricyclo compound of formula III:



III

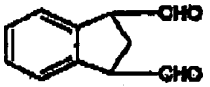
wherein 'R' represents a nitrogen protecting group, comprising:

a) oxidizing 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol of formula X:



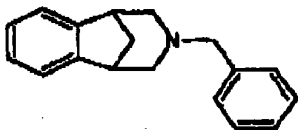
X

in the presence of an oxidizing agent in a solvent, optionally in the presence of a phase transfer catalyst, to provide indane-1,3-dicarbaldehyde of formula IX:



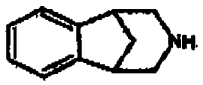
IX

b) reacting the compound of formula IX with benzyl amine in the presence of a reducing agent, optionally in the presence of a Lewis acid, in a solvent to provide 10-benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VIII:



VIII

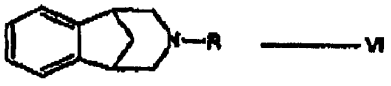
c) hydrogenating the compound of formula VIII using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide 10-aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene of formula VII:



VII

or an acid addition salt thereof, wherein the hydrogen source is a formate salt;

d) protecting the compound of formula VII with a nitrogen protecting group 'R' to provide a protected compound of formula VI:



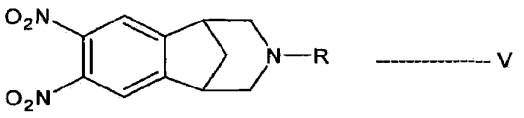
VI

wherein 'R' represents a nitrogen protecting group;



RECTIFIED SHEET (RULE 91) ISA/EP

e) nitrating the compound of formula VI in the presence of a mixture of nitric acid and sulfuric acid in a solvent, to provide a dinitro compound of formula V:



wherein R is as defined in formula VI; and

f) hydrogenating the compound of formula V using a hydrogenation catalyst in the presence of a hydrogen source in a solvent to provide the protected diaminoazatricyclo compound of formula III, wherein the hydrogen source is a formate salt.

14. The process of claim 13, wherein the nitrogen protecting group 'R' in the compounds of formulae III, V and VI is selected from the group consisting of acetyl, trifluoroacetyl, trichloroacetyl, pyrrolidinylmethyl, cumyl, benzhydryl, trityl, benzyloxycarbonyl (Cbz), 9-fluorenylmethyloxy carbonyl (Fmoc), benzyloxymethyl (BOM), pivaloyloxymethyl (POM), trichloroethxoycarbonyl (Troc), 1-adamantyloxycarbonyl (Adoc), allyl, allyloxycarbonyl, trimethylsilyl, tert.-butyldimethylsilyl, triethylsilyl (TES), triisopropylsilyl, trimethylsilylethoxymethyl (SEM), t-butoxycarbonyl (BOC), t-butyl, 1-methyl-1,1-dimethylbenzyl, pyrridinyl and pivaloyl.

15. The process of claim 14, wherein the nitrogen protecting group 'R' is trifluoroacetyl.

16. The process of claim 13, wherein the solvent used in step-(a) is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof.

17. The process of claim 16, wherein the solvent is a mixture of water and methylene chloride.

18. The process of claim 13, wherein the oxidizing agent used in step-(a) is selected from the group consisting of sodium periodate, sodium chlorate, sodium hypochlorite, collins reagent, barium permanganate, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO), iodine/$K_2CO_3$, N-chlorosuccinimide/ dimethylsulfide and ceric ammonium nitrate.

19. The process of claim 13, wherein the reaction in step-(a) is carried out at a temperature of about 0°C to about 40°C for at least 30 minutes.

20. The process of claim 13, wherein the oxidation in step-(a) is carried out in the presence of a phase transfer catalyst, wherein the phase transfer catalyst is selected from the group consisting of tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutyl ammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzyl ammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexyl ammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanyl ammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethyl ammonium chloride, tetrabutylphosphonium chloride and 1-dodecanylpyridinium chloride.

21. The process of claim 20, wherein the phase transfer catalyst is benzyltriethylammonium chloride or tetrabutylammonium bromide.

22. The process of claim 13, wherein the solvent used in steps-(b) and (e) is, each independently, selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, acetonitrile, ethyl acetate, isopropyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof.

23. The process of claim 22, wherein the solvent is selected from the group consisting of methylene chloride, toluene, and mixtures thereof.

24. The process of claim 13, wherein the reducing agent used in step-(b) is selected from the group consisting of sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride, diisobutyl aluminium hydride, borane and its derivatives; and wherein the Lewis acid is selected from the group consisting of aluminium chloride, calcium chloride, boron triflouride and zinc chloride.

25. The process of claim 24, wherein the reducing agent is sodium cyanoborohydride; and wherein the Lewis acid is aluminium chloride.

26. The process of claim 13, wherein the solvent used in steps-(c) and (f) is, each independently, selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, n-propanol, tert-butanol, n-butanol, amyl alcohol, hexanol, acetone, methyl isobutyl ketone, tetrahydrofuran, acetonitrile, ethyl acetate, isopropyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof.

27. The process of claim 26, wherein the solvent is methanol.

28. The process of claim 13, wherein the hydrogenation catalyst used in steps-(c) and (f) is, each independently, selected from the group consisting of platinum plate, platinum sponge, platinum black, colloidal platinum, platinum oxide, platinum wire, palladium sponge, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, reduced nickel, nickel oxide and Raney nickel.

29. The process of claim 28, wherein the hydrogenation catalyst is palladium hydroxide.

30. The process of claim 13, wherein the formate salt used in steps-(c) and (f) is, each independently, selected from the group consisting of ammonium formate, sodium formate and potassium formate.

31. The process of claim 13, wherein the reaction in steps-(c) and (f) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used.

32. The process of claim 31, wherein the reaction is carried out at the reflux temperature of the solvent used for about 30 minutes to about 5 hours.

33. The process of claim 13, wherein the reaction in step-(e) is carried out at a temperature of about 0°C to about 30°C for about 3 hours to about 20 hours.

34. The process of claim 13, wherein the diaminoazatricyclo compound of formula III obtained in step-(f) is isolated from a solvent by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum drying, spray drying, freeze drying, or a combination thereof; wherein the solvent is selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, t-butanol, acetone, tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, monoglyme, diglyme, and mixtures thereof.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/007081

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08

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)
C07D

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)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | US 2002/072524 A1 (WADSWORTH JOTHAM [US] ET AL) 13 June 2002 (2002-06-13)<br>scheme 4 and p. 9 paragraphs 0075-0080;<br>scheme 8 and scheme 1<br>----- | 13-34<br>1-12 |
| Y | DAS ET AL: "An efficient and convenient protocol for the synthesis of quinoxalines and dihydropyrazines via cyclization-oxidation processes using HClO4.SiO2 as a heterogeneous recyclable catalyst"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL,<br>vol. 48, no. 31, 4 July 2007 (2007-07-04), pages 5371-5374, XP022141736<br>ISSN: 0040-4039<br>Scheme 1<br>-----<br>-/-- | 1-12 |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 December 2009 | 21/01/2010 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040.<br>Fax: (+31-70) 340-3016 | Wolf, Claudia |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/007081

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 2004/108725 A1 (PFIZER PROD INC [US]; RAINVILLE JOSEPH PHILIP [US]; TABER GERALDINE PA)<br>16 December 2004 (2004-12-16)<br>cited in the application<br>claim 1;<br>----- | 1-34 |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/007081

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | JP 2006526607 T | 24-11-2006 |
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| | | SI 1638971 T1 | 31-12-2008 |
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| | | US 2007185327 A1 | 09-08-2007 |

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(74) Agent: **ONC Lawyers**; Unit 1510, No.9 Queen's Road Central, Hong Kong (CN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *of inventorship (Rule 4.17(iv))*

**Published**:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: ELECTRONIC SMOKE

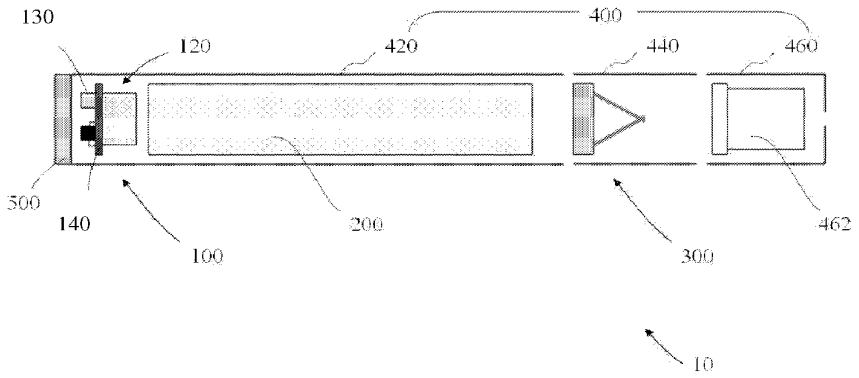



Figure 8

(57) Abstract: An electronic smoke comprising an inhale detector and a smoke effect generating circuitry. The inhale detector comprises an air-flow sensor which is arranged to detect direction and rate of air flow through the smoke apparatus, and the smoke effect generating circuitry is arranged to operate the smoke effect generating circuitry to generate smoking effect when the air flow direction corresponds to inhaling through the apparatus and the air flow rate reaches at predetermined threshold. Such an electronic smoke alleviates the problem of inadvertent triggering due to environmental vibration or noise or children playing by blowing into the device.

WO 2011/033396 A2

# ELECTRONIC SMOKE

## Field of the Invention

The present invention relates to electronic smoke apparatus (or electronic smoke in short), and more particularly to electronic cigarettes. The present invention also relates to air-flow rate and direction detector for use in an electronic smoke apparatus.

## Background of the Invention

Electronic smoke apparatus such as electronic cigarettes provide a smoking alternative to smokers. An electronic smoke is a non-naked flame smoking apparatus which typically comprises a battery powered heater arranged to vaporize liquid nicotine or nicotine substitutes upon actuation by a user. The heater is usually automatically actuated by a controller when a user inhales through the electronic smoke to simulate a smoking action. Typically, an inhaling detector is provided in an electronic smoke and the controller, such as a digital signal processor (DSP) will actuate the heater when inhaling is detected by the inhaling detector. An exemplary equivalent application circuit of a conventional electronic cigarette is shown in Figure 1.

The inhaling detector of a conventional electronic smoke apparatus typically comprises an air-flow sensor having a structure similar to that of a conventional microphone condenser of Figure 2. A typical air-flow sensor of a conventional electronic smoke comprises a variable capacitor (Cs) comprising a membrane and a

back plate, a pre-charged electret layer (Vs), and a junction field effect transistor (JFET) arranged as schematically shown in Figure 2. The DSP of the smoking circuitry is arranged to actuate the heater automatically when vibration, which is assumed to be due to inhaling, is detected by the air-flow sensor. However, such an arrangement is not very reliable since false actuations are common, especially in a noisy environment. Furthermore, the structure of a conventional air-flow sensor is relatively complicated and more expensive, since a JFET stage is required to amplify signals detected by the vibrating membrane and an electret layer is in combination with a back plate to form a reference capacitive surface.

Therefore, it would be advantageous if an improved air-flow sensor for an electronic smoke could be provided.

In this specification, the terms electronic smoke and electronic smoke apparatus are equivalent and includes electronic smoke apparatus which are commonly known as electronic cigarettes, electronic cigar, e-cigarette, personal vaporizers etc., without loss of generality.

**Summary of Invention**

According to the present invention, there is provided an electronic smoke comprising an inhale detector and a smoke effect generating circuitry, wherein the inhale detector comprises an air-flow sensor which is arranged to detect direction and rate of air flow through the smoke apparatus, and wherein the smoke effect generating circuitry is arranged to operate the smoke effect generating circuitry to generate smoking effect when the air flow direction corresponds to inhaling through the

apparatus and the air flow rate reaches at predetermined threshold. Such an electronic smoke alleviates the problem of inadvertent triggering due to environmental vibration or noise or children playing by blowing into the device.

In an embodiment, the air-flow sensor may comprise an air-baffle surface which is adapted to deform in response to movement of air through the apparatus, the extent of deformation of the air-baffle surface being measured to determine both the direction and rate of air flow through the apparatus. Measure of deformation within a predetermined period of time further mitigates the risk of inadvertent triggering due to vibrations or environmental noise.

As an example, the capacitance or the change in capacitance of the air-flow sensor may be measured to determine the extent of deformation of the air-baffle surface.

In an embodiment, the smoke effect generating circuitry may comprise a processor which is adapted to measure the capacitance or change in capacitance of the air-flow sensor. As a controller or processor is usually require to operate the heater of the smoke, measuring the capacitance or change in capacitance by the processor means an unexpected cost effective solution.

As a further example, the air-flow sensor may form part of an oscillator circuit, and the processor is arranged to measure the oscillation frequency of the oscillation circuit to determine the air-flow rate and direction. As the oscillation frequency of an oscillator circuit, especially an LC oscillator circuit, is dependent on the capacitance value, this provides a cost effective solution to provide a low cost and compact

solution.

As an example, the predetermined threshold of air flow rate may correspond to the flow rate of a typical smoke inhaling action by a user through the apparatus. This would operate to prevent triggering of the smoke generating circuitry by mischief or accidental vibration or noise.

In an embodiment, the air-flow sensor may comprise a conductive air baffle surface which is spaced apart from a base conductive surface, and the air baffle surface is adapted to deform in response to air flow through the apparatus; characterized in that the variation in capacitance between the baffle surface and the base surface is indicative of the direction and rate of air flow.

In another aspect of the present invention, there is provided an air-flow rate and direction detector comprising an air-flow sensor and a controller, wherein the air flow sensor comprises a baffle surface which is adapted to deform in response air flow, and the controller is adapted to determine the air-flow rate and direction with reference to the extent of deformation of the baffle surface.

The controller of the detector may be adapted to determine the air-flow rate and direction with reference to the capacitance or variation of capacitance of the air-flow sensor.

The controller may comprise an oscillation circuit, and the air-flow rate sensor forms part of the oscillator circuit; characterized in that the controller is adapted to determine the air-flow rate and direction with reference to the oscillator frequency or

variation in oscillator frequency of the oscillator.

The detector may be adapted for use in electronic cigarettes or smoke for heater triggering, or in articles operated by suction- or blowing, such as wind-blow instruments like electronic recorders or toys.

**Brief Description of Figures**

Embodiments of the present invention will be explained below by way of example with reference to the accompanying drawings, in which:-

Figure 1 is a schematic equivalent circuit diagram of an actuation circuit of a conventional electronic smoke,

Figure 2 is a schematic diagram of an air-flow sensor typically used in a conventional electronic smoke,

Figure 3 is a schematic diagram of an actuation circuit of an electronic smoke according to an embodiment of an electronic smoke of the present invention,

Figure 4 is a schematic diagram of an air-flow sensor for an electronic smoke according to an embodiment of the present invention,

Figure 5 shows an exemplary relationship between capacitance and air-flow rate of the air-flow sensor of Figure 4,

Figures 6A, 6B and 6C are schematic diagrams illustrating the air-flow sensor of Figure 4 in standby mode (no air flow), under inhaling condition (suction), and under exhaling condition (blowing) respectively,

Figure 7 is a schematic equivalent circuit diagram of an embodiment of an electronic smoke according to the present invention, and

Figure 8 is a schematic diagram illustrating an exemplary embodiment of an electronic smoke of the present invention.

**Detailed Description of Exemplary Embodiments**

The electronic cigarette (10) as an example of an electronic smoke as shown in Figure 8 comprises an inhale detector (100) as an example of an air-flow rate and direction detector, a battery (200) as an example of stored power source, a nicotine source as a example of a smoke or favor (or aroma) source, and a heating element (300) as a heating means. The inhale detector, the battery and the heating element are all housed within a main housing (400) which comprises a first tubular portion (420) in which the battery and the inhale detector are mounted, a second tubular portion (440) in which the heating element and the nicotine source are mounted, and a third tubular portion (460) containing a mouth piece (462). In addition, a transparent or translucent cover (500) is attached to the downstream end of the first tubular portion.

The inhale detector is a modular assembly comprising an air-flow sensor (120), an actuation circuit and an LED light source (130), which are all mounted on a printed circuit board (140). Referring to Figure 4, the air-flow sensor comprises a rigid or semi-rigid conductive membrane (121), such as a metallic sheet which are mounted above a conductive back plate (122) in a spaced apart manner and separated by an insulating spacer (123). The sub-assembly comprising the conductive membrane and the conductive back plate arranged in a spaced apart and substantially parallel

manner forms a capacitive component, the instantaneous capacitance value or variation in capacitance value of which will be utilized in a manner to be discussed in more detail below.

As the conductive will need to respond rapidly to repeated inhaling and to return to its neutral or standby condition quickly or immediately after inhaling stops, a metallic sheet having a good axial resilience property is preferred to be used as the conductive membrane. The conductive back plate is connected to an earth plate (124), which is in turn mounted on a PCB, by a conductive ring (125) to form a reference ground of the capacitive component. This sub-assembly of the air-flow senor and PCB is housed within a metallic can (126) which defines an air inlet and an air outlet at its axial ends.

The capacitive properties of the air-flow sensor of Figure 4 would be readily apparent from the schematic representations of Figures 6A to 6C. The schematic diagram of Figure 6A shows the air-flow sensor when there is no or negligible air flow through the sensor. In this condition, the conductive membrane and the conductive back plate are substantially parallel with a separation distance d. The capacitive value of the sensor in this stand-by or rest condition is given by the relationship $C=\varepsilon A/d$, where C is the capacitance, $\varepsilon$ is the dielectric constant of the spacing medium, and is the overlapping surface area between the conductive membrane and the back plate. As an example, the capacitance value of a sensor with a diameter or 8 mm and a separation of 0.04mm is about 10pF.

When air flows through the air-flow sensor in the direction as shown in Figure

6B, suction due to the air flow will cause the resilient metallic membrane to bulge away from the back plate. As the separation (d) between the metallic membrane and the back plate increases in general under this condition, the capacitance value of the air-flow sensor will decrease in response to air flow in this direction.

On the other hand, when air flows in an opposite direction as shown in Figure 6B, the resilient membrane is caused to deflect towards the back plate. As the separation distance between the metallic membrane and the back plate will decrease in general in this condition, the capacitance value will increase in response to air flow of this direction.

In ether cases, the resilience of the metallic membrane will return the membrane to the neutral condition of Figure 6A when the air flow stops or when the air-flow rate is too low to cause instantaneous deflection or deformation of the metallic membrane. An exemplary variation of capacitance value of the air-rate sensor in response to air flow in the direction of Figure 6B is shown in Figure 5.

An application of the air flow sensor of Figure 4 is depicted in an exemplary circuit of Figure 7. Referring to Figure 7, the air-flow sensor (marked CAP) is connected to a capacitance value measurement unit (150). The result of the capacitance value is transmitted to a microcontroller (160). If the result of the capacitance value measurement corresponds to a suction action of a sufficient air-flow rate, the microcontroller will send an actuation signal to operate the heater to cause vaporization of the nicotine stored in a nicotine pool. The nicotine vapor will be inhaled by a user through the mouth piece as a result of the inhaling action. The

heater is connected to the BAT terminal of the circuit of Figure 7. In addition, the actuation signal will also operate an LED driver (170) to operate an LED light source to provide a smoking indicator as a decoration.

To provide a simplified capacitance measurement arrangement, a digital signal processor (DSP) (180) is used as an example of the controller, and the air-flow sensor is used as a capacitor of an oscillator circuit of the DSP. In this regards, the capacitive output terminals of the air-flow sensor are connected to the oscillator input terminals of the DSP. Instead of measuring the actual capacitance of the air flow sensor, the present arrangement uses a simplified way to determine the capacitance value or the variation in capacitance by measuring the instantaneous oscillation frequency of the oscillator circuit or the instantaneous variation in oscillation frequency of the oscillator circuit compared to the neutral state frequency to determine the instantaneous capacitance value or the instantaneous variation in capacitance value. For example, the oscillation frequency of an oscillator circuit increases and decreases respectively when the capacitor forming part of the oscillator decreases and increases.

To utilize these frequency characteristics, the neutral frequency of the oscillator, that is, the oscillation frequency of the oscillator circuit of the DSP with the air-flow sensor in the condition of Figure 6A is calibrated or calculated and then stored as a reference oscillation reference. The variation in oscillation frequency in response to a suction action is plotted against flow rate so that the DSP would send an actuation signal to the heater or the heater switch when an inhaling action reaching a threshold air-flow rate has been detected. On the other hand, the DSP will not actuate the heater if the action is a blowing action to mitigate false heater triggering.

Naturally, the detection threshold frequency would depend on the orientation of the air-flow sensor. For example, if the air-flow sensor is disposed within the main housing with the upper aperture facing the LED end of the electronic smoke, an increase in oscillation frequency (due to decrease in capacitance as Figure 6B) of a sufficient threshold would correspond to a suction action of a threshold air-flow rate requiring heating activation, while a decrease in oscillation frequency (due to increase in capacitance as Figure 6C) would correspond to a blowing action requiring no heating activation regardless of the air flow rate.

On the other hand, if the air-flow sensor is disposed in an opposite orientation such that the lower aperture is opposite the LED end, an increase in oscillation frequency (due to decrease in capacitance as Figure 6B) of a sufficient threshold would correspond to a blowing action requiring no heater activation regardless of the air flow rate, while a decrease in oscillation frequency (due to increase in capacitance as Figure 6C) would correspond to a suction action requiring heating activation when a threshold deviation in frequency is detected.

The schematic equivalent circuit of Figure 3 provides an useful reference to the characteristics above.

While the present invention has been explained with reference to the embodiments above, it will be appreciated that the embodiments are only for illustrations and should not be used as restrictive example when interpreting the scope of the invention.

**Table of Numerals**

| | | | |
|---|---|---|---|
| 10 | Electronic cigarette | | |
| 100 | Inhale detector | | |
| | 120 | | Air-flow sensor |
| | | 121 | Conductive membrane |
| | | 122 | Conductive back plate |
| | | 123 | Insulating spacer |
| | | 124 | Earth plate |
| | | 125 | Conductive ring |
| | | 126 | Metallic can |
| | 130 | | LED light source |
| | 140 | | Printed Circuit Board |
| | 150 | | Capacitance measurement unit |
| | 160 | | Microcontroller |
| | 170 | | LED driver |
| | 180 | | Digital signal processor (DSP) |
| 200 | Battery | | |
| 300 | Heating element | | |
| 400 | Main housing | | |
| | 420 | | First tubular portion |
| | 440 | | Second tubular portion |
| | 460 | | Third tubular portion |
| | | 462 | Mouth piece |
| 500 | Cover | | |

**CLAIMS:**

1. An electronic smoke apparatus comprising an inhale detector and a smoke effect generating circuitry, wherein the inhale detector comprises an air-flow sensor which is arranged to detect direction and rate of air flow through the smoke apparatus, and wherein the smoke effect generating circuitry is arranged to operate the smoke effect generating circuitry to generate smoking effect when the air flow direction corresponds to inhaling through the apparatus and the air flow rate reaches at predetermined threshold.

2. An apparatus according to Claim 1, wherein the air-flow sensor comprises an air-baffle surface which is adapted to deform in response to movement of air through the apparatus, the extent of deformation of the air-baffle surface being measured to determine both the direction and rate of air flow through the apparatus.

3. An apparatus according to Claim 2, wherein the capacitance or the change in capacitance of the air-flow sensor is measured to determine the extent of deformation of the air-baffle surface.

4. An apparatus according to any of the preceding Claims, wherein the smoke effect generating circuitry comprises a processor which is adapted to measure the capacitance or change in capacitance of the air-flow sensor.

5. An apparatus according to Claim 4, wherein the air-flow sensor forms part of an oscillator circuit, and the processor is arranged to measure the oscillation

frequency of the oscillation circuit to determine the air-flow rate and direction.

6. An apparatus according to any of the preceding Claims, wherein the predetermined threshold of air flow rate corresponds to the flow rate of a typical smoke inhaling action by a user through the apparatus.

7. An apparatus according to any of the preceding Claims, wherein the air-flow sensor comprises a conductive air baffle surface which is spaced apart from a base conductive surface, and the air baffle surface is adapted to deform in response to air flow through the apparatus; characterized in that the variation in capacitance between the baffle surface and the base surface is indicative of the direction and rate of air flow.

8. An air-flow rate and direction detector comprising an air-flow sensor and a controller, wherein the air flow sensor comprises a baffle surface which is adapted to deform in response air flow, and the controller is adapted to determine the air-flow rate and direction with reference to the extent of deformation of the baffle surface.

9. A detector according to Claim 8, wherein the controller is adapted to determine the air-flow rate and direction with reference to the capacitance or variation of capacitance of the air-flow sensor.

10. A detector according to Claim 9, wherein the controller comprises an oscillation circuit, and the air-flow rate sensor forms part of the oscillator circuit; characterized in that the controller is adapted to determine the air-flow rate and

direction with reference to the oscillator frequency or variation in oscillator frequency of the oscillator.

11. A detector according to any of Claims 8-10, wherein the detector is adapted for use in an electronic smoke apparatus or in a wind-instrument.

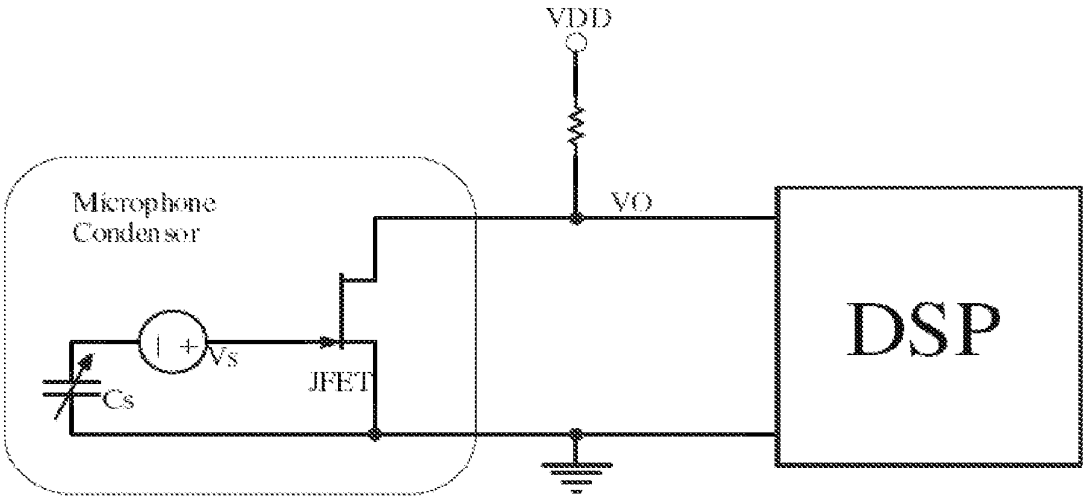



**Figure 1 (Prior Art)**

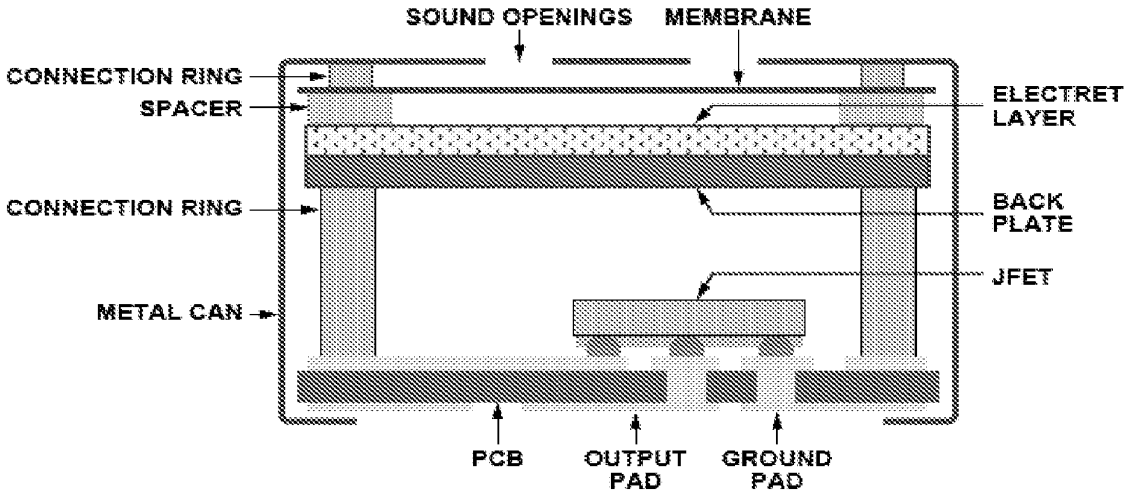



**Figure 2 (Prior Art)**

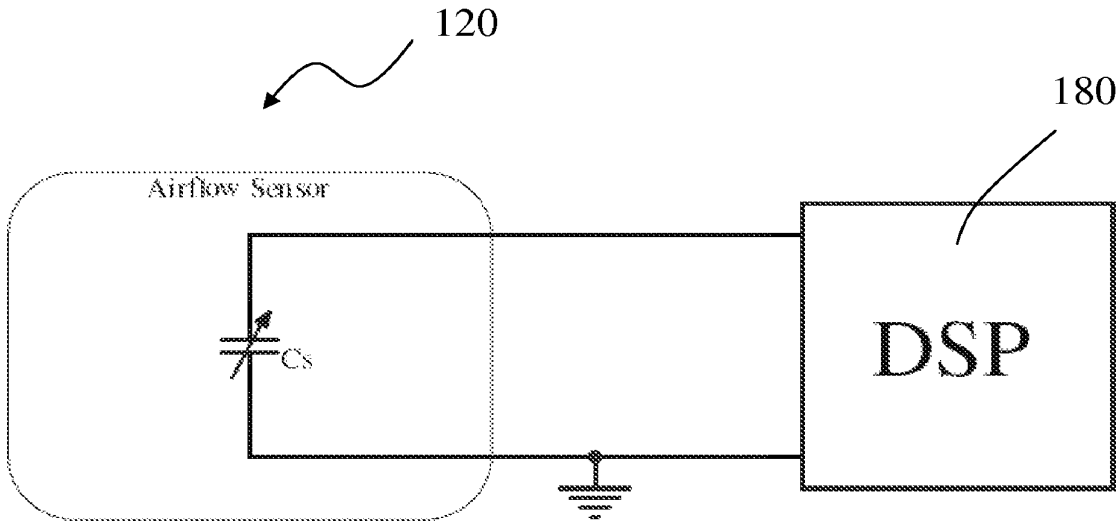



**Figure 3**

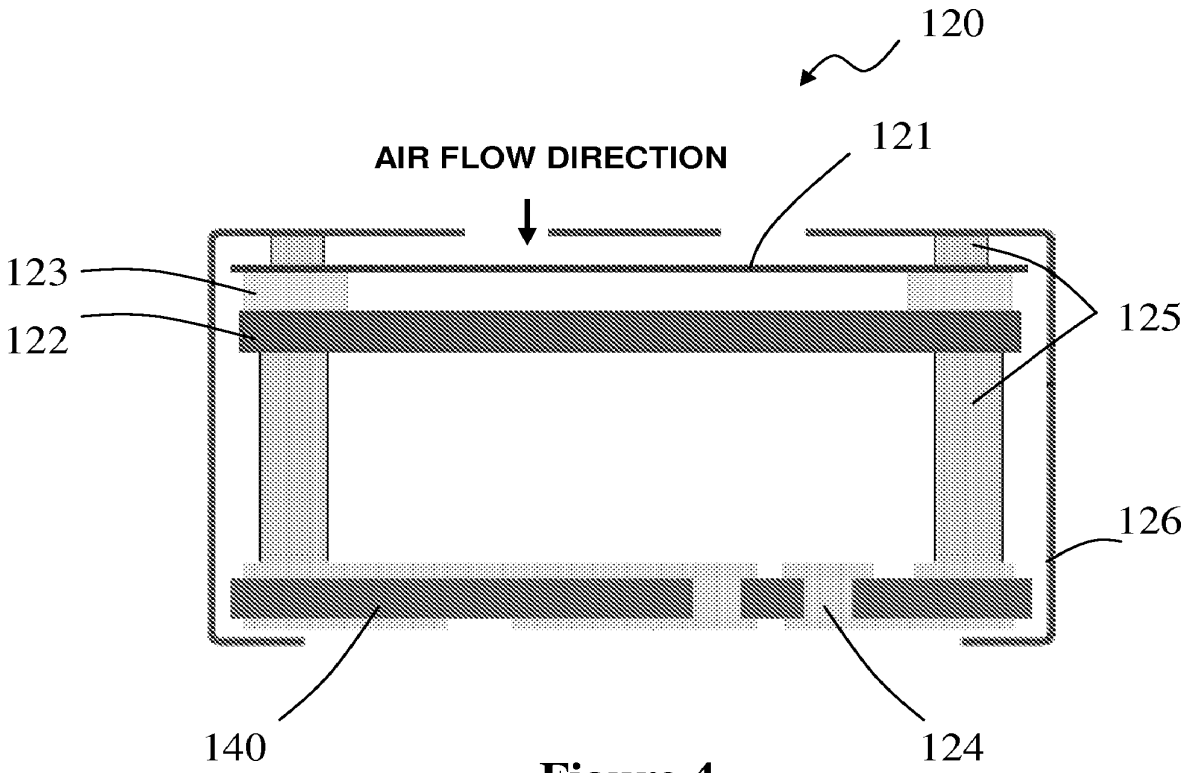



**Figure 4**

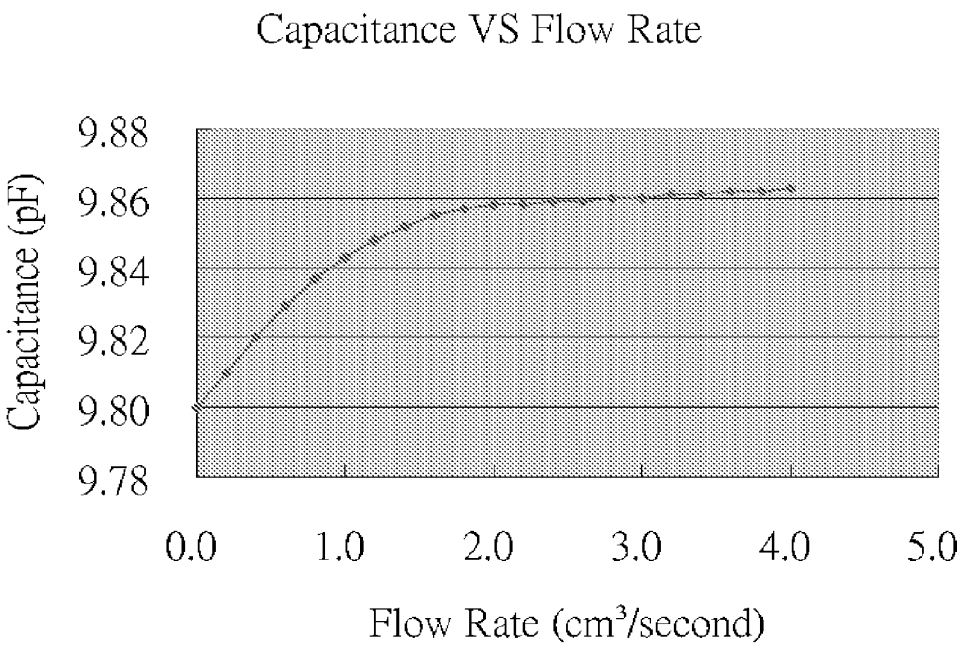



**Figure 5**

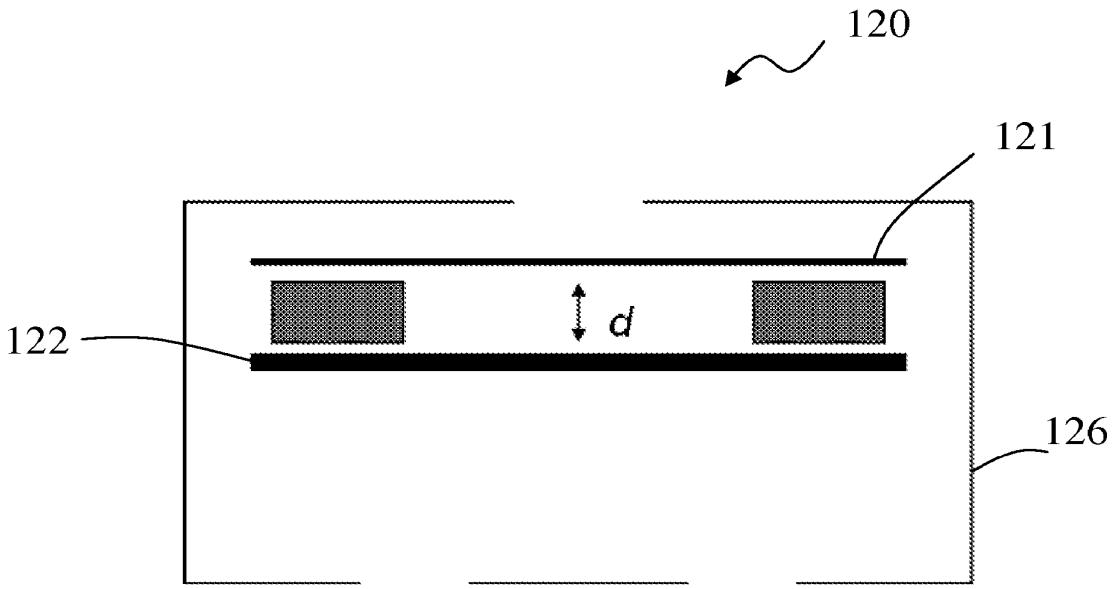



**Figure 6A**

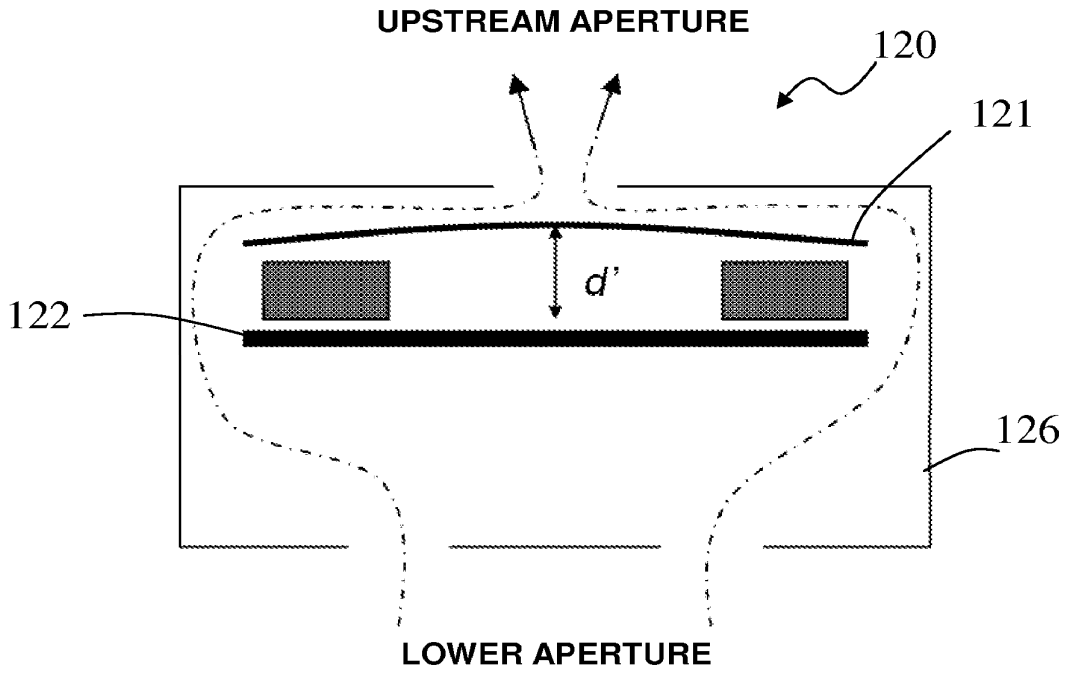



**Figure 6B**

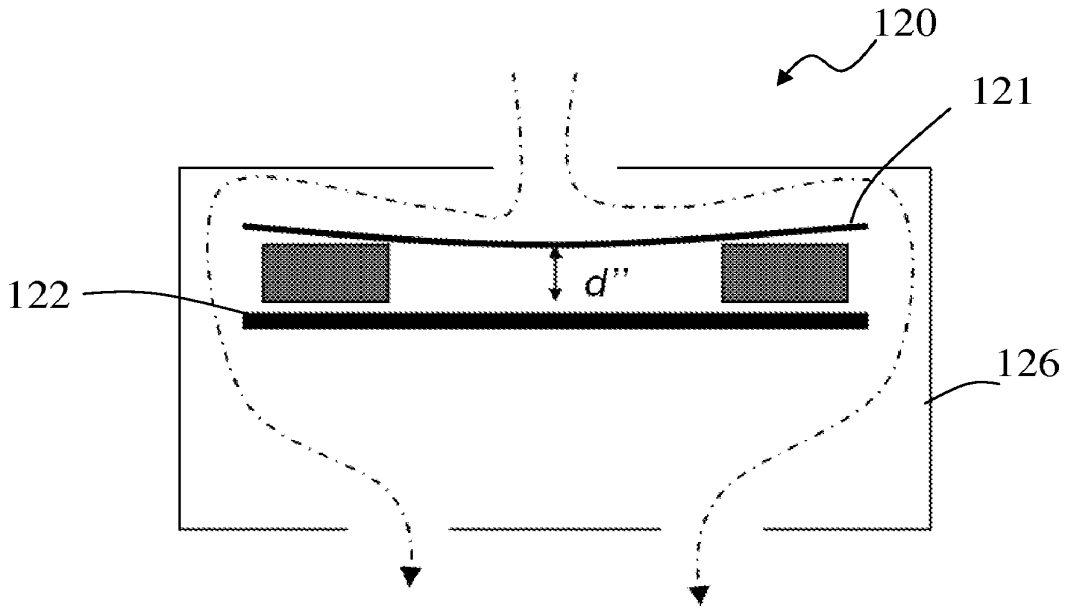



**Figure 6C**

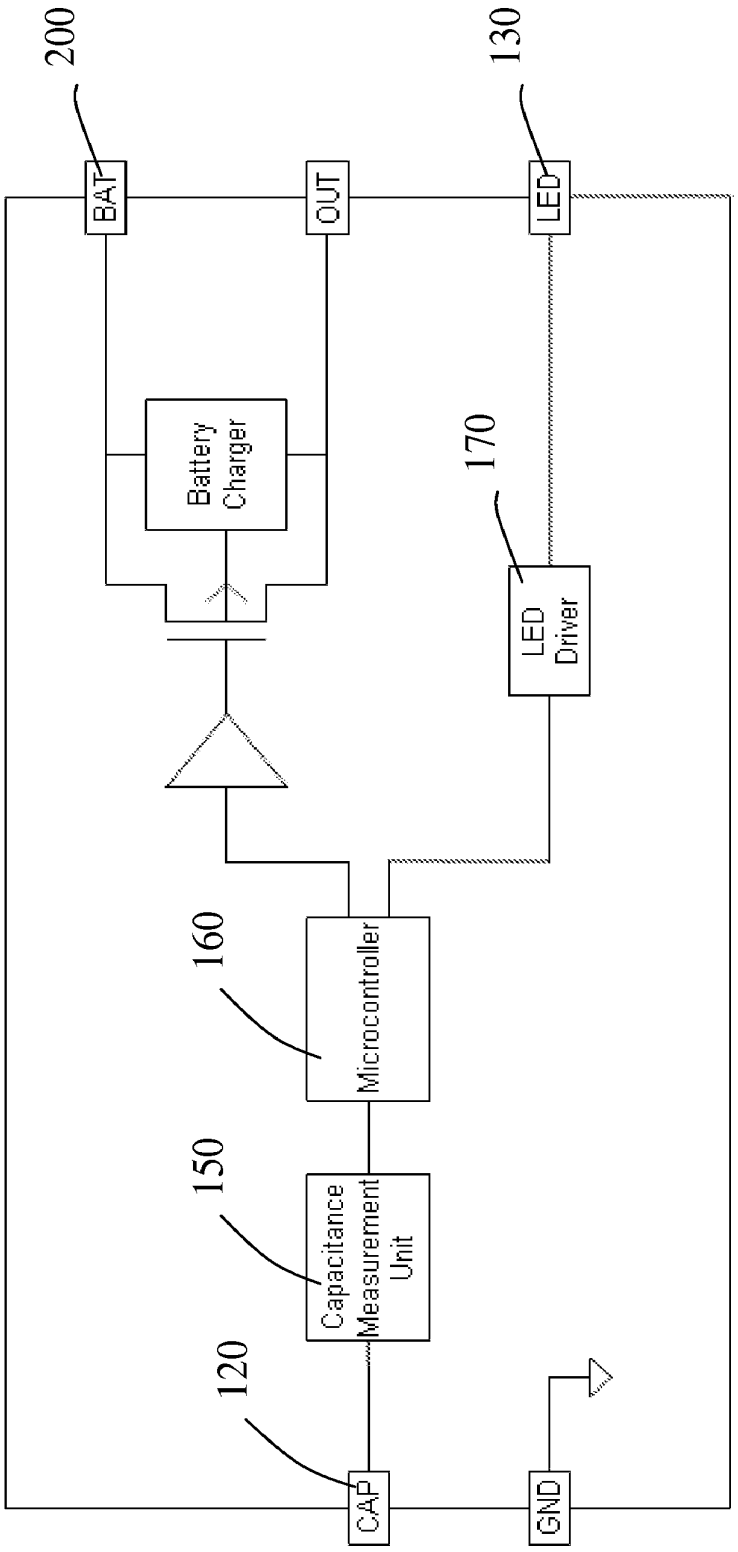



Figure 7

1365

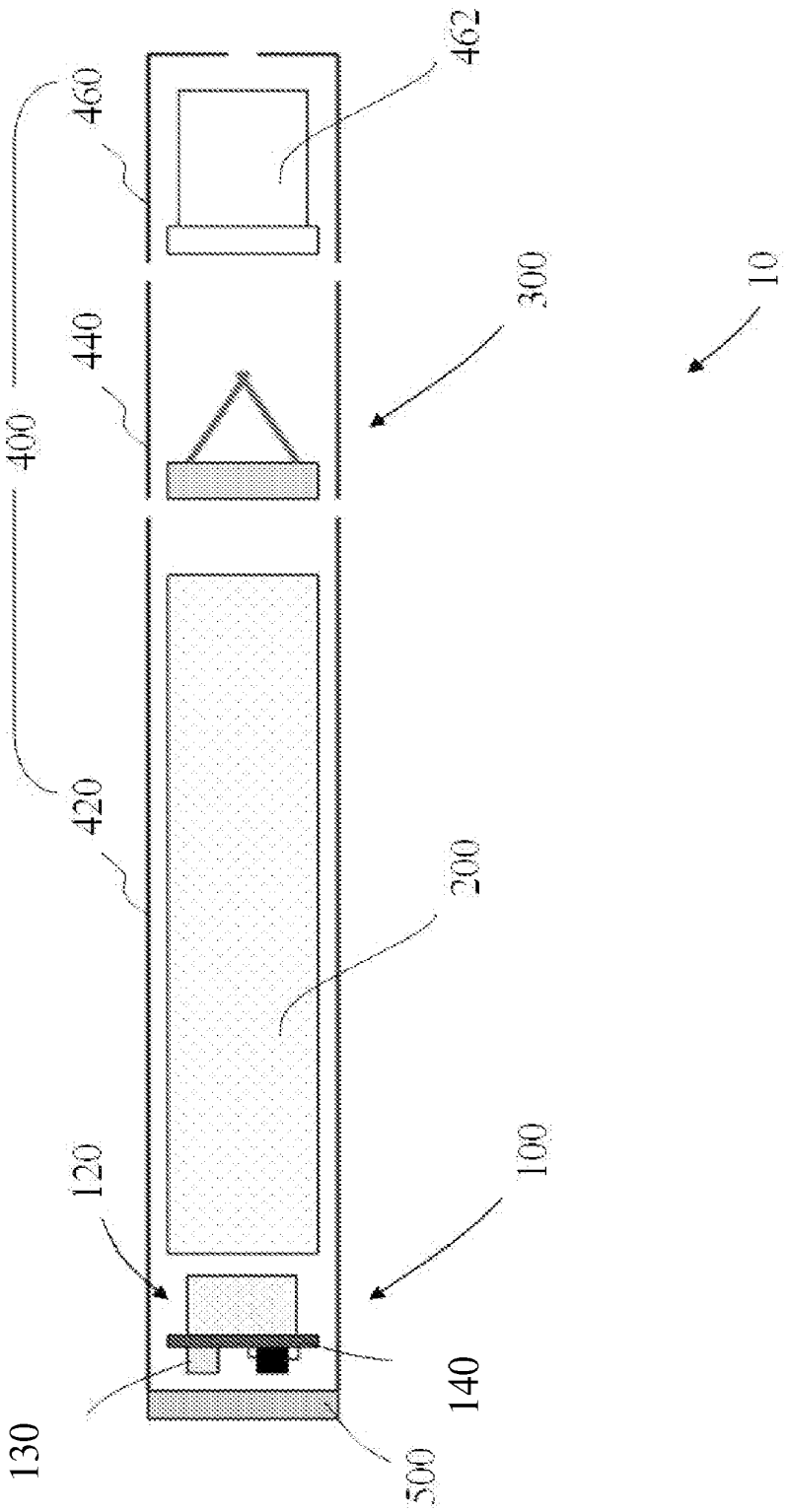



Figure 8

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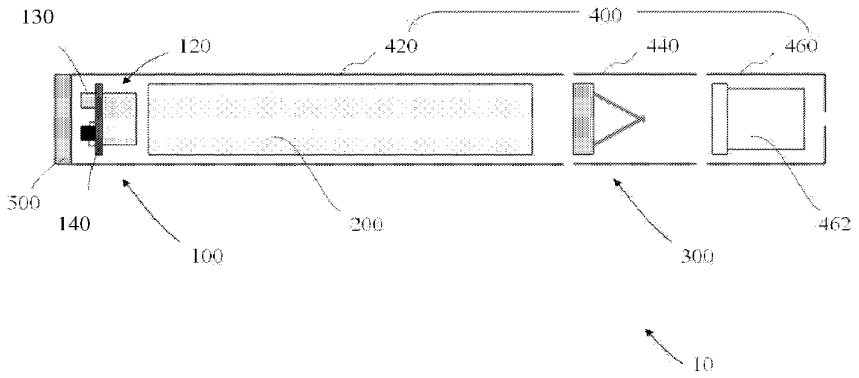



Figure 8

(57) Abstract: An electronic cigarette (10) comprises an inhale detector (100) and a smoke effect generating circuitry. The inhale detector (100) comprises an air flow sensor (120) which is arranged to detect the direction and rate of the air flow through the smoke apparatus. The smoke effect generating circuitry is arranged to generate smoking effect when the air flow direction corresponds to inhaling through the smoke apparatus and the air flow rate reaches a predetermined threshold. Such an electronic cigarette alleviates the problem of inadvertent triggering due to environmental vibration or noise or children playing by blowing into the smoke apparatus.

WO 2011/033396 A3

# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**

A24F 47/00 (2006.01) i

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A24F 47/00; A24D 1/18;G05F 1/-; G01F

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 practicable, search terms used)

CNPAT, WPI, EPODOC: electr+, smoke, cigarette, tobacco, rate, speed, velocity, air flow, air steam, inbreathe, inhale, detect+, direction, orientation, threshold, predetermined, sensor, capacity+, membrane, film, deform+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | CN101518361A (BEIJING GELIN WORLD SCI&TECH DEV. CO.) 02 Sep. 2009(02.09.2009) the whole document | 1-11 |
| A | CN101524187A (WANJIA TONGDA TECHNOLOGY BEIJING CO., LTD.) 09 Sep. 2009 (09.09.2009) the whole document | 1-11 |
| A | CN201490998U (DONGGUAN TRANSOUND ELECTRONICS CO., LTD.) 26 May 2010 (26.05.2010) the whole document | 1-11 |
| A | WO2004/080216A1(HON, Lik) 23 Sep. 2004 (23.09.2004) the whole document | 1-11 |
| A | EP0488488A1(PHILIP MORRIS PRODUCTS INC.) 03 Jun. 1992 (03.06.1992) the whole document | 1-11 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&"document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 02 Mar. 2011 (02.03.2011) | **21 Apr. 2011 (21.04.2011)** |
| Name and mailing address of the ISA/CN<br>The State Intellectual Property Office, the P.R.China<br>6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088<br>Facsimile No. 86-10-62019451 | Authorized officer<br>CUI, Haibo<br>Telephone No. (86-10)62414194 |

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**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
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| | | JP6315366A | 15.11.1994 |
| | | NO176545B | 16.01.1995 |
| | | CA2035761C | 24.04.2001 |

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(71) Applicant *(for all designated States except US)*: **KIND CONSUMER LIMITED** [GB/GB]; Lighterman House, 26-36 Wharfdale Road, London N1 9RY (GB).

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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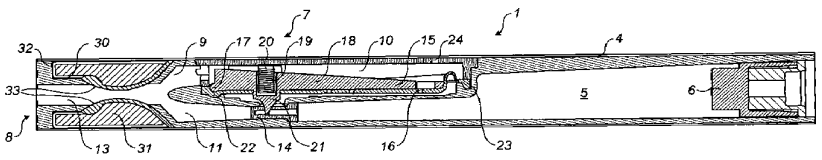



FIG. 1

(57) Abstract: A simulated cigarette which has a reservoir (5) of an inhalable composition and an outlet valve (21) to control the outlet flow. The outlet end is provided with a deformable material (31) to provide a more realistic feel and optionally to allow the user to vary the flow characteristics in the manner of a real cigarette. The outlet end can also be provided with a chemical heater. The simulated cigarette is wrapped in a paper or paper-like wrap (4) to provide a more realistic feel.

# A SIMULATED CIGARETTE

The present invention relates to a simulated cigarette comprising a housing having a generally cigarette-like shape and size; a reservoir of inhalable composition within the housing; an outlet valve controlling the flow from the reservoir; an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales the composition. Such a simulated cigarette will subsequently be referred to as "of the kind described".

A simulated cigarette of the kind described is disclosed in our earlier WO 2009/001078 and WO 2009/001082.

These documents disclose a simulated cigarette device which is refillable in combination with a refill pack which has a size and shape of a cigarette pack. The user removes the simulated cigarette from the pack and holds it against an outlet port in the pack to refill it. This is designed to mimic the action of removing a real cigarette from a pack. By replicating the smoking act, the device is more likely to gain acceptance from a consumer.

However, the simulated cigarette device disclosed in these applications and, indeed, similar cigarette devices disclosed in other applications such as US 4,393,884 and DE 4030257 are simply cylindrical plastic tubes.

The present invention aims to provide a simulated cigarette device which more closely resembles the physical feel of a real cigarette.

According to a first aspect of the present invention, a simulated cigarette of the kind described is characterised in that the housing adjacent to the outlet end has a deformable material at its outer periphery.

This deformable material is able to be squeezed or flexed by the index finger and thumb of a smoker. This is an important feature for a smoker and part of the behavioural cycle of the smoking ritual. The first aspect of the present invention therefore provides a tactile sense akin to a conventional cigarette. Also, the deformable material provides a more realistic smoking experience for the user when it comes to inhalation. Users typically purse inhalation devices with their lips or teeth so it is advantageous to make the material against which they press deformable accordingly.

As well as providing increased comfort, the deformable material can also be used to affect the flow characteristics of the inhalable composition. Preferably, the deformable material is configured to be deformable with respect to the outlet passage to change the flow characteristics from the outlet passage. With such a deformable material, the user can disrupt the flow of inhalable material giving rise to vortices that will modify the delivery from the reservoir. This mimics the manner in which smokers modify the delivery of a conventional tobacco cigarette by squeezing the filter to reduce the pore size thereby modifying the flow of the smoke accordingly. This allows the user to modify the flow by narrowing the outlet passage and thereby quickening the velocity of the flow.

In order to further enhance the control being exercised by a user, the outlet valve is preferably a breath-activated valve which is actuated by a flow of air through the housing in an actuation passage parallel to the flow through the outlet passage and wherein the deformable material is positioned so that it is deformable into the housing to a position in which it affects the flow through at least one of the actuation passage and the outlet passage so as to affect the dosage of inhalable composition that a user receives from the cigarette.

If the user constricts the actuation passage, the suction force required to open the valve increases while constricting the outlet passage increases the velocity of the flow. This is an important adaptable behavioural mode for smokers since when they desire a deeper inhalation, normally in a spike of craving, they can modify the suction chamber through this action and modestly increase the velocity of the flow, and therefore the speed of uptake to the lung allowing sophisticated control of the flow characteristics. Additionally if the user exerts a lower than usual suction force and constricts the chamber, the device may function in the opposite manner by creating a limitation on the breath force exerted on the breath-activation system and therefore limiting the valve opening and thus the flow rate by the user. Thus by allowing distortion of the flow path, akin to a tobacco cigarette, a more sophisticated control of the flow characteristics is allowed.

The deformable material may be elastomeric, or may be a flexible skin containing a fluid or gel.

When the deformable material includes liquid or a gel, as a further enhancement of the invention, this may be supersaturated and arranged to come into contact with nucleation sites upon tapping of the cigarette, to form crystals and undergo an exothermic reaction.

This can produce a warming sensation at the tip of the cigarette which a user will find pleasant and again replicates the heating effect in a real cigarette of drawing smoke through the filter.

As the cigarette device is designed to be refilled a number of times, there are preferably a plurality of compartments containing liquid or gel which are separately actuatable to produce an exothermic reaction.

In addition to, or as an alternative to, using the exothermic reaction to provide a warm sensation adjacent to a mouthpiece of a cigarette, the cigarette may be configured to direct the heat produced inwardly, so as to heat the inhalable composition in the outlet passage.

This forms a second aspect of the present invention which may be defined, in the broadest sense, as a simulated cigarette of the kind described further comprising a chemical heater provided adjacent to the outlet passage and arranged to be activated to undergo an exothermic reaction to heat the inhalable composition as it travels along the outlet passage.

The generation of heat in a simulated cigarette is known, for example, in EP 1 618 803 and in WO 2009/155957. However, in these cases, the heat is used to vaporise the composition. In this second aspect of the present invention, the inhalable composition is released from a reservoir and is subsequently heated by a heater.

The inhalable composition is released from the reservoir will generally be cold. It is warmed, to some extent, by the surrounding housing as it travels around the outlet passage and, if present, by dilution of air from the actuation passage. However, if the device is used repeatedly, the mouthpiece itself can become cold to touch. This can be avoided by heating the mouthpiece, which also has a beneficial effect on the temperature of the inhalable composition flowing through the mouthpiece.

Preferably, the outlet valve is at least 4mm from the outlet. This allows sufficient time for the inhalable composition to mix with ambient air to allow the warming effect referred to above. This allows sufficient time for the inhalable composition to mix with ambient air to allow the warming effect referred to above.

Preferably, the heater is provided by a gel or liquid which is supersaturated and which is arranged to come into contact with nucleation sites upon tapping of the cigarette, to form crystals and undergo an exothermic reaction.

As the cigarette device is designed to be refilled a number of times, there are preferably a plurality of compartments containing liquid or gel which are separately

actuatable to produce an exothermic reaction. These components are preferably provided by rupturable microcapsules.

According to a third aspect of the present invention, a simulated cigarette of the kind described is wrapped in a wrap comprising an adhesive layer to stick to the housing, a paper or paper-like layer and a polymer film to cover and protect the paper or paper-like layer.

In the prior art referred to above, all simulated cigarettes of this type have only a plastic housing as they are designed to be durable. US 2004/0003820 discloses a cigarette substitute with a chamber lined with a scratch-releasable-coated paper which is scratched with a wire brush to release a cigarette-like aroma. This document discloses that the vessel is coated or lined with a white, paper-like material for improved realism but there is no indication of the underlying material of the housing, or how this is implemented. JP2010/35663 discloses an inhaler containing a string of capsules. These are crushed by a user's fingers to release their contents for inhalation. The device is covered in a paper-like material as it is required to be deformable to crush the capsules.

The third aspect of the present invention replicates more closely the feel of a real cigarette. Further, it is suited to the arrangement described in WO 2009/001078 which is designed to be refilled only a relatively small number of times such that longevity is less of an issue. The polymer film is able to protect the paper as the time for which it is used, while for less than the prior art above, is still

significantly longer than a real cigarette or the devices of US 2004/0003820 and JP 2010/035663.

Preferably, the wrap is hydrophobic so that it does not absorb moisture from the user's mouth, from the ambient environment or from the filling process. The wrap is preferably a wipe-clean paper. It is preferably also fire retardant in case of hazard or mistaken ignition. Preferably, the wrap is provided with a flavour (e.g. menthol) and/or an antibacterial agent.

Such an example of a wrap is a co-extruded biaxially orientated corona treated polyproplyene situated with an acrylic based adhesive. The adhesive is a water-borne acrylic based adhesive comprising acrylic esters copolymerised with acrylic acid.

This is laminated over a supercalendered glassine paper, which gives the image and texture of a paper wrap, where the transparency is around 30-60%, most preferably 45%. A compatible ink, preferably a raw material consisting of an acrylate mixture, which in its finished cured form in a acrylate polymer contains very little residual monomer such to improve the chemical stability of the system. Such a system can also be impregnated with Silver Ion spray coating on top of the glassine paper to limit any microbial activitiy over continued use, and the end tip can be sprayed with a compatible fire retardent material before the adhesive layer and extruded polyproplyene applied.

Additionally a laminate is layered over the system to improve stability and use duration. A higher strength

acrylic adhesive is employed to attach the laminate underlay of the glassine paper to the plastic chassis tubing of the inhaler, such that it will remain in fixed position without uncurling or unwrapping over the alotted shelf life. Such a system should incorporate as low a density co-extruded biaxially orientated corona treated polyproplyene as possible without compromising resistance, in order to improve the fixation stability of the wrap.

The system should comply with the guidelines laid down under ISO 10993 when relating to component biocompatibility. As such, plastic coating should comply with a material safety test guidance under the European Pharmacopiea in order to ensure compatability with transient oral mucocal contact, with adhesive layers ensuring compatability with the European food directive legislations, FDA 175.105 and the German recommendations XIV as published by BfR. This construction should also be classed as a safe product in accordance with the material description as given by EC directive 92/59, article 2(b) which will ensure safety for repeated use.

The wrap may be used in its own right, but is particularly advantageous when used in combination with the deformable material of the first aspect of the present invention and/or the heater of a second aspect of the present invention, as the overall effect most closely resembles a real cigarette.

In all aspects of the invention, the reservoir is preferably pressurised and is preferably refillable. The

refill is preferably carried out through a refill valve at the end of the cigarette opposite to the outlet.

Examples of a simulated cigarette in accordance with the various aspects of the present invention will now be described with reference to the accompany drawings, in which:

Fig. 1 is a cross-section of a simulated cigarette;

Fig. 2 is an exploded view of the simulated cigarette;

Figs. 3A to 3C are perspective views of alternative deformable members; and

Fig. 4 is a cross-section of the Fig. 3A example.

The device has a housing 1 made up of a main chassis 2 and a closure element 3 as shown in Fig. 2. This is held in place by label 4. Within the housing, there is a reservoir 5 containing the inhalable composition. This is preferably pressurised but could also work with a non-pressurised reservoir in combination with a Venturi nozzle to generate an enhanced suction force on the reservoir. It may be refillable as described in WO 2009/001082 through the filling valve 6, or the device may be a single use device, or may be arranged so that the reservoir 5 is a replaceable component.

The breath-activated valve 7 is positioned between an outlet end 8 and the reservoir 5. The breath-activated valve is arranged so that, when a user sucks on the outlet end 8, the breath-activated valve 7 opens to allow the inhalable composition from the reservoir 5 to be inhaled.

The housing downstream at the valve 7 has two passages. The first of these is the suction passage 9 which communicates with a chamber 10 as will be described in greater detail below and the second is a composition passage 11 from which the inhalable composition is dispensed. This is also described in more detail below. The suction passage and composition passage meet at outlet passage 13 which leads to outlet end 8.

A deformable tubular nozzle 14 is provided between the reservoir 5 and composition passage 11. The element is selectively deformable between open and closed configurations by a mechanism as described below.

This mechanism comprises a pivotally mounted vane 15 and a membrane 16. The pivotally mounted vane has a pivot 17 at the end closest to the outlet end 8 and a central reinforcing rib 18 running along its length and tapering away from the outlet end. At around the midpoint, the vane 15 is provided with a recess 19 for receiving a spring 20 which biases it into the closed position shown in Fig. 1. Below the recess 19 is a jaw 21 having a triangular cross-section which is configured to apply the force provided from the vane 15 to the nozzle 14 over a narrow area (although the nozzle is shown in Fig. 1 in its uncompressed, open state, whereas in use, with the vane in this position it would deform the nozzle to seal the reservoir). The vane 15 is supported by the diaphragm 16 which is sealed to the housing at its ends 22, 23.

An inlet 24 is provided into the chamber 10, while the underside of the membrane 16 is open to atmospheric pressure

as a leakage path exists through the housing 1 which is not shown in the drawings as it is not shown in the plane of Figs. 1 and 2.

When a user sucks on the outlet end 8 air is sucked through inlet 24 through chamber 10 and out of suction passage 9 thereby lowering the pressure in the chamber 10. This causes the vane 15 to be lifted against the action of the spring 20 deforming the diaphragm and lifting the jaw 21 to allow the deformable nozzle 14 to open, thereby allowing the inhalable composition from the reservoir 5 along composition passage 11 into the outlet passage 13 where it mixes with the suction air. The degree of suction applied by the user will determine the extent to which the vane 15 moves and therefore the amount of composition that the user receives. As soon as a user stops sucking, atmospheric pressure will return to the chamber 10 and the spring 20 will push the vane down thereby pinching the nozzle 14 closed.

The simulated cigarette described to date is generally as described in WO 2011/015825.

The housing 1 is provided at the outlet end with a generally annular recess 30 surrounding the outlet passage 13. Within this annular recess is a deformable member 31 which, in situ, is flush with the surface of the housing 1 as shown in Fig. 1. The deformable member 31 may be an elastomeric member, or may be a thin-walled capsule containing a liquid or gel which is described in more detail below. An annular lip 32 is present at the outlet end of

the cigarette. This may be thinner than the illustrated lip, or may not be present at all.

The deformable member 31 is generally positioned in the area that would be occupied by the filter of a conventional cigarette. Thus, the user is able to squeeze the end of the cigarette in the manner that they would squeeze the filter of a cigarette, and hold this end of the cigarette in their mouth and, in both cases, obtain a tactile sensation comparable to that of a real cigarette.

Further, the housing 1 in the vicinity of the outlet passage 31 is provided with a pair of diametrically opposed openings 33 and, as shown in Fig. 1, the deformable member 31 is arranged to bulge through these to project into the outlet passage 13. As the user presses on the deformable member, the degree to which the deformable member bulges into the passage 13 is varied. If the user presses on the top of the deformable member 31 (with reference to the orientation shown in Fig. 1), they will restrict the flow through the suction passage 9 with the effect that the user will need to suck harder on the device to achieve the desired inhalation profile. If they press on the lower part of the deformable member 31, they will restrict the flow through the composition passage 11 with the effect that if the valve is fully open, the velocity of the flow will increase and quicken the route of delivery. Pressing on the top and bottom of the deformable member 31 simultaneously will increase the resistance and necessatitate sucking harder on the device but also by nature of construction of the composition passage 11, quicken the flow and speed of delivery. This is a useful feature for smokers who wish to

quicken the rate of absorption when undergoing a spike in craving. Thus a user is able to self-regulate the flow of inhalable composition from the cigarette, much as they are able to do with a conventional cigarette by squeezing on the filter.

As well as providing tactile benefits, and the ability to regulate the flow, the deformable member 31 may also be designed as a heater.

As mentioned above, the deformable member 31 may contain liquid or gel. This may be an acetate, and preferably sodium acetate that is super saturated. This may be encapsulated into microcapsules having a polymeric or celluostic casing. If there are around 20 such microcapsules, the device can be re-used a number of times, each time breaking a small number of the capsules. Inside the deformable member 31 and surrounding the inner wall is a layer, disc or film of ferrous metal or other that have been coursed to provide a greater reactive surface area. When the user taps the outer wall of the deformable element 31, such as a smoker is accustomed to do to release ash that has built-up on the tip of the cigarette, crystals of sodium acetate are released into the solution which then act as nucleation sites. This causes the solution to crystallise suddenly, releasing energy and thereby creating a heating effect to the surrounding material, which the user can perceive. This heat can be controlled to ensure that the temperature is pleasant and warming and does not approach higher temperatures that may impact on the integrity of the device. In order to last over several refills of the device, the deformable member 31 may be composed of multiple

layers or compartments 34, each connected individually to separate solutions and ferrous metals. It is possible that the outer wall of the deformable member 31 may be a good insulator which allows minimal heat to be conducted out of the device so that the heat is, instead, directed inwardly to heat the flow through the upper passage 13.

Alternative designs of deformable element 31 are shown in Figs. 3A-3C and 4. In Figs. 3A and 4, a plurality of frangible balls 35 containing acetate are each positioned on a ferrous disc 36 which provides the nucleation sites. Pressure on the outer wall of the deformable member breaks some of the frangible balls so that the acetate comes into contact with the ferrous disc initiating nucleation and causing an exothermic reaction.

In Fig. 3B, the compartments 34 are filled with calcium powder and frangible balls 37 containing water are arranged along the length of each compartment. Again, pressure on the deformable member 31 breaks the balls 37 and the water and calcium chloride react exothermically.

In Fig. 3C, each compartment 34 contains an elongate ferrous disc 38, the compartment filled with acetate. In this case, pressure on the deformable member 31 causes a sudden "snap" deformation of a disc 38 to trigger nucleation.

Other chemical heating sources for example can include, but not limited to, utilising an in situ combination of calcium chloride and reservoir containing pure distilled water. The calcium chloride is separated from water by a the

film or a diaphragm which when tapped or pushed, loses the integrity of its casing and allows the water to dissipate and therefore causing an exothermic reaction to take place. For use in a multi-phase manner, the distilled water can be manufactured into microcapsules, pellets or spheres encompassed either a polymeric or cellulosic casing that are no more than 2mm in diameter. These microcapsules can be located within the chamber and distributed evenly around a surrounding layer of finely milled calcium chloride powder. When a user squeezes the deformable member 31, element of the mouthpiece, pressure is applied to the microcapsules such that they casing ruptures and releases its containment of the distilled water. There can be arranged around 20 microspheres within the deformable chamber such that there scope for multi-activation during the use of the cigarette device.

As can be seen in Fig. 1, the jaw 21 which represents the effective outlet from the reservoir 5 is positioned some considerable distance from the outlet end 8. This distance is preferably greater than 10mm. This means that the composition has to flow a reasonable distance through the device before it is inhaled by the smoker. Thus, it can be warmed by the housing surrounding the composition passage 11 and outlet passage 13. It is diluted and warmed by the air from the suction passage 9 and is also heated by the heat generated in the deformable member 31 if this is designed as the exothermic element described above. The smoker therefore inhales composition which is warmed to a degree ideally replicating the temperature of smoke from a real cigarette, but at least warmed to a degree so as not to cause discomfort.

The label 4 is an overwrap that surrounds substantially the entire curved surface of the simulated cigarette. As shown in Fig. 2, it is divided into two sections 40 and 41 which are coloured and patterned to resemble a conventional cigarette with a filter tip. In combination with the deformable member 31, the outlet end of the cigarette both looks and feels like the filter of a conventional cigarette. The label has at least one hole laser drilled so as not to obstruct inlet 24.

The coatings applied to the label 4 demonstrate hydrophobic properties, but also create a lipophobic and oleophobic surface to repel water, dirt on surfaces and any formulation that may be spilled or accidentally emitted during the refilling process. This makes sure that the cigarette paper does not tear or blemish as the formulation may contain propylene glycol, PEG or aromatic oils which will lead to quick discolouration of the paper, and reduce its structural integrity. As such coatings can be used such as a phosphonate based application, and applied in a monolayer. This can be provided by for example Aculon Inc. This will also impart an additional wipe clean quality, so that the dirt does not build up on the mouthpiece. Since the device is intended to be disposable, a coating can be applied solely to the mouthpiece and to the distal end where the refill valve is, to reduce the likelihood of dirt ingress and paper tear. This also provides an enhanced consumer response so that users can clean the mouthpiece end easily without fear or paper or fabric tear, for example if lipstick is accidentally applied.

Additionally fluropolymers can be used, either applied directly to the paper or fabric coating as a powder or spray and provide necessary oil-repellant/water-repellant properties. These can include PTFE (polytetrafluoroethylene), PFA (perfluoroalkoxy polymer resin), FEP (fluorinated ethylene-propylene) and ETFE polyethylenetetrafluoroethylene but not limited to these types of fluoropolymers. Care is taken when choosing a coating that they demonstrate suitable biomaterial compatibility especially if in frequent contact with the skin.

The wrap may be paper-like material such as a tightly woven cotton, or other fabric and a coating of silica or titania particles can be used to provide hydrophobic properties on devices where the oleophobic property is not needed due to a different composition of formulation.

Preferably a material is used that contains a hydrophobic, lipophobic and oleophobic property but also has a fire retardant capability. This is to protect the device in case it unduly exposed to fire or naked flame. Such coatings can include Aluminium Trihydride (ATH), Antimony Trioxide (Sb2O3) and Zinc Borate. Zinc Oxides can also be used at a pharmaceutical grade specifications for use in this respect.

A specialty chemical, MP Protect, available at ISC Ltd, can also be applied which incorporates a fire retardant system for cellulose rich substrates, such as wood, paper cotton and certain textile applications. This will allow it to be capable of withstanding flames in accordance with the

DIN 53438 standard burn test, but also has a property to impart an anti-bacterial quality which can destroy micro-organisms such as influenza, salmonella and Legionella. This can be an important attribute to the device if shared routinely in social situations.

An anti-bacterial coating on the mouthpiece may be especially advantageous as part of one coating or in addition to several coatings but locally applied on the mouthpiece. Such coatings can include a thin layer of silver, Ionizable silver incorporated into fabric, silver alloy or oxide which will help in reducing the bacteria spread and have been approved for use in respiratory devices such as endotracheal breathing tubes by the FDA. This will offer an improved hygienic aspect to the device if used multiple times before it is eventually disposed of.

**CLAIMS**:-

1. A simulated cigarette comprising a housing having a generally cigarette-like shape and size; a reservoir of inhalable composition within the housing; an outlet valve controlling the flow from the reservoir; an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales the composition characterised in that the housing adjacent to the outlet end has a deformable material at its outer periphery.

2. A simulated cigarette according to claim 1, wherein the deformable material is configured to be deformable with respect to the outlet passage to change the flow characteristics from the outlet passage.

3. A simulated cigarette according to claim 1, further comprising a breath-activated valve which is actuated by a flow of air through the housing in an actuation passage parallel to the flow through the outlet passage, and wherein the deformable material is positioned so that it is deformable into the housing to a position in which it affects the flow through at least one of the actuation passage and the outlet passage so as to affect the dosage of inhalable composition that a user receives from the cigarette.

4. A simulated cigarette according to any one of the preceding claims, wherein the deformable material is capable of generating heat.

5. A simulated cigarette according to claim 4, wherein the deformable material contains liquid or gel which is supersaturated and which is arranged to come into contact with nucleation sites upon tapping of the cigarette, to form crystals and undergo an exothermic reaction.

6. A simulated cigarette according to claim 5, wherein the deformable material comprises a plurality of compartments containing liquid or gel which are separately actuatable to produce an exothermic reaction.

7. A simulated cigarette according to any one of claims 4 to 6, wherein the deformable material is configured to direct the heat produced inwardly, so as to heat the inhalable composition in the outlet passage.

8. A simulated cigarette comprising a housing having a generally cigarette-like shape and size; a reservoir of inhalable composition within the housing; an outlet valve controlling the flow from the reservoir; an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales the composition; further comprising a chemical heater provided adjacent to the outlet passage and arranged to be activated to undergo an exothermic reaction to heat the inhalable composition as it travels along the outlet passage.

9. A simulated cigarette according to claim 8, wherein the outlet valve is at least 4mm from the outlet.

10. A simulated cigarette according to claim 8 or claim 9, wherein the heater is provided by a gel or liquid which is

supersaturated and which is arranged to come into contact with nucleation sites upon tapping of the cigarette, to form crystals and undergo an exothermic reaction.

11. A simulated cigarette according to claim 10, wherein there are a plurality of compartments containing liquid or gel which are separately actuatable to produce an exothermic reaction.

12. A simulated cigarette according to claim 11, wherein the compartments are rupturable microcapsules.

13. A simulated cigarette according to any one of claims 8 to 12, wherein the heater is configured to direct the heat produced inwardly, so as to heat the inhalable composition in the outlet passage.

14. A simulated cigarette comprising a housing having a generally cigarette-like shape and size; a reservoir of inhalable composition within the housing; an outlet valve controlling the flow from the reservoir; an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales the composition, wherein the housing is wrapped in a wrap comprising an adhesive layer to stick to the housing a paper or paper-like layer and a polymer film to cover and protect the paper or paper-like layer.

15. A simulated cigarette according to claim 14, wherein the polymer is hydrophobic, lipophobic and/or oleophobic.

16. A simulated cigarette according to claim 14 or 15, wherein the wrap has at least one hole aligned with a flow path in the housing.

17. A simulated cigarette according to any one of claims 14 to 17, wherein the wrap is provided with a fire retardant material at least in the region opposite to the outlet.

18. A simulated cigarette according to any one of claims 14 to 17, wherein the wrap adjacent to the outlet is provided with an antibacterial agent.

19. A simulated cigarette according to any one of claims 14 to 18, wherein the wrap comprises a number of layers, beginning with the side closest to the housing, the layers comprise, in order, the adhesive, a laminate, the paper or paper-like layer, an ink and the polymer film.

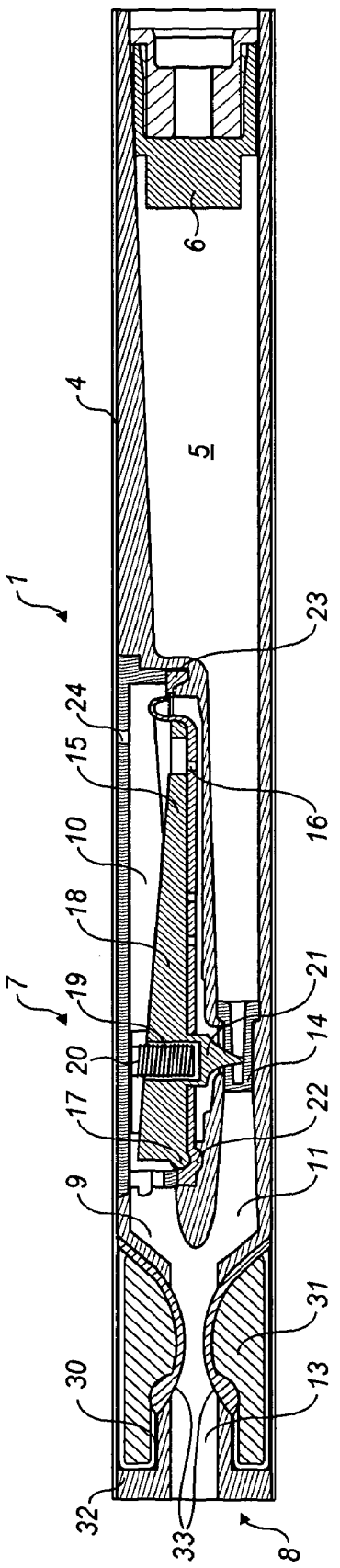



FIG. 1

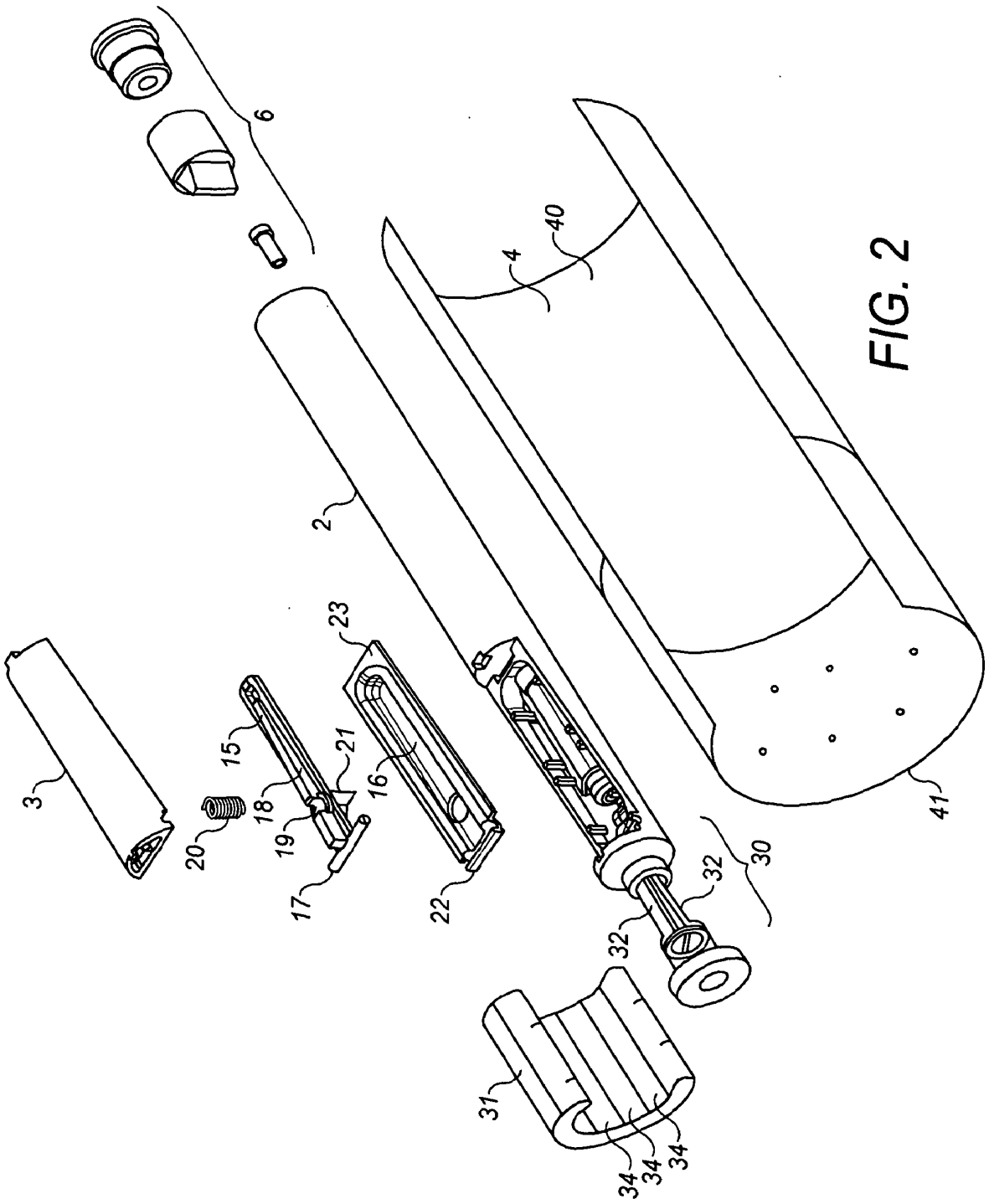



FIG. 2

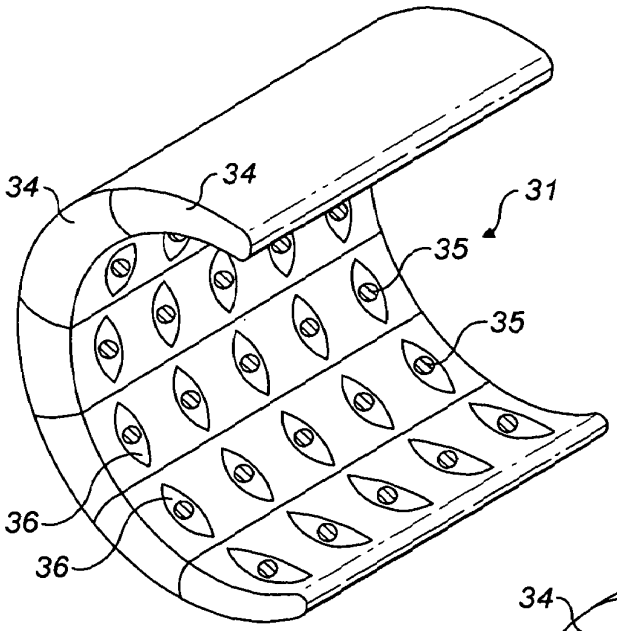



FIG. 3A

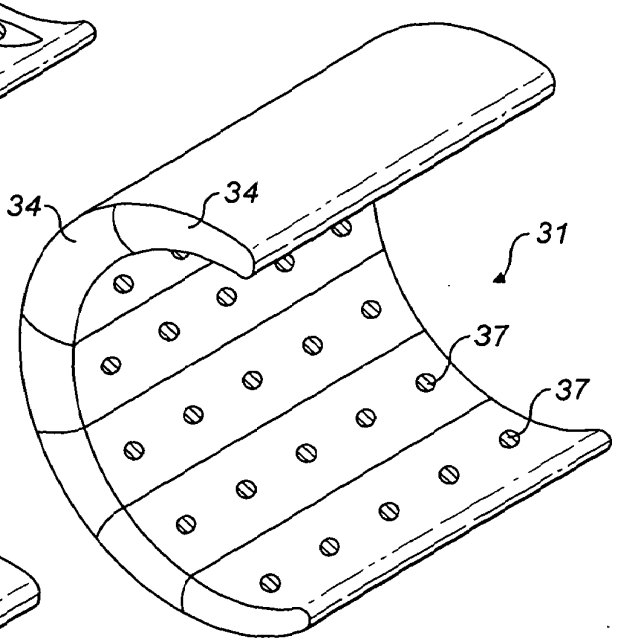



FIG. 3B

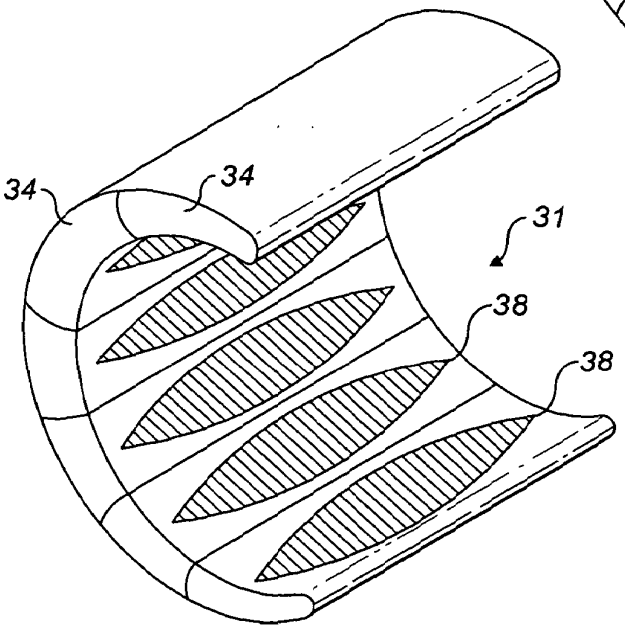



FIG. 3C

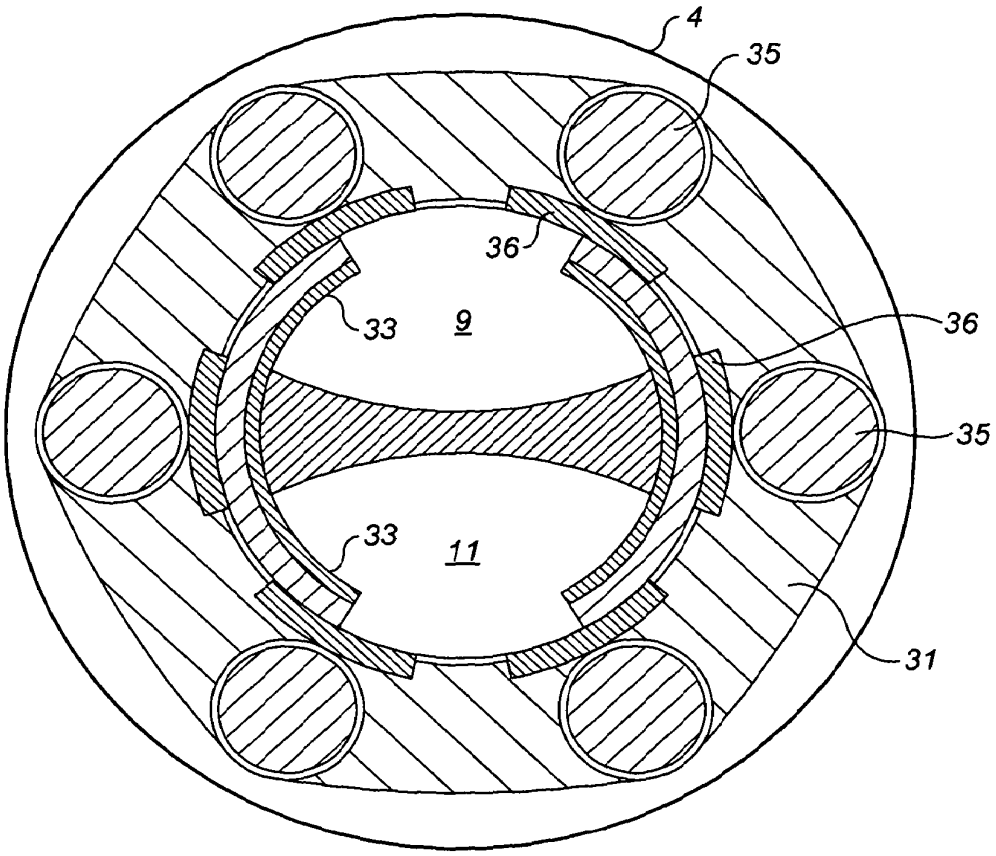



FIG. 4

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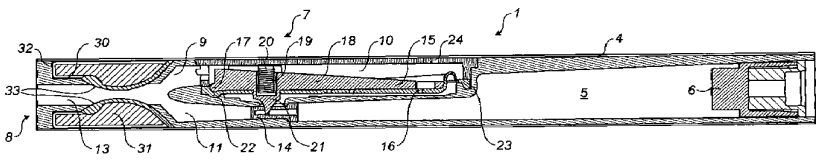



FIG. 1

(57) Abstract: A simulated cigarette which has a reservoir (5) of an inhalable composition and an outlet valve (21) to control the outlet flow. The outlet end is provided with a deformable material (31) to provide a more realistic feel and optionally to allow the user to vary the flow characteristics in the manner of a real cigarette. The outlet end can also be provided with a chemical heater. The simulated cigarette is wrapped in a paper or paper-like wrap (4) to provide a more realistic feel.

WO 2011/117580 A3

# INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/000416

A. CLASSIFICATION OF SUBJECT MATTER
INV. A24F47/00 A24D1/02
ADD.

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)
A24F A24D 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)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4 945 931 A (GORI GIO B [US])<br>7 August 1990 (1990-08-07) | 1-3 |
| Y | column 2, line 4 - column 3, line 64 | 8-10 |
| X | US 3 631 856 A (TAYLOR HAROLD V)<br>4 January 1972 (1972-01-04) | 1,2 |
| Y | column 1, line 62 - column 3, line 26 | 14-16 |
| Y | WO 2009/156181 A2 (OLIG AG [CH]; KOELLER MARCEL [CH]) 30 December 2009 (2009-12-30)<br>page 18, line 2 - page 28, line 13 | 8-10 |
| Y | EP 0 758 695 A2 (JAPAN TOBACCO INC [JP]; MISHIMA PAPER CO LTD [JP])<br>19 February 1997 (1997-02-19)<br>page 10, lines 15-23 | 14-16 |

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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 |
|---|---|
| 17 October 2011 | 24/10/2011 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Koob, Michael |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/000416

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2010/059070 A1 (POTTER DENNIS [JP] ET AL) 11 March 2010 (2010-03-11) paragraph [0051] - paragraph [0052] | 4 |

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2011/000416

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7

A simulated cigarette comprising a housing, a reservoir, an outlet valve and an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales a composition whereby the housing adjacent to the outlet end has a deformable material at its outer periphery.

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2. claims: 8-13

A simulated cigarette comprising a housing, a reservoir, an outlet valve and an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales a composition whereby the simulated cigarette further comprises a chemical heater provided adjacent to the outlet passage and arranged to be activated to undergo an exothermic reaction to heat the inhalable composition as it travels along the outlet passage.

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3. claims: 14-19

A simulated cigarette comprising a housing, a reservoir, an outlet valve and an outlet passage from the outlet valve to an outlet in the housing from which outlet a user inhales a composition whereby the housing is wrapped in a wrap comprising an adhesive layer to stick to the housing a paper or paper-like layer and a polymer film to cover and protect the paper or paper-like layer.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/000416

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4945931 A | 07-08-1990 | NONE | |
| US 3631856 A | 04-01-1972 | NONE | |
| WO 2009156181 A2 | 30-12-2009 | AU 2009262422 A1 | 30-12-2009 |
| | | CA 2712412 A1 | 30-12-2009 |
| | | CN 102131411 A | 20-07-2011 |
| | | EA 201071208 A1 | 30-06-2011 |
| | | EP 2303043 A2 | 06-04-2011 |
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| | | JP 9049188 A | 18-02-1997 |
| | | US 5849153 A | 15-12-1998 |
| US 2010059070 A1 | 11-03-2010 | NONE | |

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2,712,624 19 August 2010 (19.08.2010) CA

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(74) Agent: **AGENCE DE BREVETS FOURNIER**; 216 St-Laurent, La Prairie, Québec J5R 1H4 (CA).

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**Published**:
— *with international search report (Art. 21(3))*

(54) **Title**: CONTAINER FOR THE MANAGEMENT OF PHARMACY PRESCRIPTIONS, CARES AND SERVICES

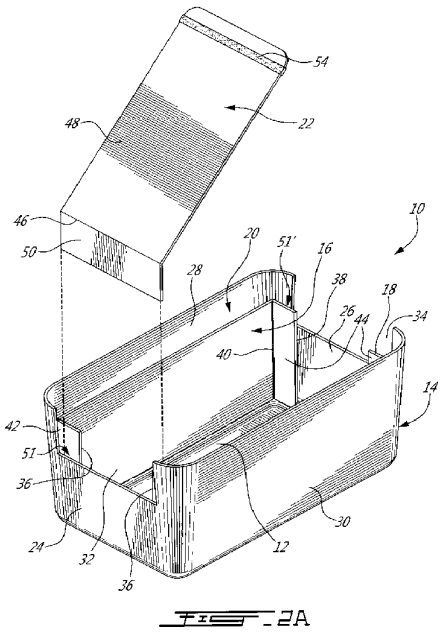



FIG. 2A

(57) **Abstract**: Embodiments of a container for managing pharmacy prescription, care and/or service described herein comprises a bottom, a peripheral wall extending from said bottom, a secondary wall mounted to the peripheral wall to define a document-receiving compartment; and an information-receiving card mounted to the peripheral wall. The information-receiving card is positionable in either one of an upright position and a tilted position and allows receiving directly thereon or indirectly via cardboard card information that characterizes the pharmaceutical prescription, care and/or service.

WO 2012/021972 A1

## TITLE

Container for the Management of Pharmacy Prescriptions, Cares and Services

## BACKGROUND

**[0001]** Pharmaceutical care services that are provided in pharmacy community settings involve many actors, including the pharmacist, technicians and clerk.

**[0002]** The pharmacist is involved typically in the verification of the drug distribution process, the analysis of patient medication profiles of the patients, including identifying potential drug or condition interactions checking for drug compatibility and contraindication. Also, the pharmacist is called to give counselling to patient about their medication and advices on general health topics to the patients.

**[0003]** The technician typically receives phone orders, welcome patients arriving at the laboratory, computes the prescriptions and other patient-related information in the pharmacy software (preparation of the prescription labels, receipts, etc.), works at the cash register, manages drug supplies, makes conditioning of medication, etc.

**[0004]** The clerk typically works at the cash, but may also help the technician.

**[0005]** The pharmaceutical care and services are carried out following the assignment of specific tasks to each actor in the laboratory which acts and interacts within a logical and sequential activity workflow.

**[0006]** With reference to Figure 1, a typical pharmacy laboratory can be seen as a production line, including a plurality of areas, which allows the pharmaceutical care delivery process (from left to right in Figure 1).

**[0007]** A typical laboratory includes:

**[0008]** – a reception, wherein a technician defines the pharmaceutical care or service to the patient/client. In addition to requests from on-site clients, pharmaceutical care requests are received over the phone. This includes the determination of prescription path and handling priority. Possibilities of path include mail or courier delivery and immediate or later pick-up by the client. A container, usually in the form of a tray is then selected by the technician, wherein the colour of the tray often allows indicating the priority/path of the pharmaceutical care;

**[0009]** – a production terminal, in the form of a computer usually connected to a remote server, allows the technician to create an indentifying label and invoice and insurance receipts. During this step, a series of pharmaceutical care characteristics are defined with regards to the drugs and/or professional acts to be performed by the pharmacist. For example, indications regarding any specific request by the client or insurer, for example, are written on a Post-It™ or directly onto the label;

**[0010]** – a conditioning area, wherein the prescription labels are inserted in empty vial and the medications are counted or measured. At this step, further information can be provided, for example on a Post-It™ or else. Examples of such further information include prescription storing instructions, any invoicing specification, etc. Different identification means are currently used by pharmaceutical professionals and technicians as reminders for a future step

or for another actor. Such other identification means are for example coloured clips;

**[0011]** – a verification terminal, wherein the pharmacist verifies the content of the tray, including the prescription vial or another medication container and its label. In this step, the pharmacist also considers any other document included in the basket. The pharmacist also proceeds with a pharmaceutical analyse of the client file before providing any counselling at...

**[0012]** - ... the consultation area;

**[0013]** – a cash for invoicing the client; and

**[0014]** – a confidential counselling/ consultation area, wherein more elaborate, delicate and/or complex care or advices are provided by the pharmacist.

**[0015]** As can be seen from the above, the community pharmaceutical practice results in concrete and abstract matter, including the actual prescription medication, expert advices, pharmaceutical case analyses, etc.

**[0016]** Following the above, one can see that numerous ordered information and pharmaceutical care characteristics are provided from one actor to the other and to the client and from one area to the next within the laboratory.

**[0017]** In a typical pharmacy laboratory, wherein a simple basket or container is used to receive and convey all the above mentioned information

and characteristic of the pharmaceutical care, one can see how such basic container shows many limitations and often leads i) to a waste of time in searching for the information, ii) misunderstandings and confusion in actor dealing with the information, iii) lost of some information and iv) difficulty in defining and quantifying of requests, etc.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0018]** In the appended drawings:

**[0019]** Figure 1 is a top plan schematic view of a typical community pharmacy laboratory;

**[0020]** Figure 2A is a perspective view of a first embodiment of a container for the management of pharmacy prescriptions; the container being showed with its information-receiving card removed therefrom;

**[0021]** Figure 2B is a perspective view similar to Figure 2A, showing the information-receiving card mounted to the container in a tilted position;

**[0022]** Figure 2C is a perspective view similar to Figure 2A, showing the information-receiving card mounted to the container in an upright position;

**[0023]** Figure 3 is a perspective view similar to Figure 2A, showing the container having a bag therein;

**[0024]** Figure 4 is a perspective view similar to Figure 2A, showing a further container inserted in the first container to form a stack;

**[0025]** Figure 5 is a template for inserting information on the information-receiving card from Figure 2A; and

**[0026]** Figure 6 is a perspective of a second embodiment of a container for the management of pharmacy prescriptions.

## DETAILED DESCRIPTION

**[0027]** An object of the present invention is to provide an improved container for the management of pharmacy prescriptions.

**[0028]** In accordance with an illustrative embodiment, there is provided a container for the management of a pharmaceutical care or product comprising:

**[0029]** a bottom;

**[0030]** a peripheral wall extending from said bottom;

**[0031]** a secondary wall mounted to the peripheral wall so as to define a document-receiving compartment between the peripheral wall and the secondary wall for receiving at least one document; and

**[0032]** an information-receiving card mounted to the peripheral wall for receiving and displaying information thereon.

**[0033]** Other objects, advantages and features will become more apparent upon reading of the following non-restrictive description of illustrative

embodiments thereof, given by way of example only with reference to the accompanying drawings.

**[0034]** In the following description, similar features in the drawings have been given similar reference numerals, and in order not to weigh down the figures, some elements are not referred to in some figures if they were already identified in a precedent figure.

**[0035]** The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one", but it is also consistent with the meaning of "one or more", "at least one", and "one or more than one". Similarly, the word "another" may mean at least a second or more.

**[0036]** As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "include" and "includes") or "containing" (and any form of containing, such as "contain" and "contains"), are inclusive or open-ended and do not exclude additional, unrecited elements.

**[0037]** The expressions "pharmaceutical care" and "pharmaceutical service" should be construed broadly as including any charged or free act that occurs directly or indirectly in relation to a costumer. Such an act can occur on site or remotely with regards to the care and service provided and can be done by a health care professional, technician, clerk, cashier, or else. For concision purposes, the expression "pharmaceutical care" will be used herein to also include the meaning of "pharmaceutical prescription".

**[0038]** The expressions customer, client and patient are used herein to refer to any person requesting and/or receiving the pharmaceutical care or service.

**[0039]** A container 10 for the management of pharmacy prescriptions according to a first embodiment is illustrated in Figure 2A.

**[0040]** The container 10 comprises a bottom 12, a peripheral wall 14 extending from the bottom 12, two secondary walls 16 and 18, respectively defining first and second document-receiving compartments 20 (only one shown), and an information-receiving card 22 for removably mounting to the container 10 as will be explained hereinbelow in more detail.

**[0041]** According to the first embodiment, the bottom 12 and the cross section of the peripheral wall 14 are generally rectangular.

**[0042]** The peripheral wall 14 is defined by opposite front and back longitudinal end walls 24 and 26 and two opposite lateral walls 28 and 30. The edges between each lateral wall 28 and 30 and the longitudinal end walls 24 and 26 are rounded. According to another embodiment (not shown), these edges are acute.

**[0043]** The top edges of the front and back walls 24 and 26 include respective rectangular cuts 32 and 34, yielding surbased walls 24 and 26 relative to the lateral walls 28 and 30.

**[0044]** Each of the secondary walls 16 and 18 is generally rectangular in shape and has longitudinal ends 36 and 38. Each of the secondary walls 16 and 18 include two transversal linear thinner portion 40

located near respective longitudinal ends 36 and 38 (only one shown). These portions are weakness lines 40 defining front and back pivotable wings 42 and 44. The secondary walls 16 and 18 are so dimensioned and the weakness lines 40 so positioned that the walls 16 and 18 extend generally along respective lateral walls 28 and 30 and the weakness lines 40, that act as hinges, are generally aligned along the edges.

**[0045]** The secondary walls 16 and 18 are secured to the respective lateral walls 28 and 30 along the bottom edge thereof using glue, plastic welding, fasteners or else, so as to allow biasing the secondary wall 16 or 18 from the lateral wall 28 or 30 for inserting documents therebetween without removing the secondary wall 28 and 30. The secondary walls 16 and 18 define the first and second document-receiving compartments 20 (only one shown) with respective lateral walls 28 and 30.

**[0046]** Any type of printed document can be inserted in the document-receiving compartments 20. Example of such documents include a prescription, receipt, advice and health booklet or leaflet, memo, Post-It™, insurance card, health care card, etc.

**[0047]** As illustrated in Figure 3, the secondary walls 16 and 18, including the wings 42 and 44, further acts as a bag-receiving support, wherein the open top peripheral portion 45 of a bag 47 is inserted between the secondary walls 16 and 18 and the peripheral wall 14 of the container 10. Purposes of the bag 47 will be described hereinbelow in more detail.

**[0048]** The wings 42 and 44 can be pivoted from an unfolded position, wherein the wings 42 and 44 are generally parallel to the respective front and back wall 24 and 26, to a support position, wherein the wings 42 and 44 are folded towards the respective lateral walls 28 and 30 so as to define an

acute angle therewith and then to a storage position, wherein the wings 42 and 44 are generally parallel to the respective lateral walls 28 and 30.

**[0049]** As can be seen in Figure 4, when the wings 42 and 44 are in their support position, they act as supports for a second container 10 inserted in the first container 10. In this manner, containers 10 can be stacked in a stable manner. For that purpose, the peripheral wall 14 is tapered along its height towards the bottom 12. According to the first embodiment, each of the walls 14, 16, 24 and 26 defines a 100 degrees angle with the bottom 12.

**[0050]** According to another embodiment, the peripheral wall is not tapered but includes a wide top portion and a narrower bottom portion. The peripheral wall can also be configured so as to be generally perpendicular to the bottom 12. According to further embodiments, the wings 42 and 44 are omitted.

**[0051]** According to still another embodiment, the secondary walls are interconnected.

**[0052]** The bottom 12 is transparent so as to allow inspection of the drug container and pills, cream and/or puffer therein (not shown) in the container 10 from the bottom 12 as will be explained hereinbelow in more detail. The bottom 12 is snap fitted to the peripheral wall 14. For that purpose, the peripheral wall 14 includes a small rim (not shown) extending inwardly perpendicularly from the walls 24 to 30 and that includes a catch (not shown) for locking the bottom 12 to the rim.

**[0053]** The bottom can be made of a scratch-proof or non scratch-proof polymeric material, glass, etc.

**[0054]** According a further embodiment, the bottom is opaque.

**[0055]** According to the first embodiment, the peripheral wall 14 and the secondary walls 16 and 18 are made of a polymeric material and result, for example, from a molding process.

**[0056]** According to the first embodiment, the front, back and lateral walls 24 to 30 are integral and the bottom 12 is assembled thereto. According to another embodiment, the walls 24 to 30 and bottom 12 are all assembled. According to still another embodiment, the peripheral wall 14 and bottom 12 are integral and result, for example, from a molding process.

**[0057]** The information-receiving card 22 is a flat generally rectangular rigid plastic body having a transversal linear thinner portion adjacent one of its longitudinal side edge defining a hinge 46 and separating the card 22 in a support portion 48 and a tab 50.

**[0058]** As can be better seen in Figures 2B and 2C, the card 22 cooperates with the container 10 so as to be positioned in a slanted configuration (see Figure 2B) or in an upright configuration (see Figure 2C).

**[0059]** The slanted configuration, shown in Figure 2B, is achieved by inserting only the tab 50 of the card 22 between the slot 51 defined by the front wall 24 of the container 10 and the wings 42, so that the support portion 48 is free to tilt about the hinge 46 towards the inside of the container 10. In this configuration, the tab 50 remains visible in the rectangular cut 32.

**[0060]** The upright configuration of the card 22 results from the insertion of the tab 50 and the hinge 46 in the slot 51, so that the support

portion 48 is prevented by the wings 42 from tilting about the hinge 46 towards the inside of the container 10.

**[0061]** The slanted and upright configurations can also be obtained by inserting the card 22 between the wings 44 and the back wall 26 in a similar manner. According to the fist embodiment, the slanted configuration of the card 22 yields the support portion 48 free to tilt about the hinge 46 towards the exterior of the container 10. The card 22 can also be inserted between the wings 42 or 44 and the respective wall 24 or 26 so as to be slanted towards the interior or exterior of the container 10.

**[0062]** The card 22 allows receiving information thereon. According to the first embodiment, the card 22 is intended to receive a rectangular cardboard information card 52 having patient and/or care related-information printed thereon.

**[0063]** As can be seen for example in Figure 2B, the information card 52 is secured to the plastic card 22 using a rubber band 54. According to another embodiment, the back of the card 22 is auto adhesive. Other fastening means can be used to secure the card 52 to the card 22, including a paperclip, a staple, or any other cooperating means provided on both cards 22 and 52.

**[0064]** As can be seen in Figure 5, which shows an example of such a cardboard card 52, the card 52 can act as a roadmap including a template to enter information such as, without limitations the nature or type of the pharmaceutical care, characteristics thereof as obtained during the information gathering process or during drug conditioning, a priority or path, a blank space to enter additional information or characteristics of the care or patient, etc.

**[0065]** The information that is carried by the container 10 allows implementing a predetermined sequence of pharmaceutical care and services. An example of such a sequence broadly includes:

**[0066]** – determining the nature of the pharmaceutical care;

**[0067]** – determining the container assignments;

**[0068]** – characterizing the information;

**[0069]** – characterizing the conditioning; and

**[0070]** – classifying the container 10.

**[0071]** Considering the above, the card 52 includes first identifiers 68 displayed thereon to help the laboratory actors characterizing the pharmaceutical cares for the client. The identifiers 68 include boxes, each with a short description. The actor allows the user to check the corresponding care to be dispensed to the customer. The choices include: new client (NCx), new prescription (NPx), repeat of prescriptions (RPx); regeneration of an old prescription (GPx), request of health-related or prescription–related advices/counseling (PhCoQx), counseling required with regards to a currently requested prescription (PhCoUMx); advices on health topics or counseling on medication requested via telephone (PhCoT); or telephone message left by the client (PhMe).

**[0072]** The card 52 also includes a second group of identifiers 70, also in the form of check boxes, allowing the user to characterize the

informatics process of the prescription and the drug-conditioning process as described hereinabove.

**[0073]** The top portion of the card 52 includes a free space 72 for receiving notes or any other information. Such notes and information are either written directly in the space 72 or through a small piece of paper attached to the card 52 in the space 72 using a clip, through an adhesive or using another fastening means.

**[0074]** Examples of information that can be written in the space 72 include: a note to the effect that the prescribed drug should be stored in a refrigerator, reminder to count the pills twice, etc.

**[0075]** The top portion 72 can also be used to print or write the name of the client, its coordinates, etc.

**[0076]** A color code can be used to further characterize the information displayed in the space 72 so as to further contribute easing the identification and/or recognition of said information. For that purpose, a small colored sticker (not shown) can be affixed in the space 72 or a colored clip can be used to secure a piece of paper (not shown).

**[0077]** According to the illustrated embodiment, the bottom tab 74 is used to identify the priority or path of the pharmaceutical care. In the illustrated example, graphical symbols 76 including lines and arrows are used for such identification. The user then makes his/her selection by marking the corresponding symbol 76. As non-restrictive examples, the symbols 76 correspond to the following path/priority: simple pick-up, complex pick-up, same day pick up, later time pick-up, home delivery, and postal delivery.

**[0078]** According to another embodiment (not shown), the priority or another characteristic of the pharmaceutical care is identified by the color of the card 52 or 22.

**[0079]** Also, the card 52 is not limited to include the information or template shown in Figure 5. Any other information can be displayed on the card 52 according to any template or form.

**[0080]** According to another embodiment, the card 52 is initially blank and only the information characterizing the current pharmaceutical care is printed on the card 52 using a printer (not shown) or simply hand written thereon.

**[0081]** In addition to the document-receiving compartments 20 and information-receiving card 22, any surface of the container 10, such as the outer surface of the wall 24 under the cut 32, or the card 22 or 52 can be used to display advertisement, client, care or prescription-related information. Such additional information can be printed on a paper or plastic support or directly onto the container surface. The information support can then be secured to the surface via a clip, adhesive material, etc.

**[0082]** Any information displayed on the container or received therein can be different than the example presented hereinabove or presented according to another template.

**[0083]** According to another embodiment (not shown), the patient and/or prescription related information is directly printed onto the card 22, which is then made of paper, including thermal paper, or cardboard. The card 22 or 52 can also be in the form of a thin portable electronic device (not shown)

that can be, for example, further coupled wirelessly to a computer, a server or another electronic device including or having access to patient and/or prescription related information.

**[0084]** As will now become more apparent to a person skilled in the art of pharmaceutical care and service, the container 10 allows receiving the prescription drug and also receiving, managing and displaying any document and information characterizing the care or service, including the actual prescription drug. The container 10 acts as a contributions space, from and for the actors, that evolves during its moving along the prescription preparation process and throughout the area defined with reference to Figure 1. The container 10 allows the different actors in the laboratory to easily and rapidly found information placed on or in the container 10 by another actor.

**[0085]** Further characteristics, features and functionality of the container 10 will become more apparent upon reading the following exemplified description of its use.

**[0086]** A technician at the reception picks a container 10 and a transparent plastic bag 47 and hangs the bag 47 to the bag-receiving supports of the container 10 as illustrated in Figure 3. According to another embodiment of the present invention, the bag 47 is pre-inserted in the container 10.

**[0087]** The technician then picks a card 52 and writes the name of the client, his/her birthday and/or his/her coordinates on the top blank portion 72 and identifies on the card 52 the nature of the pharmaceutical care requested by the client using the appropriate box 68. The identification in the box is in the form of a number quantifying the care. For example, the technician writes the number '2' in the NPx box to inform the other actors that will play a

role in the pharmaceutical care or to remind herself that the care includes two (2) new prescriptions.

**[0088]** According to the first embodiment, the card 52 is selected among a plurality of different colored cards (not shown) so that its color is indicative of the priority and/or path assigned to the pharmaceutical care. The priority and/or path are further identified using one of the symbols 76 displayed on the tab 74 as described hereinabove with reference to the Figure 5.

**[0089]** As mentioned hereinabove, the assignment or care request may come from a client present in the pharmacy or over the phone.

**[0090]** Once the information is written on the card 52, the technician then picks an information-receiving card 22 and attached the card 52 thereon using for example a rubber band 54 so that the tab 74 of the card 52 is registered with the tab 50 of the card 22. Prior to its use, the card is advantageously stored in the bottom 12 of the container 10 or in one of the two (2) document-receiving compartments 20 but can be stored separately from the container 10.

**[0091]** At this point, the card 22 is positioned at the front of the container 10, in the slot 51 so that the card 22 holds in the upright configuration, as described with reference to Figure 2C.

**[0092]** Before inserting drug vials or any other drug containers (not shown) in the container 10, the card 22 with the card 52 attached thereon is removed from the slot 51 and inserted in the slot 51' defined by the back wall 26 of the container 10 and the wings 42, freeing the front access to the container 10..

**[0093]** In the case where the pharmaceutical care includes a new prescription, this prescription (not shown) from the doctor or from another health care professional is inserted for example in the front side of the left document-receiving compartments 20. This document can then be readily found and consulted by any actor in the laboratory.

**[0094]** Any empty used vial or other medication container returned by the client and that can be recycled is placed in the bottom 12 of the container 10.

**[0095]** At any step along the workflow of the processing chain, whenever there is more than one container 10, the containers are positioned in one or more stacks as shown in Figure 4. When a plurality of containers 10 is stacked, the cards 22 are positioned in their respective slot so as to be upright. In this position, the cards do not interfere with the stacking and the information on the card is readily available and can be read easily.

**[0096]** Following the first two steps described hereinabove, i.e. 1) the definition of the pharmaceutical care and 2) the determination of a priority/path using the card 52, the technician then begins the computing of the prescription for the pharmaceutical care as briefly described hereinabove and as it is believed to be well known in the art.

**[0097]** Using the card 52 and the prescription note in the information-receiving compartment 20 as references, the technician creates a new client file using the terminal or accesses it in the case of a returning client. Using the client information and the prescription note, the technician uses the production terminal (see Figure 1), or any other device allowing access to the client file, to use the client-related information to prepare the label and the invoice and insurance receipts.

**[0098]** The label and the invoice and insurance receipts as well as any other document or card are stored in either one or both of the document-receiving compartments 20 according for example to a predetermined classification protocol.

**[0099]** In addition to the label, insurance receipt and invoice, example of documents that can be inserted in the information-receiving compartments include the client insurance and health-care cards, advice leaflets and any other information document.

**[00100]** Then, during the conditioning step, the prescription labels are inserted on or in the vials, the pills are inserted in the vials and the vials are positioned upright into the container 10 and therefore into the bag 47 which is still in the container 10.

**[00101]** It is to be noted that, at any step, the card 52 is readily available to the actors to add or complement information thereon.

**[00102]** The transparent bottom 12 of the container 10 and the transparent bag 47 allow a digital picture of the content of the container 10, including any containers and any accompanying label thereon (both not shown), to be taken from the bottom thereof after the closing of the bag 47 so as to allow the identification of the right pills, puffers, tube of cream, etc. (name and strength). Such a digital picture can then be used by the pharmacist, or by any other authorized actor, to inspect the content of the container 10 and the accuracy of the prescription conditioning.

**[00103]** Since digitalization and storing of images are believed to be well-known in the art, these steps will not be described furtherin for concision

purpose. The labeling and classifying of the medication and medication containers (not shown) are also believed to be well-known in the art and, as such, will not be described furtherin. According to some embodiment, the medication container can be positioned and ordered in the container 10 according to predetermined pattern and logic, allowing maximizing their identification in the container, for example in a digital picture thereof.

**[00104]** The picture being digital and stored in a computer or server, the verification of the accuracy of the prescription can be achieved away from the laboratory by any person having access to the picture file. Of course, the client file, or at least the parts thereof relevant to the inspection process, is also made available to the pharmacist doing the inspection, in accordance to the rules and/or protocols of the local pharmaceutical laws and/or practices

**[00105]** When the pharmacist proceed to the pharmaceutical analysis of a client file, for example at the verification terminal (see on Figure 1), the card 52 is consulted, and more specifically the information conveyed thereby. Since the pharmaceutical analysis step is believed to be well-known in the art, it will not be described furtherin for concision purposes.

**[00106]** According to the first embodiment, the bag 47 includes tempered-proof closing means, such as a self-adhesive upper rim, allowing indicating any unauthorized opening of the bag 47. Such tempered-proof closing means allows ensuring that the verification by the pharmacist or by another authorized actor of the container's content remains effective until the bag 47 is in the hands of the client. Any other well-known means and/or mechanism can also be used to temper-proof or lock the bag 47. According to another embodiment (not shown), the closing means is not tempered-proof. According to still another embodiment (not shown), the closing means is omitted. In case wherein the pharmaceutical care includes a new prescription,

the pharmacist can use any advice or information leaflet left by the technician in the document-receiving compartment 20 to provide recommendations in the consultation area or elsewhere.

**[00107]** Finally, the next step concerns the invoicing of the pharmaceutical care by the technician, clerk or cashier, wherein the documents in the information-receiving compartments that are intended for the client are inserted in a second bag (not shown) along with the bag 47. A conventional plastic bag, typically including the pharmacy logo thereon, can be used as the second bag.

**[00108]** When the pharmaceutical care results from a telephone call and therefore involves a pick up or a delivery at a later time, the content of the container 10, including the prescription vials and any document inserted in the information-receiving compartment, is stored in a plastic bag provided with a handle. This second bag is then hung in storage using for example the handle. During the pick up by the client, all the above-described content is removed from the storage bag and inserted in the conventional plastic bag mentioned hereinabove.

**[00109]** It is to be noted that neither the technician nor the pharmacist are limited to the role assigned in the previous example and each of them or another person can performed anyone of the actions described hereinabove, in respect of the rules/protocols of the local pharmaceutical laws.

**[00110]** According to another embodiment, the documents are positioned in the container 10 using a different classification protocol than the one described hereinabove.

**[00111]** A container 60 for the management of pharmacy prescriptions according to a second embodiment will now be described with reference to Figure 6. Since the container 60 is similar to the container 10, only the differences between the containers 60 and 10 will be described herein for concision purposes.

**[00112]** In addition to the rectangular cuts 32 and 34 in the walls 24 and 26, the front wall 24 includes a rectangular window 62 below the cut 32. The window 62 can be used to display information on a card (not shown) when such card is inserted in the slot 51, or the window can act as a support in combination with the cut 32 or wings 42 to hold a paper or cardboard document (not shown).

**[00113]** The window 62 can further act as a slot to be used for inserting a document or else when a second container 60 is mounted on the first container 60 in a stack arrangement as illustrated in Figure 4.

**[00114]** The container 60 further includes a tablet 64 integrally mounted to the back wall 26 so as to be tiltable. More specifically, the intersection 66 of the tablet 64 with the top edge of the wall 26 is thinner than at least one of the top portion of the wall 26 and the bottom portion of the tablet 64 allowing repetitive tilting movement of the table 64 relative to the wall 26.

**[00115]** The connection of the tablet 64 to the wall 26 is not limited to the illustrated weak line 66 and can take other form allowing pivotable movement of the tablet 64. For example the tablet 64 can be mounted to the wall 26 via a hinge.

**[00116]** According to another embodiment (not shown), the tablet 64 is fixedly mounted to the wall 26 in an upright or slanted configuration.

**[00117]** One or two rubber bands 54 can be provided to secure documents to the tablet 64. Other means, such as those described with reference to the first embodiment, can be used to secure the information to the card 52. The document can be for example in the form of the card 52.

**[00118]** It is to be noted that many modifications could be made to the containers 10 and 60 described hereinabove and illustrated in the appended drawings. For example:

**[00119]** – the container is not limited to a rectangular shape and can be for example round, oval or irregular;

**[00120]** – the dimension of the container and the proportion of its component, including the information-receiving card, are adapted to the application of the container;

**[00121]** – in case of a container being generally rectangular, such as container 10 or 60, the secondary walls 16 and 18 can be configured so as to have a length shorter that the length of the longitudinal walls 28 and 30;

**[00122]** – the wings 42 and 44 are not limited to be pivotable and can also be omitted;

**[00123]** - the container is not limited to being made entirely or in parts from a polymeric material. Any other rigid material can be used, including cardboard, metal, etc.;

**[00124]** – the cuts 32 and 34 are not limited to a rectangular shape or to be identical in shape and size. The cuts 32 and 34 can be for example elliptic, irregular or else. The cuts 32 and 34 can also be omitted;

**[00125]** – other means than a transparent bottom can be used to help indentifying and/or scanning of the contents of the container. Such means can be in the form of, for example, imprints, markings, RFID (Radio-Frequence Identification) or digital tags, bar codes, etc.;

**[00126]** – in addition to the document-receiving compartment 20 and the card 22, any surface or part of the container 10 can further be used to receive information for display or support. Such information can be written or displayed directly onto the container 10 or attached or fastened thereon using a clip, adhesive paper, etc.;

**[00127]** – the card 22 can be of any shape. Also, a plurality of cards 22 of different colors can also be provided so as to allow the actors to further visually characterized the care/prescription by selecting a card 22 having a color indicative of the specific characterization of the care/prescription;

**[00128]** - the bag 47 can be transparent or opaque and can be made of any suitable material, including polymer, fabric, organic, etc.;

**[00129]** – the container 10 or 60 or bag 47 can be colored so as to further help managing the prescription therein. For example, specific colors can be associated to anyone of the characteristics identified on the card 52; and

**[00130]** – any other characterization of the patient, care, or prescription than those illustrated and/or described herein can be used.

**[00131]** Although the present invention has been described hereinabove by way of illustrated embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

**CLAIMS**

1. A container for the management of a pharmaceutical care comprising:

a bottom;

a peripheral wall extending from said bottom;

a secondary wall mounted to the peripheral wall so as to define a document-receiving compartment between the peripheral wall and the secondary wall for receiving at least one document; and

an information-receiving card mounted to the peripheral wall for receiving and displaying information thereon.

2. A container as recited in claim 1, wherein the information-receiving card is removably mounted to the peripheral wall.

3. A container as recited in claim 1, wherein the information-receiving card is pivotably mounted to the peripheral wall.

4. A container as recited in claim 1, wherein the information-receiving card is fixedly mounted to the peripheral wall.

5. A container as recited in claim 1, wherein the secondary wall further defines with the peripheral wall a slot for receiving the information-receiving card.

6. A container as recited in claim 5, wherein the information-receiving card includes a support portion, a tab portion and a hinge allowing movement of the information-receiving card between an upright configuration, wherein the support and tab portions generally lie within a same plane, and a slanted configuration, wherein the support portion is tilted relative

to the tab portion; the information-receiving card cooperating with the slot to be moved between the upright and slanted configuration.

7. A container as recited in claim 6, wherein the peripheral wall includes a cut registered with the slot.

8. A container as recited in claim 1, wherein the secondary wall is a first secondary wall and the document-receiving compartment is a first document-receiving compartment; the container further comprising a second secondary wall mounted to the peripheral wall so as to define a second document-receiving compartment therebetween.

9. A container as recited in anyone of claims 1 to 8, wherein the peripheral wall includes top and bottom edges and being tapered from the top edge to the bottom edge.

10. A container as recited in claim 8, wherein each of the first and second secondary walls having longitudinal ends and including first and second pivotable wings at respective longitudinal ends.

11. A container as recited in claim 10, wherein the peripheral wall includes top and bottom edges and being tapered from the top edge to the bottom edge; the first and second pivotable wings being pivotable between an unfolded position wherein the wings are generally parallel to at least a portion of said peripheral wall to a support position wherein each of the wings define an acute angle with the peripheral wall; the container being a first container; the wings defining stoppers for a further container when a second container, similar to the first container is inserted therein in a stack arrangement.

12. A container as recited in claim 8, wherein the first and second secondary walls define a support for a bag.

13. A container as recited in claim 12, wherein both the bag and the bottom of the container are transparent to allow inspection of medication inserted in the container to be verified from the bottom.

14. A container as recited in claim 1, wherein the at least one document is selected from the group consisting of a prescription, insurance and cash receipts, a memo note, a booklet, a leaflet, a drug label and insurance and health-care cards.

15. A container as recited in claim 1, wherein the information is provided directly onto the information-receiving card.

16. A container as recited in claim 1, wherein the information is provided indirectly onto the information-receiving card via an information card mountable to the information-receiving card.

17. A container as recited in claim 16, wherein the information card further includes an information template.

18. A container as recited in claim 16, wherein the information card is secured to the information-receiving card by at least one of a rubber band, a clip, and an adhesive.

19. A container as recited in claim 16, wherein at least one of the information-receiving card and the information card includes color thereon.

20. A container as recited in claim 1, wherein the bottom is transparent.

21. A container as recited in claim 1, wherein the information relates to at least one of characteristics of the pharmaceutical care, notes, a

piece of paper; a priority of the pharmaceutical care, and a path of the pharmaceutical care.

22. A container as recited in claim 1, wherein at least one of the bottom and a cross-section of the peripheral wall is rectangular.

23. A container as recited in claim 1, wherein at least one of the peripheral wall and bottom is made of a plastic material.

24. A container as recited in claim 1, wherein advertisement is displayed on at least one of the peripheral wall, the secondary wall and the information-receiving card.

25. A container as recited in claim 1, wherein an insertion of a document in the document-receiving compartment and adding information onto the information-receiving card is achieved following a predetermined protocol.

26. A container as recited in claim 1, wherein the peripheral wall includes a cut defining a window therein to define a support for the document with the secondary wall.

27. A container as recited in anyone of claims 1 to 26, wherein the pharmaceutical care is selected from the group consisting of a drug prescription, a health-related advice and a health-related service.

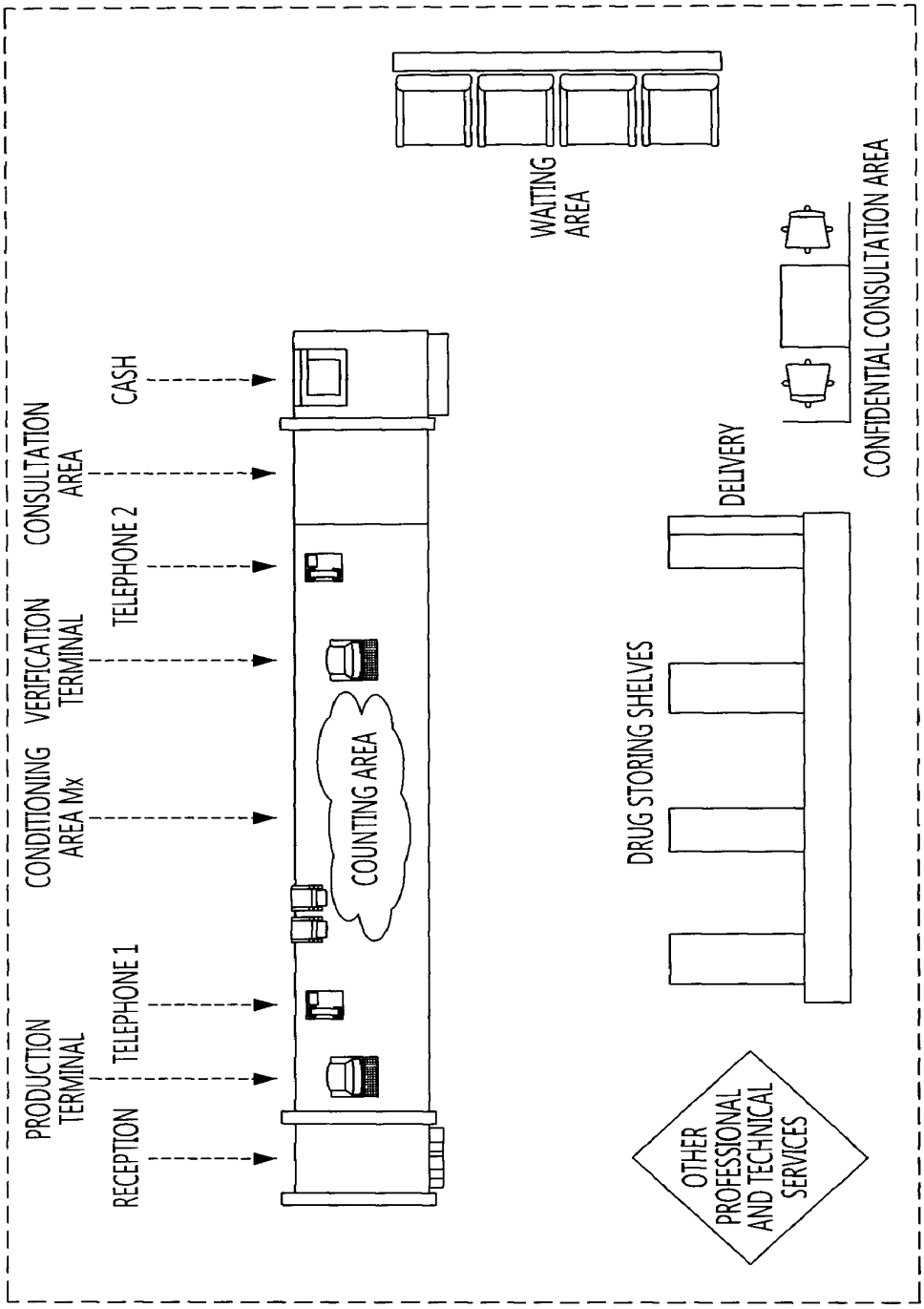

WAITING AREA
CONFIDENTIAL CONSULTATION AREA
DELIVERY
DRUG STORING SHELVES
OTHER PROFESSIONAL AND TECHNICAL SERVICES
COUNTING AREA
CASH
CONSULTATION AREA
TELEPHONE 2
VERIFICATION TERMINAL
CONDITIONING AREA Mx
TELEPHONE 1
PRODUCTION TERMINAL
RECEPTION

Fig. 1

1432

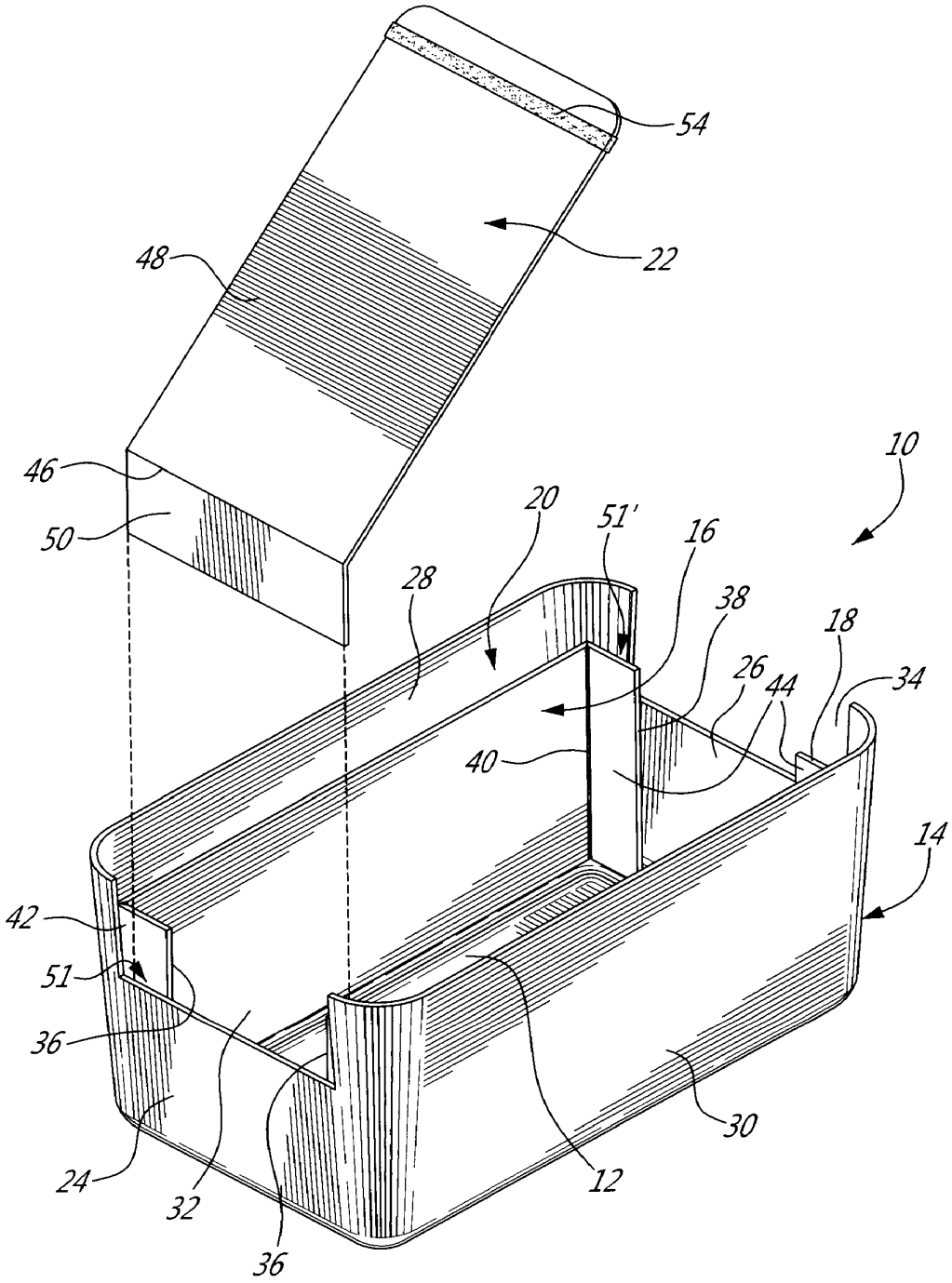

54
22
48
46
50
10
20
51'
16
28
38
18
26
44
34
40
14
42
51
36
24
32
36
12
30

FIG. 2A

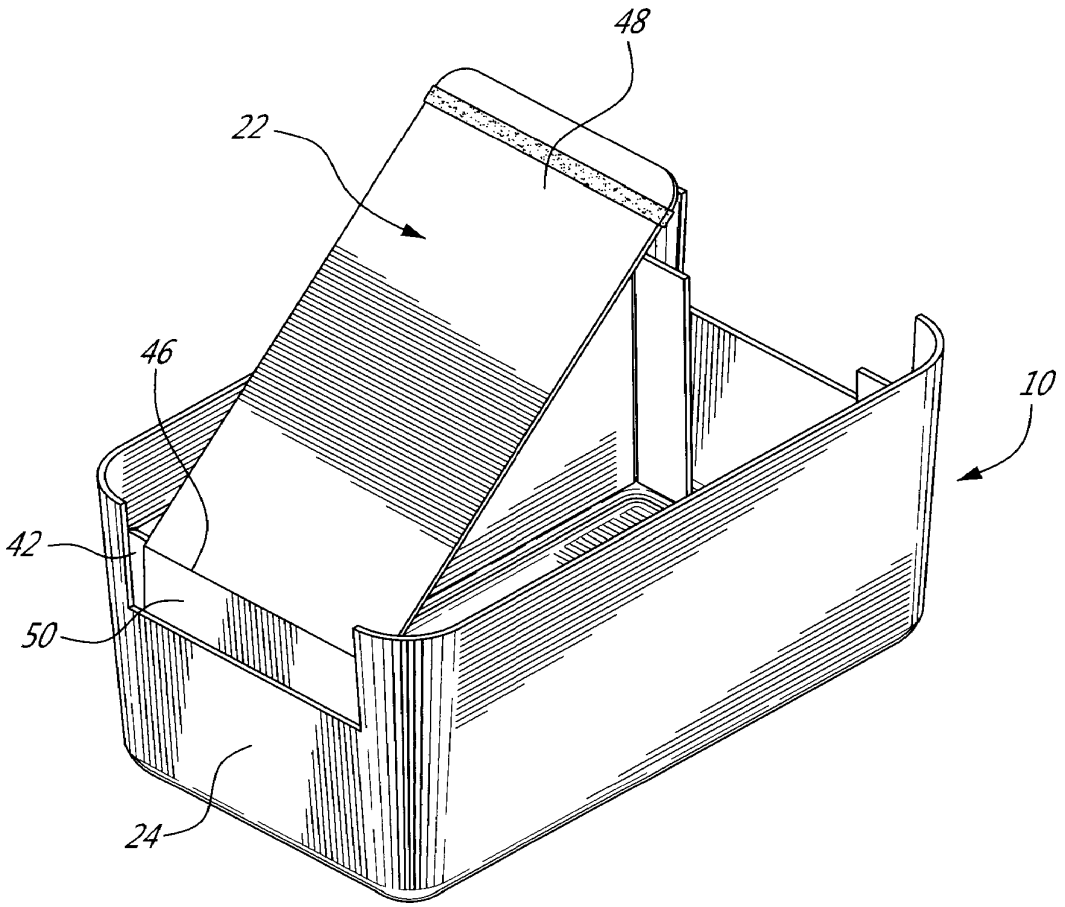



Fig. 2B

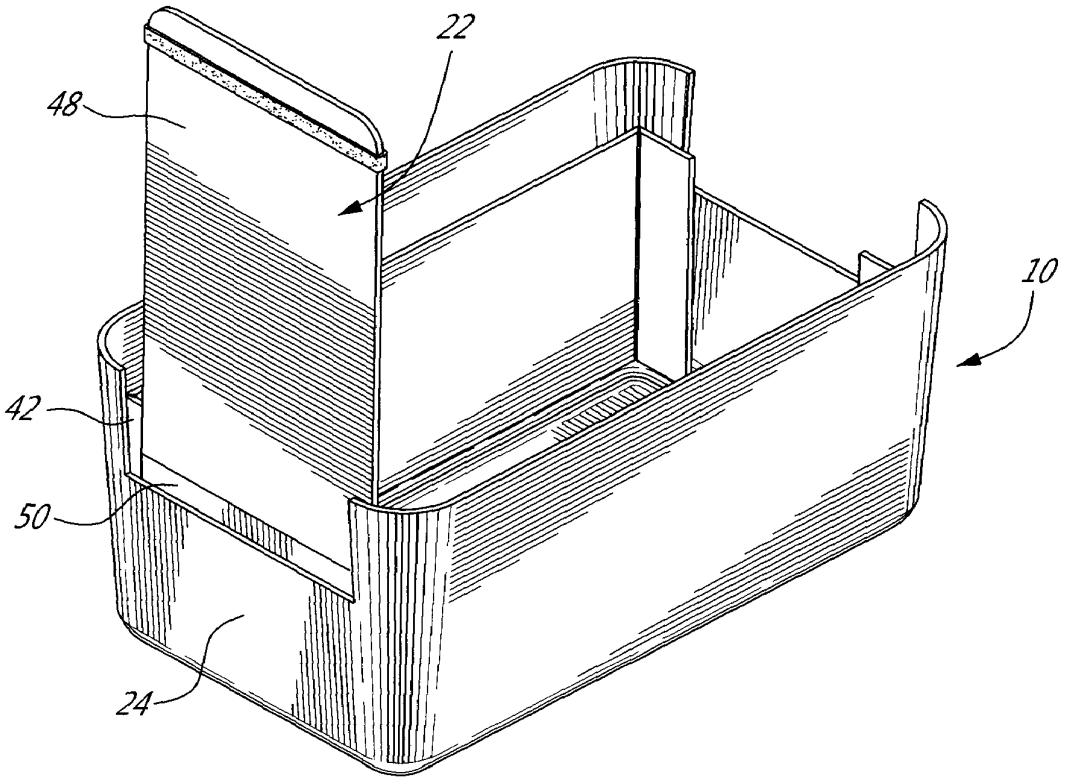



Fig. 2C

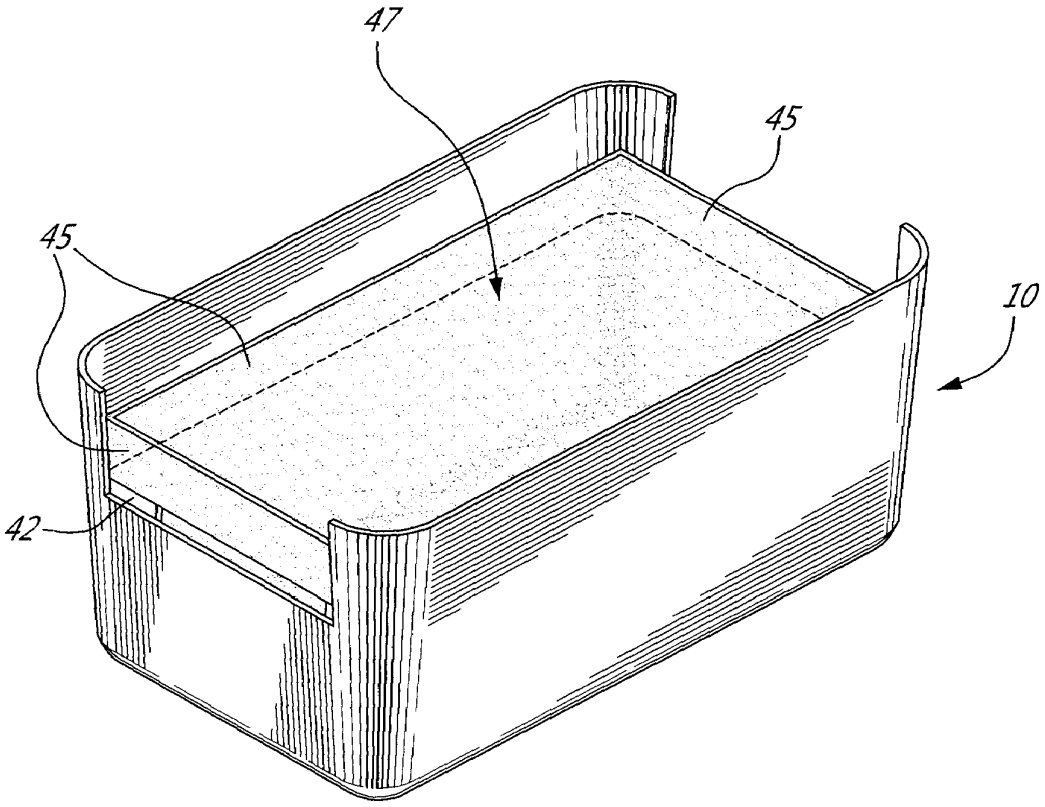



Fig. 3

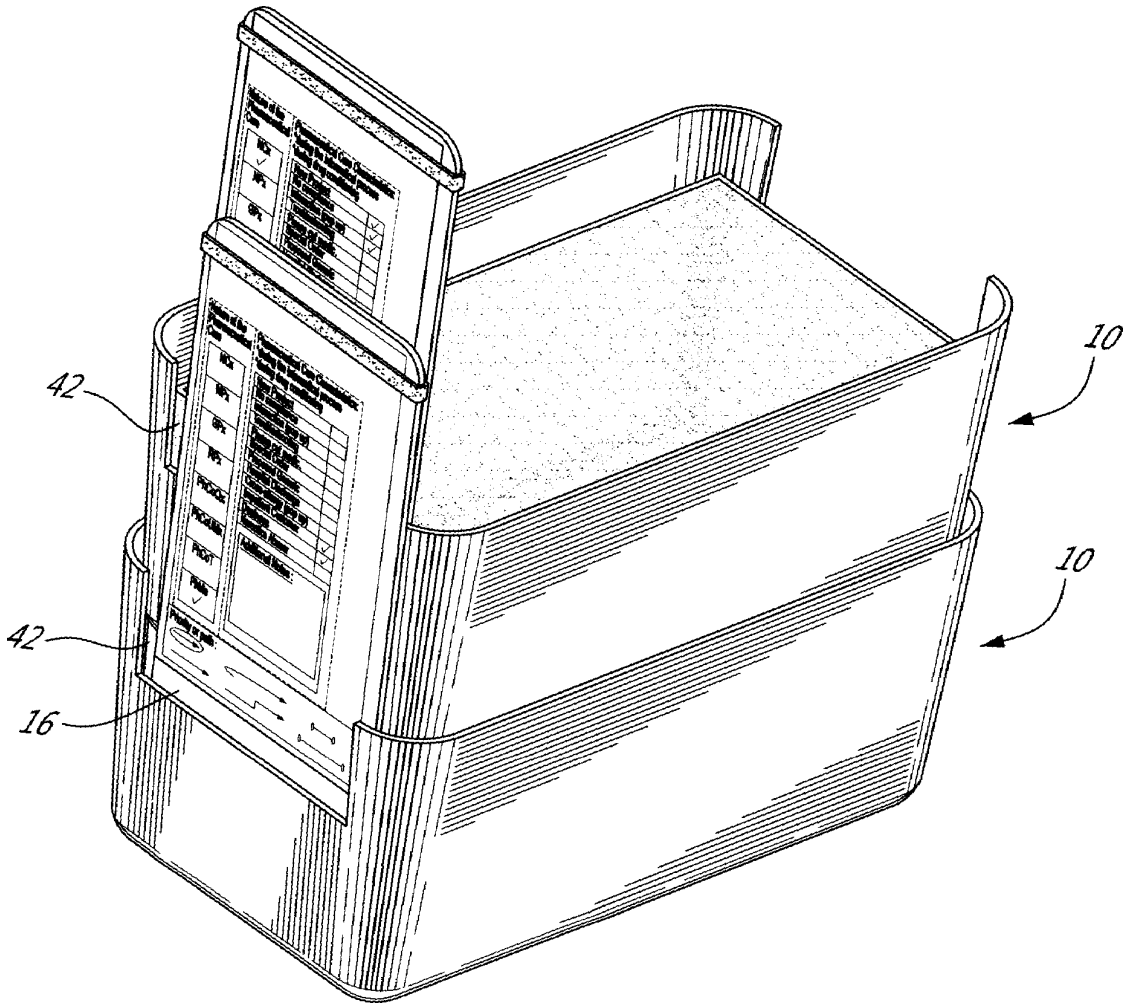



Fig. 4

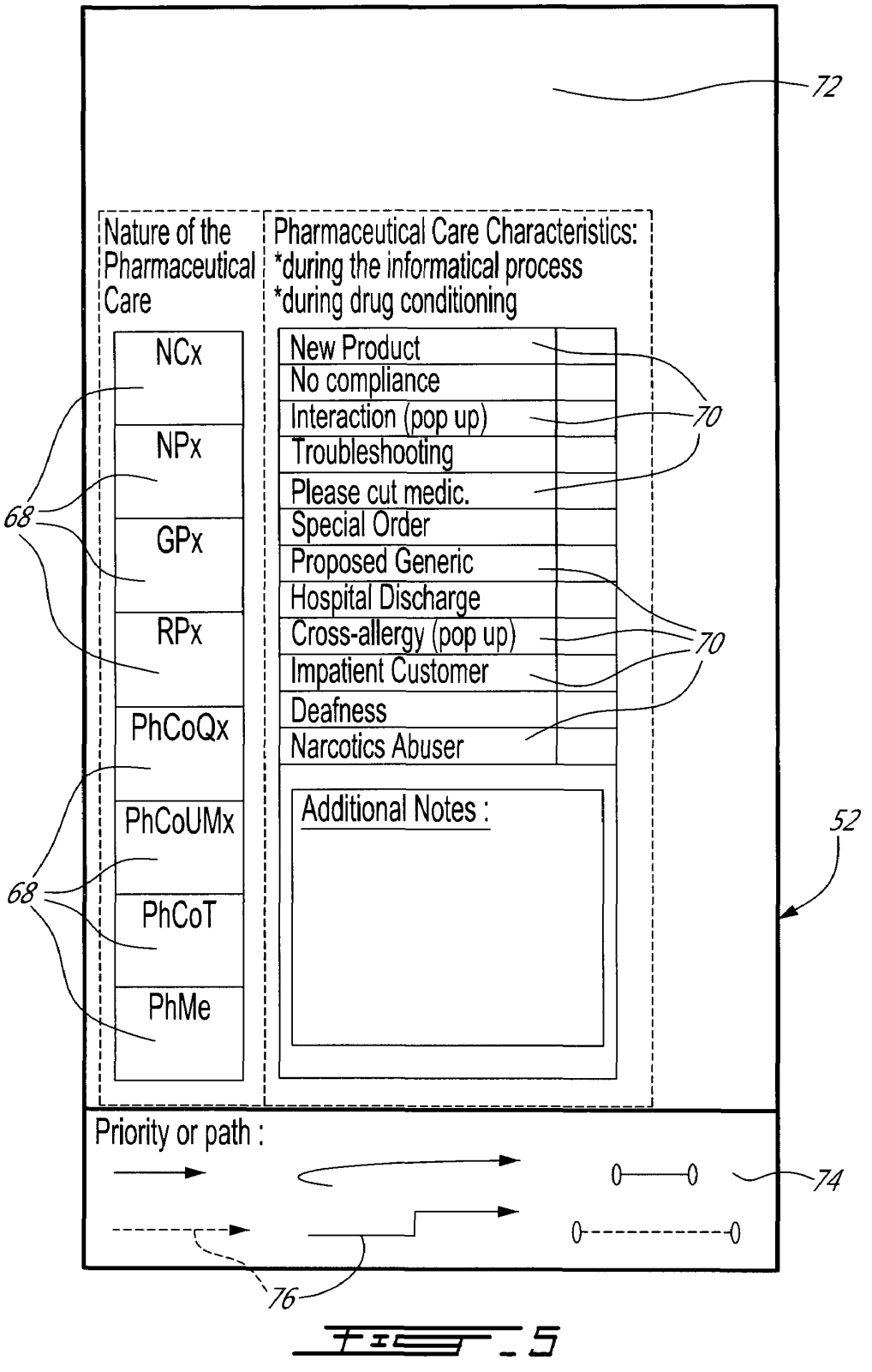

72
Nature of the Pharmaceutical Care
Pharmaceutical Care Characteristics:
*during the informatical process
*during drug conditioning
NCx
NPx
GPx
RPx
PhCoQx
PhCoUMx
PhCoT
PhMe
New Product
No compliance
Interaction (pop up)
Troubleshooting
Please cut medic.
Special Order
Proposed Generic
Hospital Discharge
Cross-allergy (pop up)
Impatient Customer
Deafness
Narcotics Abuser
Additional Notes :
68
70
52
Priority or path :
74
76

Fig. 5

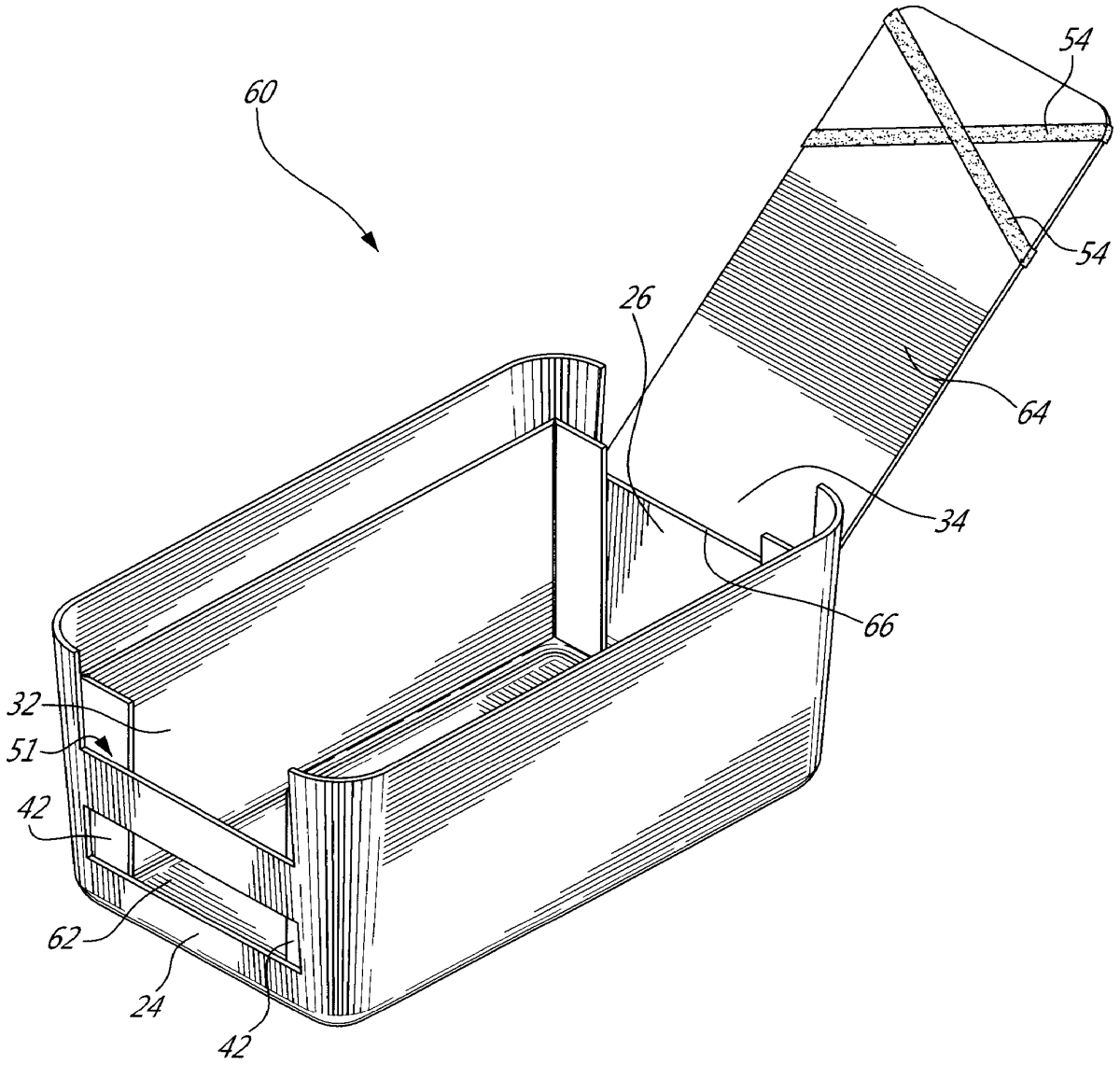



Fig. 6

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/CA2011/000929

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***B65D 1/34*** (2006.01) , ***A61J 1/00*** (2006.01) , ***B65D 25/54*** (2006.01)
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 (2006.01): B65D*, A61J
USCL: 206/528; 220/665

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, Epoque, Total Patent, USPTO
keywords:container, wall, peripheral, double, inside, second, information card, slot, pivotal, suprt tab, hinge, stack, transparent, window

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US2005/0173290 A1 (Shoji Y. et al.) 11 August 2005 (11-08-2005) *par. 0042, Fig's 11, 12* | 1, 2, 5, 8, 14, 15, 20-23, 26, 27 |
| X | CA2486361A1 (Adler D.) 27 November 2003 (27-11-2003) *page 14, line 25-page 15, line 22, Figures* | 1-5, 14, 15, 21, 23-25, 27 |
| A | US5662239A (Heuvelman G. M.) 2 September 1997 (02-09-1997) *see whole document* | 1 |

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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 |
|---|---|
| 28 October 2011 (28-10-2011) | 2 November 2011 (02-11-2011) |
| Name and mailing address of the ISA/CA<br>Canadian Intellectual Property Office<br>Place du Portage I, C114 - 1st Floor, Box PCT<br>50 Victoria Street<br>Gatineau, Quebec K1A 0C9<br>Facsimile No.: 001-819-953-2476 | Authorized officer<br><br>Goran Basic (819) 953-2098 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/CA2011/000929

| Patent Document Cited in Search Report | Publication Date | Patent Family Member(s) | Publication Date |
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| | | NO20045671A | 22 March 2005 (22-03-2005) |
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| | | WO2004078095A1 | 16 September 2004 (16-09-2004) |
| CA2486361A1 | 27 November 2003 (27-11-2003) | AU2003230408A1 | 02 December 2003 (02-12-2003) |
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| | | AU2009200954A1 | 09 April 2009 (09-04-2009) |
| | | AU2009200954B2 | 08 July 2010 (08-07-2010) |
| | | EP1509821A2 | 02 March 2005 (02-03-2005) |
| | | EP1509821A4 | 29 December 2010 (29-12-2010) |
| | | MXPA04011341A | 30 September 2005 (30-09-2005) |
| | | US2007029788A1 | 08 February 2007 (08-02-2007) |
| | | US7942451B2 | 17 May 2011 (17-05-2011) |
| | | US2003214129A1 | 20 November 2003 (20-11-2003) |
| | | US8025314B2 | 27 September 2011 (27-09-2011) |
| | | WO03098275A2 | 27 November 2003 (27-11-2003) |
| | | WO03098275A3 | 25 March 2004 (25-03-2004) |
| US5662239A | 02 September 1997 (02-09-1997) | None | |

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International Bureau

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PCT

(10) International Publication Number
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*A61M 15/06* (2006.01)

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PCT/US2011/048782

(22) International Filing Date:
23 August 2011 (23.08.2011)

(25) Filing Language: English

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(30) Priority Data:
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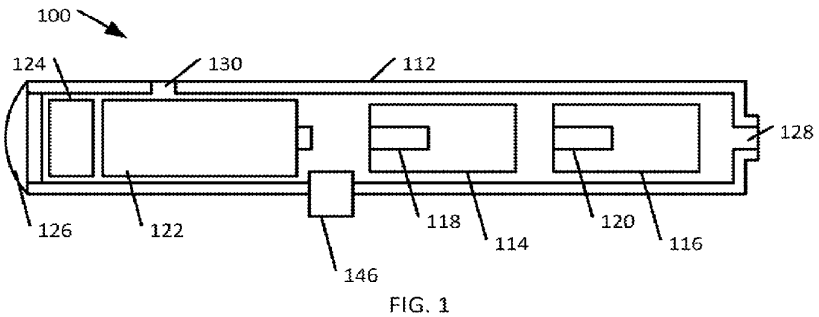



FIG. 1

(57) Abstract: An apparatus including a first cartridge, a sensor, and a controller. The first cartridge can include a first release device configured to release a first substance into a housing. The controller can be configured to receive data from the sensor. The controller can determine an amount of first substance released by the first cartridge based on the data. The first release device can be controlled based on the determined amount of first substance.

WO 2012/027350 A2

# INHALATION DEVICE INCLUDING SUBSTANCE USAGE CONTROLS

## CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

**[0001]** This application claims the benefit of U.S. Provisional Application 61/402,136, filed August 24, 2010, which is incorporated herein by reference in its entirety.

## BACKGROUND

**[0002]** The present disclosure relates generally to the field of smoke inhalation devices and more particularly to control mechanisms for smoke inhalation devices.

**[0003]** Smoke inhalation devices, commonly known as e-cigarettes, can be used to simulate a cigarette or a cigar. For example, a smoke inhalation device can vaporize a liquid including nicotine. A user of the smoke inhalation device can inhale the vapor and have an experience similar to smoking a traditional cigarette or cigar.

## SUMMARY

**[0004]** One illustrative embodiment is related to an apparatus including a first cartridge, a sensor, and a controller. The first cartridge can include a first release device configured to release a first substance into a housing. The controller can be configured to receive data from the sensor. The controller can determine an amount of first substance released by the first cartridge based on the data. The first release device can be controlled based on the determined amount of first substance.

**[0005]** Another illustrative embodiment is related to a method for metering an inhalation device. The method can include receiving data from a sensor. An amount of a first substance released by a first cartridge can be determined based on the data. The first cartridge can

include a first release device configured to release the first substance into a housing. The first release device can be controlled based on the determined amount of first substance.

**[0006]** Another illustrative embodiment is related to a non-transitory computer-readble medium having instructions stored thereon that, if executed by a computing device, cause the computing device to perform operations for metering an inhalation device. The method can include receiving data from a sensor. An amount of a first substance released by a first cartridge can be determined based on the data. The first cartridge can include a first release device configured to release the first substance into a housing. The first release device can be controlled based on the determined amount of first substance.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0007]** The foregoing and other features of the present disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings depict only several embodiments in accordance with the disclosure and are, therefore, not to be considered limiting of its scope, the disclosure will be described with additional specificity and detail through use of the accompanying drawings.

**[0008]** FIG. 1 is a section view of an inhalation device in accordance with an illustrative embodiment.

**[0009]** FIG. 2 is a schematic of an inhalation device control system in accordance with an illustrative embodiment.

**[0010]** FIG. 3 is a schematic of the inhalation device control system of FIG. 2 with additional sensors in accordance with an illustrative embodiment.

**[0011]** FIG. 4 is a diagram of a first inhalation device in accordance with an illustrative embodiment.

**[0012]** FIG. 5 is a diagram of a second inhalation device in accordance with an illustrative embodiment.

**[0013]** FIG. 6 is a diagram of a third inhalation device in accordance with an illustrative embodiment.

**[0014]** FIG. 7 is a diagram of a fourth inhalation device in accordance with an illustrative embodiment.

**[0015]** FIG. 8 is a diagram of a fifth inhalation device in accordance with an illustrative embodiment.

**[0016]** FIG. 9 is a diagram of a sixth inhalation device in accordance with an illustrative embodiment.

## DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

**[0017]** In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented here. It will be readily understood that the aspects of the present disclosure, as generally described herein, and illustrated in the figures, can be arranged, substituted, combined, and designed in a wide variety of different configurations, all of which are explicitly contemplated and make part of this disclosure.

**[0018]** The present disclosure is directed to an inhalation device including a substance usage control mechanism. The inhalation device can comprise a housing to hold and contain parts, at least one cartridge containing a substance such as nicotine, at least one releasing device such as a heater or an atomizer to work with the cartridge, a power source such as a battery, and a controller. The controller can collect data and control the cartridge and the releasing device to deliver a predetermined amount of the substance to the user. The inhalation device can be a long cylindrical shape similar to a cigarette or cigar. Advantageously, the inhalation device can control and/or limit amount of substance delivered the usage to help the user limit the consumption of a certain substance such as nicotine.

Advantageously, the inhalation device can control and/or limit amount of substance delivered such that a user can set a limit on an intake amount of the substance per use or for a certain period by the user. Advantageously, the inhalation device can receive and transmit data related to settings and usage. Advantageously, the inhalation device can monitor an amount of substance delivered to a user.

**[0019]** Referring to FIG. 1, a section view of an inhalation device 100 in accordance with an illustrative embodiment is shown. The inhalation device 100 can include a housing 112, a first cartridge 114, a second cartridge 116, a power source 122, a controller 124, a communication device 146, and a light device 126. In other embodiments, one or any number of cartridges can be used.

**[0020]** The housing 112 can be a long cylindrical shape, for example, the shape and size of a cigar, cigarillo, or cigarette. In other embodiments, the inhalation device 100 can be configured as other smoking or vapor delivery articles such as a hookah, a pipe, an inhaler, or a humidifier. The housing 112 can include an outlet hole 128 at a first end (i.e., a mouth end), where a user can place his lips to breathe in vapor or gas generated by inhalation device 100. The housing 112 can include an inlet hole 130 to allow air to enter the housing 112 when a user sucks on the first end. The housing 112 can be made of paper (e.g., paper rolled up in tubular shape), plastic, metal, wood, glass, or any other material.

**[0021]** The first cartridge 114 can be configured to retain and release a first substance such as nicotine. For example, the first cartridge 114 can include a medium such as a cotton fabric or a comparable material rolled up or shaped to fit inside housing 112. The cotton fabric can be soaked with the first substance. The first substance can include any drug, scent, transport agent, coloring, or a combination thereof. In one embodiment, the first substance is configured such that the substance can be vaporized or gasified. The first cartridge 114 can include a first release device 118. The first release device 118 can be embedded in or placed near the medium of the first cartridge 114. The first release device 118 can include one or a combination of a heating element, a vibration generator such as an ultrasonic or a piezoelectric transducer, an atomizer, or any other actuator to energize particles of the first substance such that the particles are released from the first cartridge 114 into a gas form or

microscopic droplets that can be carried off by air stream, for example, an airstream between the inlet hole 130 and outlet hole 128. The first release device 118 can be configured to control or meter the amount or rate of first substance released from the first cartridge 114. In some embodiments, the inhalation device includes a single cartridge.

**[0022]** The second cartridge 116 can be configured to retain and release a second substance such as a scent. For example, the second cartridge 116 can include a medium such as a cotton fabric or a comparable material rolled up or shaped to fit inside housing 112. The cotton fabric can be soaked with the second substance. The second substance can include any drug, scent, transport agent, coloring, or a combination thereof. In one embodiment, the first substance and the second substance are difference substances. In another embodiment, the first substance and the second substance are the same substance. In one embodiment, the second substance is configured such that the substance can be vaporized or gasified. The second cartridge 116 can include a second release device 120. The second release device 120 can be embedded in or placed near the medium of the second cartridge 116. The second release device 120 can include one or a combination of a heating element, a vibration generator such as an ultrasonic or a piezoelectric transducer, an atomizer, or any other actuator to energize particles of the second substance such that the particles are released from the second cartridge 116 into a gas form or microscopic droplets that can be carried off by airstream, for example, an airstream between the inlet hole 130 and outlet hole 128. The second release device 120 can be configured to control or meter the amount or rate of second substance released from the second cartridge 116. The first cartridge 114 and the second cartridge 116 can be arranged such that the airstream passes over and/or through both the first cartridge 114 and the second cartridge 116. In other embodiments, the inhalation device can include multiple cartridges.

**[0023]** The power source 122 can provide power to the first cartridge 114, first release device 118, the second cartridge 116, second release device 120, the controller 124, the communication device 146, and the light device 126. The power source 122 can be a battery such as an alkaline battery, a nickel metal hydride battery, a lithium-ion battery, a rechargeable battery or any other energy source. In other embodiments, the power source 122 can be external to the housing 112.

**[0024]** The light device 126 is configured to simulate the burning on the tip of a cigar or cigarette. The light device 126 can include a light emitting diode (LED), a resistance-type lamp, an organic light emitting diode (OLED), or any other light emitting device. The light device 126 can be configured to vary intensity based on the amount of airflow between the inlet hole 130 and outlet hole 128.

**[0025]** The controller 124 can be configured to control the first release device 118, the second release device 120, the communication device 146, the power source 122, and the light device 126. The controller 124 can be operatively and communicatively coupled to the first release device 118, the second release device 120, the communication device 146, and the light device 126. The controller 124 can be a processor such as a central processing unit, an application specific integrated circuit (ASIC), a state machine or any other controller. The controller 124 can include memory which can be any type of permanent or removable computer memory known to those of skill in the art. The memory of controller 124 can be a computer-readable storage medium. The controller 124 can include software for controlling the first release device 118, the second release device 120, the communication device 146, and the light device 126, which can be implemented as computer-readable instructions configured to be stored on the memory of controller 124.

**[0026]** The communication device 146 can be configured to allow a user to change and monitor the settings and state of the inhalation device 100. For example, in one embodiment, communication device 146 can be used to reprogram a part of the control logic of controller 124 to limit the usage of the inhalation device 100. The communication device 146 can include at least one of a switch, a keypad, a display, an input/output port, and a wireless transceiver. In one embodiment, the input/output port and the wireless transceiver can be employed to create a communications link between the controller 124 and an external computer, such as a cell phone or personal computer.

**[0027]** Referring to FIG. 2, a schematic of an inhalation device control system 200 in accordance with an illustrative embodiment is shown. The inhalation device control system 200 can include a first release device 218 associated with a first cartridge 214, a second release device 220 associated with a second cartridge 216, a power source 222, a controller

224, a timer 248, a counter 242, sensors 240, a communication device 246, and a light device 226. The controller 224 can be operatively and communicatively coupled to the first release device 218, the second release device 220, the power source 222, sensors 240, the communication device 246, and the light device 226. The inhalation device control system 200 can be, for example, discrete, integrated as a chip, or a printed circuit board assembly.

**[0028]** The first cartridge 214 and second cartridge 216 may each contain a unique substance or a mixture of two or more substances and the mixture composition for one cartridge is different from another. For this reason, the first release device 218 and the second release device 220 can each be operated in a unique way to optimize the effect of the substance for the user. Furthermore, different techniques can be employed for releasing the substances of different cartridges.

**[0029]** Sensors 240 can be, for example, a flow sensor, a thermocouple or pressure sensor to detect the air stream passing through the device or a group of sensors to detect any one of or a combination of airflow, temperature change, pressure change, illumination of light, current change, voltage change, and other physical and electrical properties. Sensors 240 can be located within or on a housing associated with the inhalation device control system 200.

**[0030]** The controller 224 can be configured to control and monitor the first release device 218, the second release device 220, sensors 240, the communication device 246, the power source 222, and the light device 226. The controller 224 can be a processor such as a central processing unit, an application specific integrated circuit (ASIC), a state machine or any other controller. The controller 224 can include a memory 280 which can be any type of permanent or removable computer memory known to those of skill in the art. The memory 280 of controller 224 can be a computer-readable storage medium. The controller 224 can include software for controlling the first release device 218, the second release device 220, the communication device 246, and the light device 226, which can be implemented as computer-readable instructions configured to be stored on the memory 280 of controller 224.

**[0031]** The communication device 246 can include at least one of a switch 271, a keypad 273, a display 250, an input/output port 277, and a wireless transceiver 279. The input/output

port 277 can be, for example, a serial port. The wireless transceiver 279 can be, for example, a Wi-Fi transceiver compliant with the IEEE 802.11 standard or a Bluetooth transceiver.

**[0032]** In one embodiment, the switch 271 can be a simple manual switch on a housing for sending reprogramming instructions to the controller 224 by clicking the switch 271 (e.g., clicking the switch five times with the clicking speed at one click per second or faster can reprogram the controller 224 to allow five puffs in a given period and then turn the device off). In another embodiment, the switch 271 can be a dial located on or in the middle of the housing for sending reprogramming instructions to the controller 224 such that by turning the dial the user can set the limit amount of the substance to be taken or inhaled. The dial switch can also be a section of the housing itself. In another embodiment, the switch 271 can be a shock or sound sensor such as a microphone for the user to tap for sending reprogramming instructions to the controller 224. The user can give the device taps at certain speed to set a desired amount of the substance to intake or inhale in a given period. In another embodiment, the switch 271 can be a light sensor to detect energy emitted by a laser, infrared, or other visible or invisible light source. Reprogramming instructions to the controller 224 can be on or off signals from the light source.

**[0033]** The user may use communication device 246 to reprogram the limit value in the controller 224. For example, a simple form of communication device 246 can be a manual switch the user can press or turn on or around the housing. By clicking or turning the switch manually, the user can change the limit setting in the controller 224. For example, by clicking the switch four times with a frequency of 1 Hz or higher, the user can smoke one cigarette equivalent worth of substance in each cycle or 10 each time, and clicking the switch two times will give a half cigarette worth of substance in each cycle. If the manual switch is a dial switch on the housing, the dial setting can set the limit. For example, the dial has indicator lines around it on the non-moving portion of the housing, and setting the dial at one can be equivalent to one cigarette dose per cycle and setting it to one half means a half of a cigarette dose.

**[0034]** The display 250 can be located on within or on the housing associated with the inhalation device control system 200. The display 250 can show messages indicating the

usage to help the user keep track of his use of the device. The display 250 can be, for example, a light, a series of lights, a segmented display or a pixelated display. The display 250 can be made, for example, of LEDs, a LED panel, a liquid crystal display, a group of small light bulbs, or electronic ink. The display 250 can display indications to the user, for example, as letters, dots, symbols, a series of lines, figures, pictures, shapes or signals. The display 250 can be monotone or multi-colored.

**[0035]** The display 250 can indicate the usage level for the user to monitor the use of the device and can send out messages to encourage the user to cut down on the use based on the progress he or she makes. A display message can include a number of cigarette equivalents used or left on the inhalation device control system 200, a number of puffs (i.e., drags) used or left on the inhalation device control system 200, and it can include a real time display of a number of puffs the user is allowed to take in each cycle as he or she uses the inhalation device control system 200. This way the device alerts the user, as he or she uses it, how many cigarette equivalents he or she is taking in a given period since using the same device for a long time may lead the user to a false sense of the substance usage. For example, the inhalation device control system 200 with a full first cartridge 214 and second cartridge 216 can be equivalent to one pack of cigarettes and the display 250 can clearly indicate the number of cigarette equivalents or puffs left in the first cartridge 214 and second cartridge 216 as he or she uses the inhalation device control system 200.

**[0036]** The timer 248 can be configured to measure an amount of the substance disbursed and/or to meter a predetermined amount of the substance to a user. The timer 248 can be separate from or integrated with controller 224. The timer 248 can be configured to measure, for example, the amount of time elapsed between user puffs, the amount of time the first release device 218 and the second release device 220 are activated, and the time between uses.

**[0037]** The timer 248 can be configured to measure an amount of the substance disbursed and/or to meter a predetermined amount of the substance to a user. The timer 248 can be separate from or integrated with controller 224. The timer 248 can be configured to measure, for example, the amount of time elapsed between user puffs, the amount of time the first

release device 218 and the second release device 220 are activated, and the time between uses. The timer 248 can be activated, for example, by an airflow sensor or a pressure switch. The timer 248 can be configured to measure a duration of a puff while the sensors 240 are activated.

**[0038]** The counter 242 can be configured to count a number of puffs taken per given period by a user. The counter 242 can be separate from or integrated with controller 224. The counter 242 can be configured to measure, for example, a number of puffs taken by a user during a smoking session, a day, a week, a month, or any other time period. The counter 242 can be activated, for example, by sensors 240.

**[0039]** For a more precise control of the amount of the substance allowed in a given period, timer 248 can be used to time the airflow through the device. Each time sensors 240 such as a flow sensor or a pressure switch are activated by the airflow, timer 248 can measure the duration of the airflow and the time for duration can be accumulated in a given period to activate a limit feature according to a substance distribution limit set in the control logic. Also counter 242 can be used to count the number of activations of sensors 240.

**[0040]** Counter 242 and timer 248 can provide usage data on the number of puffs per given period and timer 248 can provide both time duration of airflow for each puff and total time accumulated for the airflow over a given period. Therefore, when the substance distribution limit is set by the user or preset by the factory, the limit can be set on the actual amount of the substance in terms of total time allowed for airflow within a given period for use, not just an allowable number of puffs. Since an amount of airflow for a puff is different from person to person, setting a number of puffs as a limit can allow different amount of the targeted substance delivered to each different user or even to a same user depending on duration of each and every puff. Therefore, using timer 248 to monitor the usage along with counter 242 can provide a more accurate estimate of the measurement of the total airflow.

**[0041]** The inhalation device control system 200 can come with a factory setting for the allowable amount of the substance contained in the cartridges (214, 216) to be released. Different users have different usage habits: One person may prefer long hard puffs and

another person may like short shallow puffs. A person having long hard puffs usually finishes a cigarette in a less number of puffs than the person having the short shallow puffs. For this reason, the amount of substance allowed can be set as total duration time that is a time accumulation value of the total puffs in a given period. Another sensor such as a current sensor for the releasing means or the power source or a flow sensor with the air speed measurement can be applied to estimate the quantity of the substance use whenever the user draws the air through the device, and this information can be used along with the timer to calculate the more accurate amount of the substance use. Once the limit value as the time accumulation is set, timer 248 measures the duration of each puff and send the data to the control logic in controller 224 and controller 224 accumulates and compares the accumulated data with the set limit value. Once the accumulated time value or the value calculated from a combination with the accumulated time and the data of the quantity of the substance from the sensor reaches or goes over the limit value, controller 224 turns the inhalation device control system 200 off or makes the inhalation device control system 200 go into a low level mode in which the inhalation device control system 200 releases the substance at a lower rate than during the earlier period. The limit value can be set with cycles. For example, once the device is on, the user can be allowed a first set time limit for the total duration time of puffs within five minutes that is roughly equal to smoking one cigarette, and within a given period such as twelve hours or a day, the user can be allowed to use the inhalation device control system 200 a set number of times. Once the limit is reached controller 224 can turn off the releasing means (218, 220) to stop the substance flow to the user until the next cycle begins after non smoking time expires between two consecutive cycles or controls the releasing means (218, 220) such that the substance flow to the user is more limited per puff until the next cycle begins.

**[0042]** Referring to FIG. 3, a schematic of the inhalation device control system 200 of FIG. 2 with additional sensors in accordance with an illustrative embodiment is shown. The inhalation device control system 200 can include a first release device 218 associated with a first cartridge 214, a second release device 220 associated with a second cartridge 216, a power source 222, a controller 224, a timer 248, a counter 242, sensors 240, a communication device 246, and a light device 226. The controller 224 can be operatively and

communicatively coupled to the first release device 218, the second release device 220, the power source 222, sensors 240, the communication device 246, and the light device 226. The communication device 246 can include at least one of a switch 271, a keypad 273, a display 250, an input/output port 277, and a wireless transceiver 279. As discussed further below, the inhalation device control system 200 can measure substance usage in ways other than using a flow sensor or a pressure switch.

**[0043]** The first release device 218 and the second release device 220 can release a first substance from the first cartridge 214 and a second substance from the second cartridge 216 using, for example, heat and/or vibration. A temperature sensor 291 located on the second cartridge 216 can be used to detect the temperature of the second cartridge 216. The controller 224 can estimate an amount of substance released by the second cartridge 216 based on temperature information from the temperature sensor 291, along with information from timer 248. A vibration sensor 292 located on the second cartridge 216 can be used to detect the agitation of the second cartridge 216. The controller 224 can estimate an amount of substance released by the second cartridge 216 based on agitation information from the vibration sensor 292, along with information from timer 248. A current sensor 293 located on the power feed to the first release device 218 can be used to determine the current used by the first release device 218. The controller 224 can estimate an amount of substance released by the first cartridge 214 based on current information from the current sensor 293. Alternatively, a voltage sensor can be used.

**[0044]** In another embodiment, a current sensor 294 located on the power feed from power source 222 can be used to estimate the current used by the first release device 218 and second release device 220. The controller 224 can estimate an amount of substance released by the first cartridge 214 and the second cartridge 216 based on current information from the current sensor 294. Alternatively, a voltage sensor can be used. In another embodiment, a light sensor 295 located in proximity to light device 226 can be used to estimate the usage of the first release device 218 and second release device 220. The controller 224 can estimate an amount of substance released by the first cartridge 214 and the second cartridge 216 based on the amount of time the light sensor 295 is activated as well as the intensity detected by the

light sensor 295. Alternatively, other sensors can be used as is known in the art. Alternatively, sensors 291-295 can be place in various locations as is known in the art.

**[0045]** An illustrative inhalation device package for the market can be, for example, a smoking device in a cigarette form that comes with a capacity for smoking about twenty cigarettes. A factory setting can be preloaded to the smoking device to allow about fifteen puffs per use within five minutes, and after the user is done smoking for the time, he or she has to wait at least 30 minutes before using the device again. A display on the inhalation device can show the number of cigarette equivalents left to go, and it can also show the user the number of puffs left to go before the current use is expired as he or she use the inhalation device. In such a setting, the inhalation device can be programmed to monitor the usage of the substance contained in a cartridge by measuring the number of intake, or calculating the quantity of consumption of the substance from data collected from timer for the duration of each and every intake of the air and another sensor such as a electric current sensor or air flow sensor for the rate of flow of the substance. The number of puffs can then be translated to actual substance used based on the calculated estimation from the data provided by the timer and the sensor. Also a counter in the system can be used to count the number of intakes to provide the data to the control means to make calculation simpler. The user may use a button or a dial to change the factory settings such as the number of puffs allowed per use (e.g., from fifteen puffs setting to twenty puffs) and the duration of off time after the use before the next use is permitted (e.g., 30 minutes factory setting to 45 minutes or to 15 minutes). There can be one or more buttons or dials on the inhalation device to reprogram the settings for the inhalation device. A first button or dial for setting the off time duration and a second button or dial for setting a number of puffs allowed per use or other settings depending on the user preference and convenience.

**[0046]** FIGS. 4 through 8 depict a number of different illustrative embodiments of the inhalation device. Referring to FIG. 4, a diagram of a first inhalation device 400 in accordance with an illustrative embodiment is shown. The first inhalation device 400 can include a housing 412, a communication device 446, and a light device 426. The communication device 446 can include a display 450 and buttons 471 and 472. The first inhalation device 400 has two separate programming modes. In a first mode, button 471 can

be used to change the limit for a number of puffs allowed per use. In a second mode, button 472 can be used to change the amount of shut off time required before the next use. The display 450 can display an indication of a setting. (e.g., "10," "30," "60," "120," "10," "15," "20," "25")

**[0047]** Referring to FIG. 5, a diagram of a second inhalation device 500 in accordance with an illustrative embodiment is shown. The second inhalation device 500 can include a housing 512, a communication device 546, and a light device 526. The communication device 546 can include a first display 550, a button 571, and a second display 551. The button 571 can be used to change the amount of shut off time required before the next use. The first display 550 can display an indication of a setting. (e.g., "10," "30," "60," "90") The second display 551 can include lights 552. The lights 552 can indicate the indicating the number of cigarette equivalent remaining in the second inhalation device 500.

**[0048]** Referring to FIG. 6, a diagram of a third inhalation device 600 in accordance with an illustrative embodiment is shown. The third inhalation device 600 can include a housing 612, a communication device 646, and a light device 626. The communication device 646 can include a first display 650, a button 671, and a second display 651. The button 671 can be used to change the amount of shut off time required before the next use. The first display 650 can display an indication of a setting. (e.g., "10," "30," "60," "90") The second display 651 can display an indication (e.g., "385") showing the number of puffs or substance quantity remaining or available in the second inhalation device 600.

**[0049]** Referring to FIG. 7, a diagram of a fourth inhalation device 700 in accordance with an illustrative embodiment is shown. The fourth inhalation device 700 can include a housing 712, a communication device 746, and a light device 726. The communication device 746 can include a first display 750 and a dial 771. The dial 771 can be implemented as part of the housing 712. For example, a bezel of the dial 771 can be located at a filter area of the housing 712. The housing 712 can include graduation markings (e.g., "10," "30") near the dial 771. The dial 771 can be used to change the amount of shut off time required before the next use. The first display 750 can display an indication (e.g., "20") showing the number of cigarette equivalents remaining or available in the fourth inhalation device 700.

**[0050]** Referring to FIG. 8, a diagram of a fifth inhalation device 800 in accordance with an illustrative embodiment is shown. The fifth inhalation device 800 can include a housing 812, a communication device 846, and a light device 826. The communication device 846 can include a first display 850, a button 871, and a second display 851. The button 871 can be used to change the usage limit settings by the user. The first display 850 can display an indication of a setting. (e.g., "10," "30," "60," "90") The second display 851 can display an indication (e.g., "20") showing the number of cigarette equivalents remaining or available in the fifth inhalation device 800.

**[0051]** Referring to FIG. 9, a diagram of a sixth inhalation device 900 in accordance with an illustrative embodiment is shown. The sixth inhalation device 900 can include a housing 912, a communication device 946, and a light device 926. The communication device 946 can include a first display 950, buttons 971 and 972, and a second display 951. The sixth inhalation device 900 has two separate programming modes. In a first mode, button 971 can be used to change the limit for a number of puffs allowed per use. In a second mode, button 972 can be used to change the amount of shut off time required before the next use. The first display 950 can display an indication of a setting. (e.g., "10," "30," "60," "120," "10," "15," "20," "25") The second display 951 can display an indication (e.g., "20") showing the number of cigarette equivalents remaining or available in the sixth inhalation device 900.

**[0052]** One or more flow diagrams may have been used herein. The use of flow diagrams is not meant to be limiting with respect to the order of operations performed. The herein described subject matter sometimes illustrates different components contained within, or connected with, different other components. It is to be understood that such depicted architectures are merely exemplary, and that in fact many other architectures can be implemented which achieve the same functionality. In a conceptual sense, any arrangement of components to achieve the same functionality is effectively "associated" such that the desired functionality is achieved. Hence, any two components herein combined to achieve a particular functionality can be seen as "associated with" each other such that the desired functionality is achieved, irrespective of architectures or intermedial components. Likewise, any two components so associated can also be viewed as being "operably connected", or "operably coupled", to each other to achieve the desired functionality, and any two

components capable of being so associated can also be viewed as being "operably couplable", to each other to achieve the desired functionality. Specific examples of operably couplable include but are not limited to physically mateable and/or physically interacting components and/or wirelessly interactable and/or wirelessly interacting components and/or logically interacting and/or logically interactable components.

**[0053]** With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity.

**[0054]** It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to inventions containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (e.g., "a" and/or "an" should typically be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, typically means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is

intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

**[0055]** The foregoing description of illustrative embodiments has been presented for purposes of illustration and of description. It is not intended to be exhaustive or limiting with respect to the precise form disclosed, and modifications and variations are possible in light of the above teachings or may be acquired from practice of the disclosed embodiments. It is intended that the scope of the invention be defined by the claims appended hereto and their equivalents.

**WHAT IS CLAIMED IS:**

1. An apparatus comprising:

a first cartridge comprising a first release device configured to release a first substance into a housing; and

a sensor;

a controller configured to:

receive data from the sensor;

determine an amount of first substance released by the first cartridge based on the data; and

control the first release device based on the determined amount of first substance.

2. The apparatus of claim 1, wherein the housing is configured to enable a user to inhale the first substance.

3. The apparatus of claim 1, wherein the sensor comprises at least one of a flow sensor, a thermocouple, a pressure sensor, a current sensor, a voltage sensor, and a light sensor; and the first release device comprises at least one of a heating element, a vibration generator an ultrasonic transducer, a piezoelectric transducer, and an atomizer.

4. The apparatus of claim 1, wherein the substance comprises a drug.

5. The apparatus of claim 4, wherein the drug comprises nicotine.

6. The apparatus of claim 1, wherein the first release device is configured to vaporize or gasify the first substance associated with the first cartridge.

7. The apparatus of claim 6, further comprising a second cartridge comprising a second release device configured to release a second substance into the housing, wherein the controller is further configured to:

determine an amount of second substance released by the second cartridge based on the data; and

control the second release device based on the determined amount of second substance.

8. The apparatus of claim 1, wherein the controller is further configured to:

compare the determined amount of first substance to a predetermined limit; and

control the first release device based on the comparison.

9. The apparatus of claim 1, wherein the predetermined limit is associated with at least one of an amount of first substance released over a period, a number of puffs detected over a period, a duration between activations of the first cartridge.

10. The apparatus of claim 1, further comprising a communications device configured to:

provide information regarding a status of the first cartridge; and

receive an input;

wherein the controller is further configured to change the predetermined limit based on the input.

11. A method for metering an inhalation device comprising:

receiving data from a sensor;

determining an amount of a first substance released by a first cartridge based on the data, wherein the first cartridge comprises a first release device configured to release the first substance into a housing; and

controlling the first release device based on the determined amount of first substance.

12. The method of claim 11, wherein the housing is configured to enable a user to inhale the first substance, and the first release device is configured to vaporize or gasify the first substance associated with the first cartridge.

13. The method of claim 11, wherein the sensor comprises at least one of a flow sensor, a thermocouple, a pressure sensor, a current sensor, a voltage sensor, and a light

sensor; and the first release device comprises at least one of a heating element, a vibration generator an ultrasonic transducer, a piezoelectric transducer, and an atomizer.

14. The method of claim 11, wherein the first substance comprises nicotine.

15. The method of claim 11, further comprising:

determining an amount of a second substance released by a second cartridge based on the data, wherein the second cartridge comprises a second release device configured to release the second substance into the housing; and

controlling the second release device based on the determined amount of second substance.

16. A non-transitory computer-readable medium having instructions stored thereon that, if executed by a computing device, cause the computing device to perform operations comprising:

receiving data from a sensor;

determining an amount of a first substance released by a first cartridge based on the data, wherein the first cartridge comprises a first release device configured to release the first substance into a housing; and

controlling the first release device based on the determined amount of first substance.

17. The computer-readable medium of claim 16, wherein the housing is configured to enable a user to inhale the first substance, and the first release device is configured to vaporize or gasify the first substance associated with the first cartridge.

18. The computer-readable medium of claim 16, wherein the sensor comprises at least one of a flow sensor, a thermocouple, a pressure sensor, a current sensor, a voltage sensor, and a light sensor; and the first release device comprises at least one of a heating element, a vibration generator an ultrasonic transducer, a piezoelectric transducer, and an atomizer.

19. The computer-readable medium of claim 16, wherein the first substance comprises nicotine.

20. The computer-readable medium of claim 16, wherein the operations further comprising:

determining an amount of a second substance released by a second cartridge based on the data, wherein the second cartridge comprises a second release device configured to release the second substance into the housing; and

controlling the second release device based on the determined amount of second substance.

21. An apparatus comprising:

a first cartridge comprising a first release device configured to release a first substance into a housing; and

a sensor;

a controller configured to:

receive data from the sensor;

determine an amount of first substance released by the first cartridge based on the data; and

estimate a remaining amount of first substance in the first cartridge based on the determined amount of first substance.

22. The apparatus of claim 21, further comprising a display, wherein the controller is further configured to:

estimate at least one of:

a number of puffs remaining,

a number of cigarette equivalents remaining, or

a number of cigar equivalents remaining

based on the estimated remaining amount of first substance;

wherein the display is configured to display an indication of at least one of the number of puffs remaining, the number of cigarette equivalents remaining, or the number of cigar equivalents remaining.

23. The apparatus of claim 22, wherein:

the sensor comprises at least one of a flow sensor, a thermocouple, a pressure sensor, a current sensor, a voltage sensor, and a light sensor;

the first release device comprises at least one of a heating element, a vibration generator an ultrasonic transducer, a piezoelectric transducer, and an atomizer; and

the display comprises at least one of a row of light emitting diodes, an alphanumeric display, a seven-segment display, or a pixelated display.

24. The apparatus of claim 21, wherein the housing is configured to enable a user to inhale the first substance and the first substance comprises nicotine.

25. A method for providing inhalation device information comprising:

receiving data from a sensor;

determining an amount of a first substance released by a first cartridge based on the data, wherein the first cartridge comprises a first release device configured to release the first substance into a housing; and

estimating a remaining amount of first substance in the first cartridge based on the determined amount of first substance.

26. The method of claim 25, further comprising:

estimating at least one of:

a number of puffs remaining,

a number of cigarette equivalents remaining, or

a number of cigar equivalents remaining

based on the estimated remaining amount of first substance;

displaying an indication of at least one of the number of puffs remaining, the number of cigarette equivalents remaining, or the number of cigar equivalents remaining.

27. The method of claim 26, wherein:

the sensor comprises at least one of a flow sensor, a thermocouple, a pressure sensor, a current sensor, a voltage sensor, and a light sensor;

the first release device comprises at least one of a heating element, a vibration generator an ultrasonic transducer, a piezoelectric transducer, and an atomizer; and

displaying an indication comprises controlling at least one of a row of light emitting diodes, an alphanumeric display, a seven-segment display, or a pixelated display.

28. The method of claim 25, wherein the housing is configured to enable a user to inhale the first substance and the first substance comprises nicotine.

29. A non-transitory computer-readable medium having instructions stored thereon that, if executed by a computing device, cause the computing device to perform operations comprising:

receiving data from a sensor;

determining an amount of a first substance released by a first cartridge based on the data, wherein the first cartridge comprises a first release device configured to release the first substance into a housing; and

estimating a remaining amount of first substance in the first cartridge based on the determined amount of first substance.

30. The computer-readable medium of claim 29, further comprising:

estimating at least one of:

a number of puffs remaining,

a number of cigarette equivalents remaining, or

a number of cigar equivalents remaining

based on the estimated remaining amount of first substance;

displaying an indication of at least one of the number of puffs remaining, the number of cigarette equivalents remaining, or the number of cigar equivalents remaining.

31. The computer-readable medium of claim 30, wherein:

the sensor comprises at least one of a flow sensor, a thermocouple, a pressure sensor, a current sensor, a voltage sensor, and a light sensor;

the first release device comprises at least one of a heating element, a vibration generator an ultrasonic transducer, a piezoelectric transducer, and an atomizer; and

displaying an indication comprises controlling at least one of a row of light emitting diodes, an alphanumeric display, a seven-segment display, or a pixelated display.

32. The computer-readable medium of claim 31, wherein the housing is configured to enable a user to inhale the first substance and the first substance comprises nicotine.

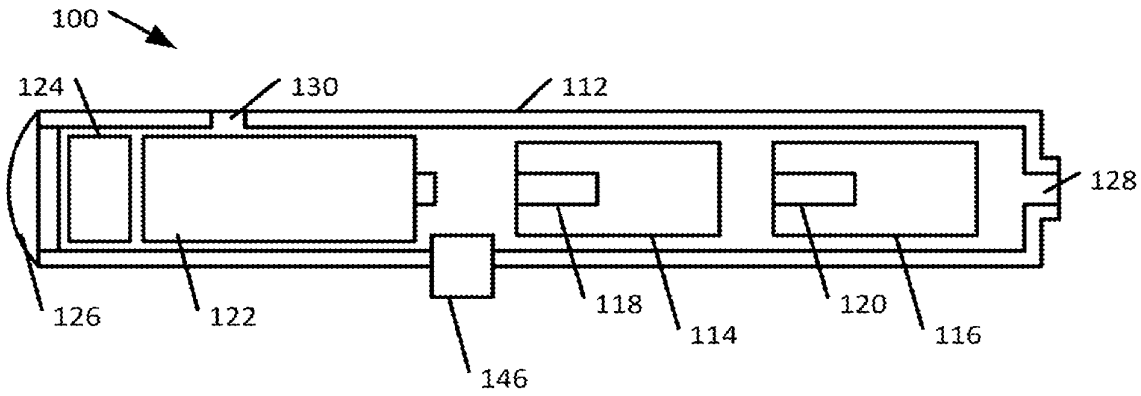

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FIG. 1

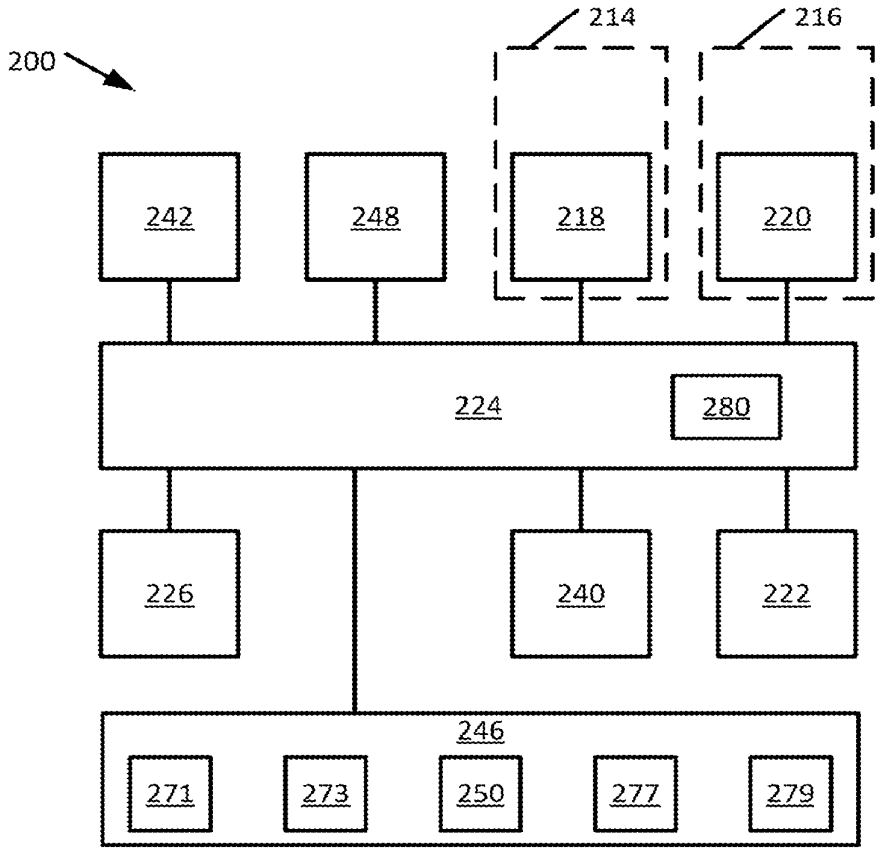

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FIG. 2

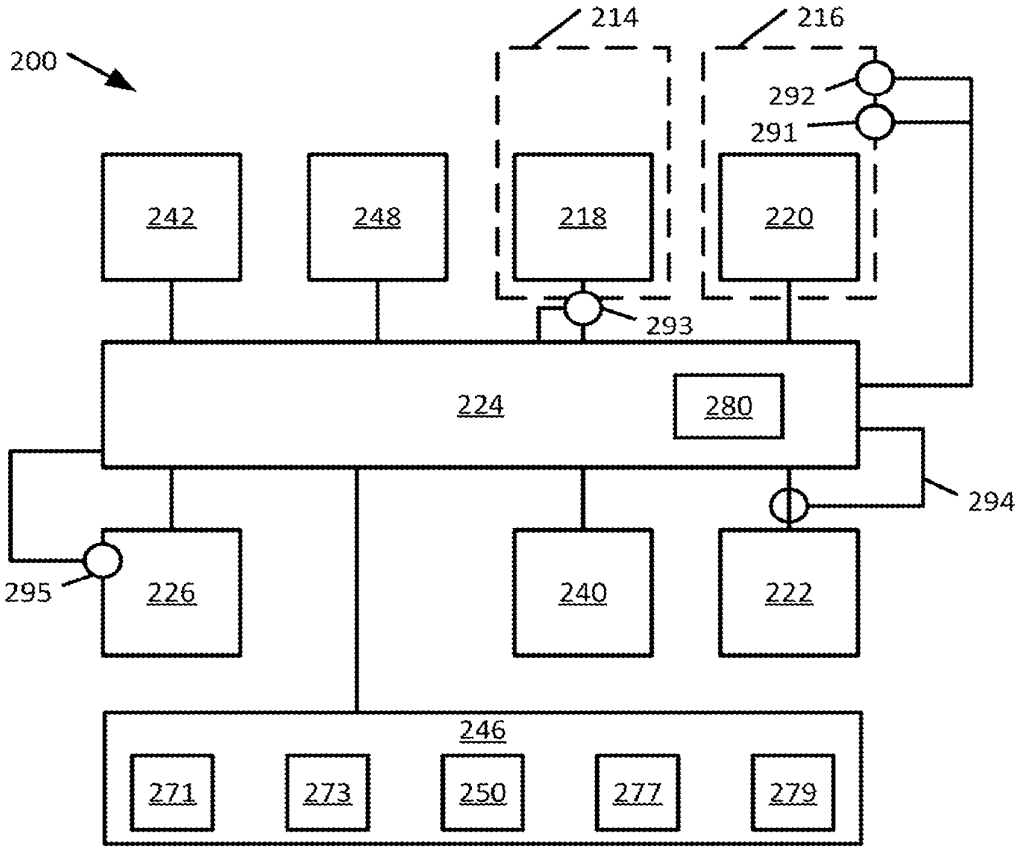

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FIG. 3

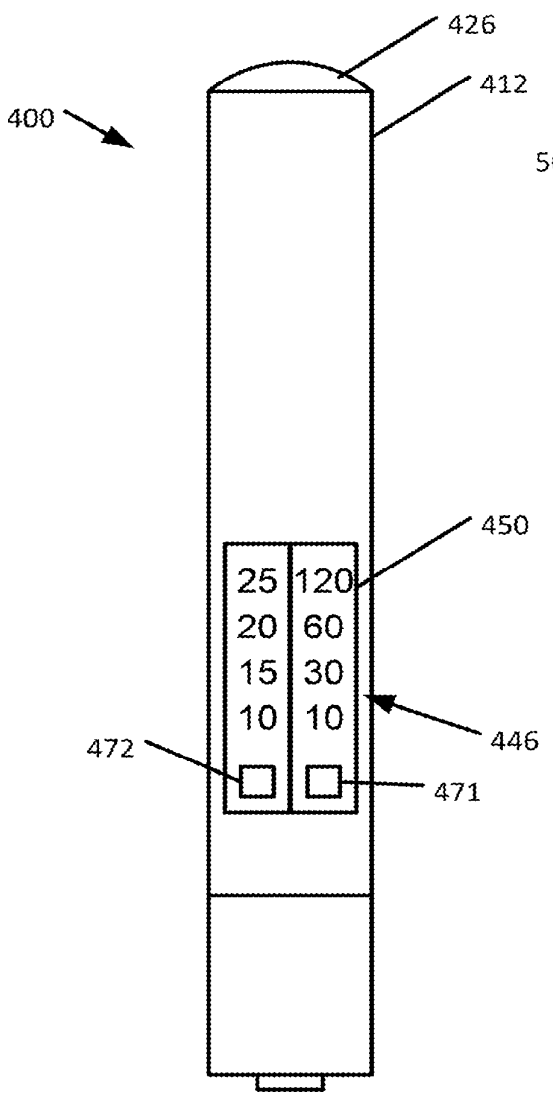

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FIG. 4

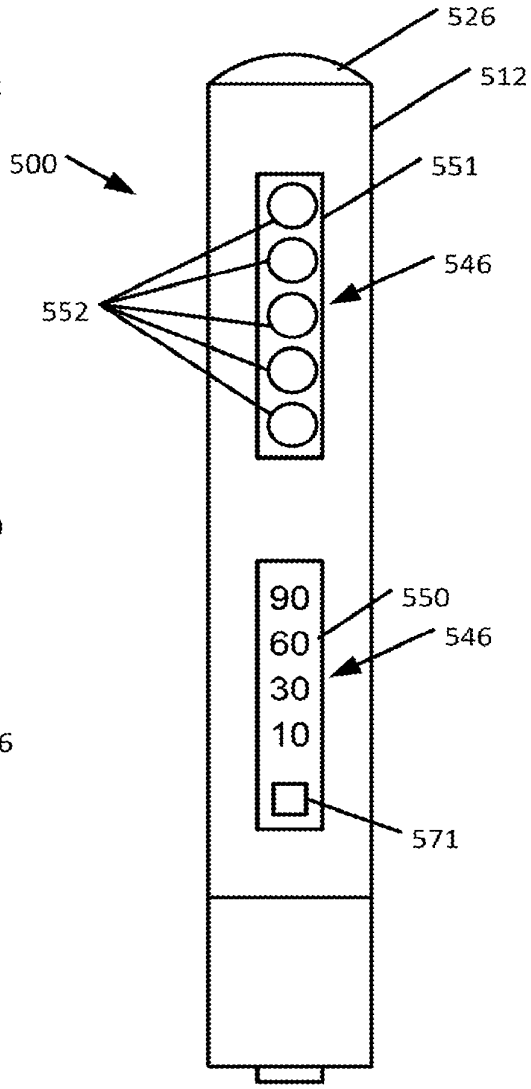

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FIG. 5

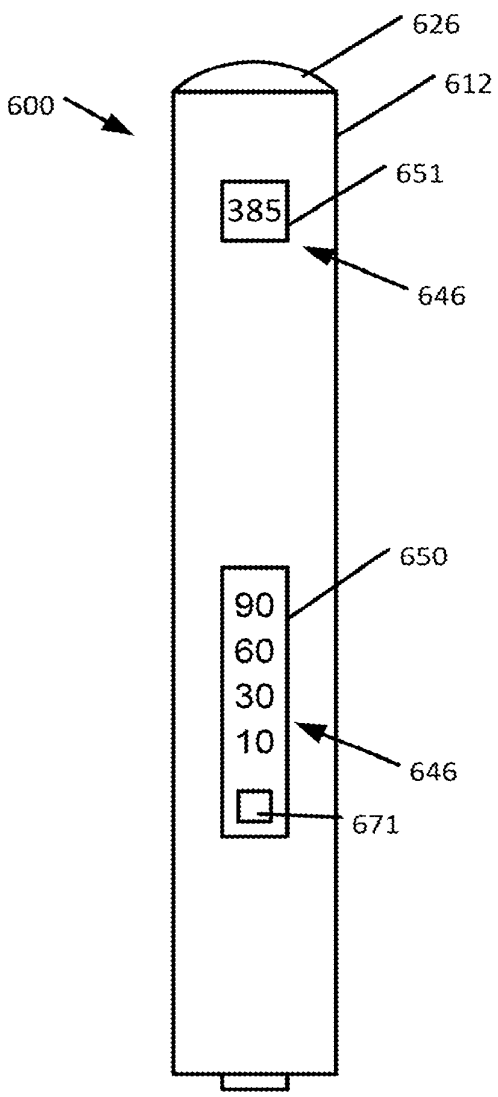

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FIG. 6

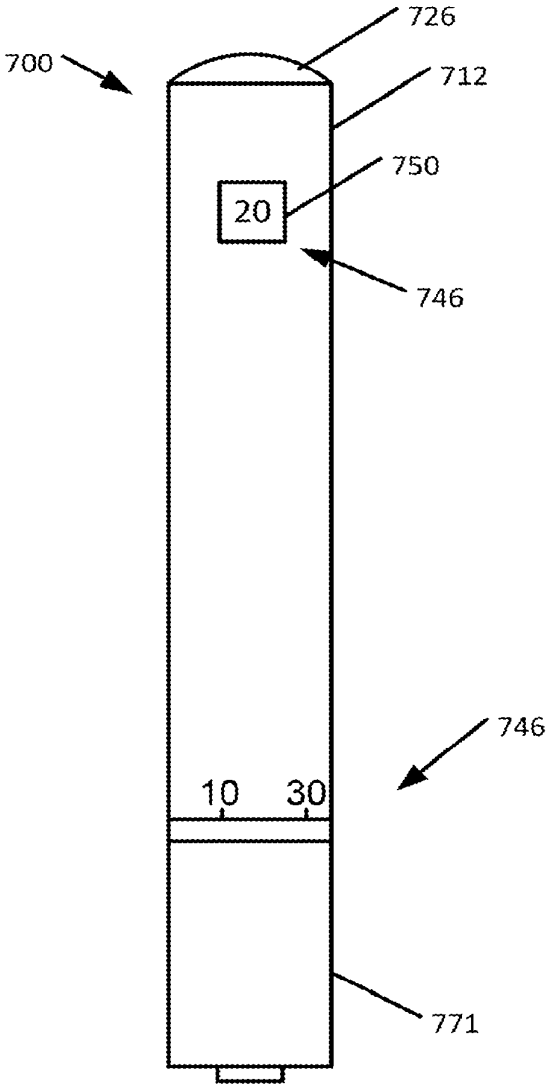

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FIG. 7

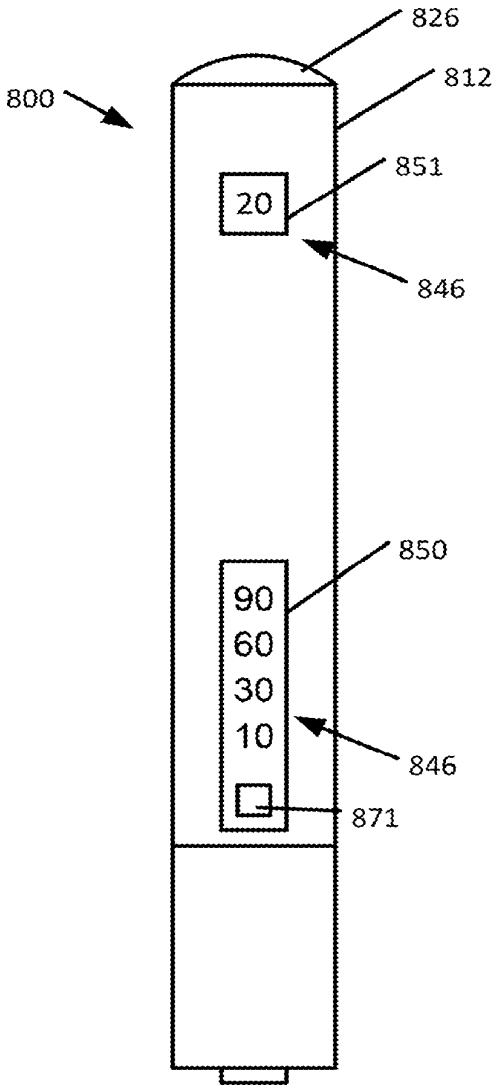

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FIG. 8

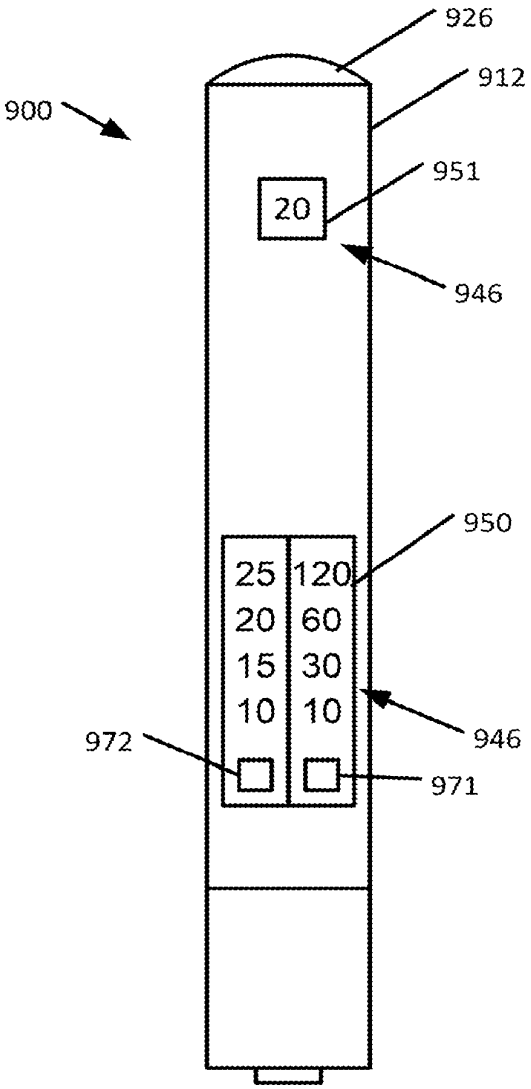

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25 120
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FIG. 9

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(74) Agents: **HUSTON, Eric N.** et al.; Foley & Lardner LLP, 150 East Gilman Street, Post Office Box 1497, Madison, Wisconsin 53701-1497 (US).

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(54) Title: INHALATION DEVICE INCLUDING SUBSTANCE USAGE CONTROLS

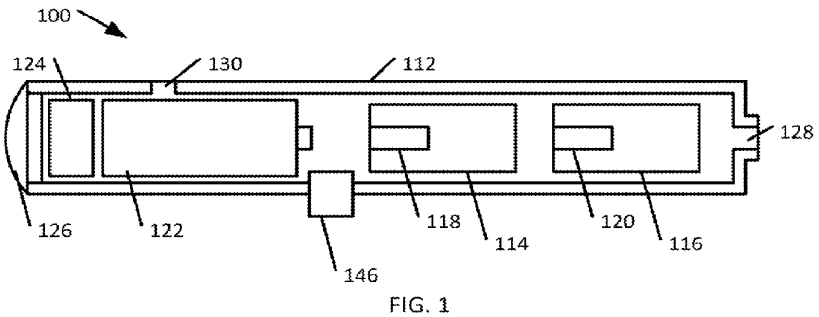



FIG. 1

(57) Abstract: An apparatus including a first cartridge, a sensor, and a controller. The first cartridge can include a first release device configured to release a first substance into a housing. The controller can be configured to receive data from the sensor. The controller can determine an amount of first substance released by the first cartridge based on the data. The first release device can be controlled based on the determined amount of first substance.

WO 2012/027350 A3

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2011/048782**

**A. CLASSIFICATION OF SUBJECT MATTER**

***A24F 47/00(2006.01)i, A61M 15/06(2006.01)i, A24F 1/14(2006.01)i***

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)
A24F 47/00; A24F 1/22; A24F 1/10; A24B 1/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: cartridge, substance.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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| A | US 2008-0257367 A1 (PATERNO GREG et al.) 23 October 2008<br>See claims 10, 14-20, figs. 1-2, paragraph [0016] | 1-32 |
| A | US 2006-0196518 A1 (LIK HON) 07 September 2006<br>See claims 1,9,11-12, 34, 36, fig. 1, paragraph [0021] | 1-32 |
| A | US 2006-0130860 A1 (GEORGES CHOLET, ORMES) 22 June 2006<br>See claims 1-15, figs. 1-2 | 1-32 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 MARCH 2012 (23.03.2012) | **26 MARCH 2012 (26.03.2012)** |
| Name and mailing address of the ISA/KR<br>Korean Intellectual Property Office<br>Government Complex-Daejeon, 189 Cheongsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea<br>Facsimile No. 82-42-472-7140 | Authorized officer<br>CHO, Sung Ho<br>Telephone No. 82-42-481-5615 |

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.
**PCT/US2011/048782**

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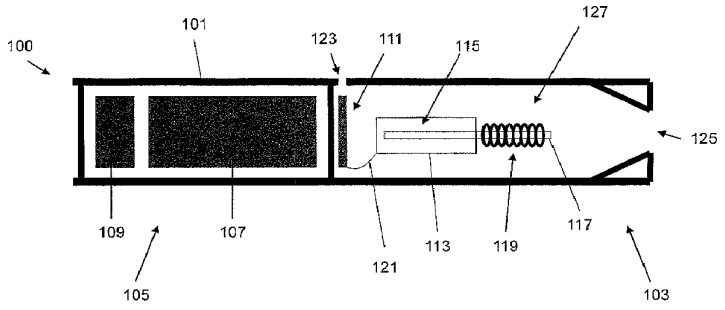
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(54) **Title**: AN AEROSOL GENERATING SYSTEM HAVING MEANS FOR HANDLING CONSUMPTION OF A LIQUID SUBSTRATE

Figure 1




(57) **Abstract**: There is provided an electrically operated aerosol generating system (100) for receiving an aerosol - forming substrate (115). The system comprises a liquid storage portion (113) for storing liquid aerosol - forming substrate, an electric heater (119) comprising at least one heating element for heating the liquid aerosol - forming substrate, and electric circuitry (109) configured to monitor activation of the electric heater and estimate an amount of liquid aerosol - forming substrate remaining in the liquid storage portion based on the monitored activation. There is also provided a method in an electrically operated aerosol generating system comprising a liquid storage portion for storing liquid aerosol - forming substrate and an electric heater comprising at least one heating element for heating the liquid aerosol - forming substrate, the method comprising: monitoring activation of the electric heater and estimating an amount of liquid aerosol - forming substrate remaining in the liquid storage portion based on the monitored activation.

WO 2012/085207 A1

# AN AEROSOL GENERATING SYSTEM HAVING MEANS FOR HANDLING CONSUMPTION OF A LIQUID SUBSTRATE

The present invention relates to an electrically operated aerosol generating system. In particular, the present invention relates to an electrically operated aerosol generating system in which the aerosol-forming substrate is liquid and is contained in a liquid storage portion.

WO 2007/078273 discloses an electric smoking utensil. A liquid is stored in a container which communicates with a heater vaporiser, powered by a battery supply, via a series of small apertures. The heater is in the form of a spirally wound electric heater mounted on an electrically insulating support. In use, the heater is activated by the mouth of a user to switch on the battery power supply. Suction on a mouthpiece by the user causes air to be drawn through holes in the container, over the heater vaporiser, into the mouthpiece and subsequently into the mouth of a user.

The electrically operated aerosol generating systems of the prior art, including the smoking system referred to above, do have a number of advantages, but there is still opportunity for improvement in the design, particularly concerning the handling of liquid aerosol-forming substrate stored in the container.

According to a first aspect of the invention, there is provided an electrically operated aerosol generating system for receiving an aerosol-forming substrate, the system comprising: a liquid storage portion for storing liquid aerosol-forming substrate; an electric heater comprising at least one heating element for heating the liquid aerosol-forming substrate; and electric circuitry configured to monitor activation of the electric heater and estimate an amount of liquid aerosol-forming substrate remaining in the liquid storage portion based on the monitored activation.

The aerosol generating system is arranged to vaporize the aerosol-forming substrate to form the aerosol. As known to those skilled in the art, an aerosol is a suspension of solid particles or liquid droplets in a gas, such as air.

Activation of the electric heater may be monitored in several ways, for example by monitoring the temperature of the heating element over time, the resistance of the heating element over time, or the power applied to the heater over time, or a combination of two or more of these parameters.

Preferably, the electric circuitry is configured to estimate a consumed amount of liquid aerosol-forming substrate, and to subtract the consumed amount from a known initial amount to provide an estimate of liquid aerosol-forming substrate remaining in the liquid storage portion.

Preferably, the electric circuitry is configured to monitor activation of the electric heater by monitoring the temperature or resistance of the heating element over time to estimate a consumed amount of aerosol-forming substrate. Preferably, the electric circuitry is configured to estimate a consumed amount of aerosol based on a first equation relating heating element temperature or resistance to aerosol-forming substrate consumption up to a first threshold of temperature or resistance and based on a second equation relating heating element temperature or resistance to aerosol-forming substrate consumption above the first threshold of temperature or resistance.

Preferably the second equation is a linear equation. Preferably, the second equation is dependent on power applied to the heating element. The second equation preferably accounts for thermal diffusion through the aerosol forming substrate and any element holding the aerosol forming substrate.

Preferably, the first equation is a non-linear equation. Preferably, the first equation is independent of power applied to the heating element. The first equation preferably accounts for the enthalpy of vaporisation of the liquid aerosol-forming substrate.

The value of the first threshold is dependent on the composition of the liquid aerosol forming substrate. Preferably, the first threshold is the boiling point of the liquid aerosol-forming substrate, and more preferably the boiling point of the liquid aerosol-forming substrate at atmospheric pressure.

The first equation and second equations are also dependent on the composition of the liquid aerosol-forming substrate, as well as the specific properties of the system, such as dimensions and material properties, and the power applied to the heater. The first and second equations are therefore preferably empirically derived and stored in the electric circuitry. A plurality of different equations may be stored in the electric circuitry for use with different compositions of liquid aerosol-forming substrate and for use at different power levels.

Of course, as an alternative to two equations to model the relationship between temperature or resistance and substrate consumption, a single more

complex equation may be used, which is derived by correlation with empirically derived data for substrate consumption. Alternatively, three or more equations may be used if appropriate. But the inventors have appreciated that for an accurate calculation of liquid substrate consumption the temperature evolution of the heating element must be considered as well as the different evaporation behaviour above and below the boiling point of the liquid substrate. It is also desirable to provide different models for different power levels applied to the heater.

Providing electric circuitry for determining an amount of liquid aerosol-forming substrate in the liquid storage portion is advantageous for a number of reasons. For example, when the liquid storage portion is empty or nearly empty, insufficient liquid aerosol-forming substrate may be supplied to the electric heater. This may mean that the aerosol created does not have the desired properties, for example, aerosol particle size. This may result in a poor experience for the user. In addition, if it can be determined when the liquid storage portion is empty or nearly empty, it may be possible to inform the user. Then the user can prepare to replace or refill the liquid storage portion.

For the liquid aerosol-forming substrate, certain physical properties, for example the vapour pressure or viscosity of the substrate, are chosen in a way to be suitable for use in the aerosol generating system. The liquid preferably comprises a tobacco-containing material comprising volatile tobacco flavour compounds which are released from the liquid upon heating. Alternatively, or in addition, the liquid may comprise a non-tobacco material. The liquid may include water, ethanol, or other solvents, plant extracts, nicotine solutions, and natural or artificial flavours. Preferably, the liquid further comprises an aerosol former. Examples of suitable aerosol formers are glycerine and propylene glycol.

An advantage of providing a liquid storage portion is that the liquid in the liquid storage portion is protected from ambient air. In some embodiments, ambient light,cannot enter the liquid storage portion as well, so that the risk of degradation of the liquid is avoided. Moreover, a high level of hygiene can be maintained. If the liquid storage portion is not refillable and the liquid in the liquid storage portion has been used up or has decreased to a predetermined threshold, the liquid storage portion has to be replaced by the user. During such replacement, contamination of the user with the liquid has to be

prevented. Alternatively, the liquid storage portion may be refillable. In that case, when the amount of liquid aerosol-forming substrate in the liquid storage portion has decreased to a predetermined threshold, the liquid storage portion may be refilled. Preferably, the liquid storage portion is arranged to hold liquid for a pre-determined number of puffs or heating cycles.

The electric heater may comprise a single heating element. Alternatively, the electric heater may comprise more than one heating elements for example two, or three, or four, or five, or six or more heating elements. The heating element or heating elements may be arranged appropriately so as to most effectively heat the liquid aerosol-forming substrate.

The at least one electric heating element preferably comprises an electrically resistive material. Suitable electrically resistive materials include but are not limited to: semiconductors such as doped ceramics, electrically "conductive" ceramics (such as, for example, molybdenum disilicide), carbon, graphite, metals, metal alloys and composite materials made of a ceramic material and a metallic material. Such composite materials may comprise doped or undoped ceramics. Examples of suitable doped ceramics include doped silicon carbides. Examples of suitable metals include titanium, zirconium, tantalum and metals from the platinum group. Examples of suitable metal alloys include stainless steel, Constantan, nickel-, cobalt-, chromium-, aluminium- titanium- zirconium-, hafnium-, niobium-, molybdenum-, tantalum-, tungsten-, tin-, gallium-, manganese- and iron-containing alloys, and super-alloys based on nickel, iron, cobalt, stainless steel, Timetal®, iron-aluminium based alloys and iron-manganese-aluminium based alloys. Timetal® is a registered trade mark of Titanium Metals Corporation. In composite materials, the electrically resistive material may optionally be embedded in, encapsulated or coated with an insulating material or vice-versa, depending on the kinetics of energy transfer and the external physicochemical properties required. The heating element may comprise a metallic etched foil insulated between two layers of an inert material. In that case, the inert material may comprise Kapton®, all-polyimide or mica foil. Kapton® is a registered trade mark of E.I. du Pont de Nemours and Company.

The at least one electric heating element may take any suitable form. For example, the at least one electric heating element may take the form of a heating blade. Alternatively, the at least one electric heating element may take

the form of a casing or substrate having different electro-conductive portions, or an electrically resistive metallic tube. The liquid storage portion may incorporate a disposable heating element. Alternatively, one or more heating needles or rods that run through the liquid aerosol-forming substrate may also be suitable. Alternatively, the at least one electric heating element may comprise a flexible sheet of material. Other alternatives include a heating wire or filament, for example a Ni-Cr (Nickel-Chromium), platinum, tungsten or alloy wire, or a heating plate. Optionally, the heating element may be deposited in or on a rigid carrier material.

The at least one electric heating element may comprise a heat sink, or heat reservoir comprising a material capable of absorbing and storing heat and subsequently releasing the heat over time to heat the aerosol-forming substrate. The heat sink may be formed of any suitable material, such as a suitable metal or ceramic material. Preferably, the material has a high heat capacity (sensible heat storage material), or is a material capable of absorbing and subsequently releasing heat via a reversible process, such as a high temperature phase change. Suitable sensible heat storage materials include silica gel, alumina, carbon, glass mat, glass fibre, minerals, a metal or alloy such as aluminium, silver or lead, and a cellulose material such as paper. Other suitable materials which release heat via a reversible phase change include paraffin, sodium acetate, naphthalene, wax, polyethylene oxide, a metal, metal salt, a mixture of eutectic salts or an alloy.

The heat sink or heat reservoir may be arranged such that it is directly in contact with the liquid aerosol-forming substrate and can transfer the stored heat directly to the substrate. Alternatively, the heat stored in the heat sink or heat reservoir may be transferred to the aerosol-forming substrate by means of a heat conductor, such as a metallic tube.

The at least one heating element may heat the liquid aerosol-forming substrate by means of conduction. The heating element may be at least partially in contact with the substrate. Alternatively, the heat from the heating element may be conducted to the substrate by means of a heat conductive element.

Alternatively, the at least one heating element may transfer heat to the incoming ambient air that is drawn through the electrically operated aerosol generating system during use, which in turn heats the aerosol-forming

substrate. The ambient air may be heated before passing through the aerosol-forming substrate. Alternatively, the ambient air may be first drawn through the liquid substrate and then heated.

Preferably, the electrically operated aerosol generating system further comprises a capillary wick for conveying the liquid aerosol-forming substrate from the liquid storage portion to the electric heater.

Preferably, the capillary wick is arranged to be in contact with liquid in the liquid storage portion. Preferably, the capillary wick extends into the liquid storage portion. In that case, in use, liquid is transferred from the liquid storage portion to the electric heater by capillary action in the capillary wick. In one embodiment, the capillary wick has a first end and a second end, the first end extending into the liquid storage portion for contact with liquid therein and the electric heater being arranged to heat liquid in the second end. When the heater is activated, the liquid at the second end of the capillary wick is vaporized by the at least one heating element of the heater to form the supersaturated vapour. The supersaturated vapour is mixed with and carried in the air flow. During the flow, the vapour condenses to form the aerosol and the aerosol is carried towards the mouth of a user. The liquid aerosol-forming substrate has physical properties, including viscosity and surface tension, which allow the liquid to be transported through the capillary wick by capillary action.

The capillary wick may have a fibrous or spongy structure. The capillary wick preferably comprises a bundle of capillaries. For example, the capillary wick may comprise a plurality of fibres or threads or other fine bore tubes. The fibres or threads may be generally aligned in the longitudinal direction of the aerosol generating system. Alternatively, the capillary wick may comprise sponge-like or foam-like material formed into a rod shape. The rod shape may extend along the longitudinal direction of the aerosol generating system. The structure of the wick forms a plurality of small bores or tubes, through which the liquid can be transported by capillary action. The capillary wick may comprise any suitable material or combination of materials. Examples of suitable materials are capillary materials, for example a sponge or foam material, ceramic- or graphite-based materials in the form of fibres or sintered powders, foamed metal or plastics material, a fibrous material, for example made of spinned or extruded fibres, such as cellulose acetate, polyester, or bonded

polyolefin, polyethylene, terylene or polypropylene fibres, nylon fibres or ceramic. The capillary wick may have any suitable capillarity and porosity so as to be used with different liquid physical properties. The liquid has physical properties, including but not limited to viscosity, surface tension, density, thermal conductivity, boiling point and vapour pressure, which allow the liquid to be transported through the capillary device by capillary action.

Preferably, the at least one heating element is in the form of a heating wire or filament encircling, and optionally supporting, the capillary wick. The capillary properties of the wick, combined with the properties of the liquid, ensure that, during normal use, the wick is always wet in the heating area. If the wick is dry, there may be overheating. Providing a capillary wick may therefore be advantageous as it will allow a measure of this overheating, which in turn can allow a determination of when the amount of liquid aerosol-forming substrate in the liquid storage portion has decreased to a predetermined threshold

The capillary wick and the heater, and optionally the liquid storage portion, may be removable from the aerosol generating system as a single component.

In one case, the electric circuitry comprises a sensor to detect air flow indicative of a user taking a puff. In that case, preferably, the electric circuitry is arranged to provide an electric current pulse to the electric heater at a predetermined power when the sensor senses a user taking a puff. The time-period of the electric current pulse may be pre-set, depending on the amount of liquid desired to be vaporized. The electric circuitry is preferably programmable for this purpose. In that embodiment, the electric circuitry may be arranged to monitor the total time of the time-periods of the electric current pulses and from the monitored total time, predict when the amount of liquid aerosol-forming substrate in the liquid storage portion will decrease to the predetermined threshold.

The electrically operated aerosol generating system may further comprise a temperature sensor for measuring the temperature of the at least one heating element and the electric circuitry configured to monitor the temperature of the at least one heating element as sensed by the temperature sensor.

In another embodiment, the electric circuitry is arranged to measure the electrical resistance of the at least one heating element, to ascertain the temperature of the heating element from the measured electrical resistance.

In that embodiment, the electric circuitry may be arranged to measure the electrical resistance of the at least one heating element by measuring the current through the at least one heating element and the voltage across the at least one heating element and determining the electrical resistance of the at least one heating element from the measured current and voltage. In that case, the electric circuitry may comprise a resistor, having a known resistance, in series with the at least one heating element and the electric circuitry may be arranged to measure the current through the at least one heating element by measuring the voltage across the known resistance and determining the current through the at least one heating element from the measured voltage and the known resistance.

In an alternative case, the electric circuitry comprises a manually operable switch for a user to initiate a puff. The electric circuitry is arranged to provide an electric current pulse to the electric heater when the user initiates a puff. The time-period of the electric current pulse is preferably pre-set depending on the amount of liquid desired to be vaporized. The electric circuitry is preferably programmable for this purpose. In that embodiment, the electric circuitry may be arranged to monitor the total time in which the manually operable switch is activated and, from the monitored total time, estimate an amount of liquid aerosol-forming substrate in the liquid storage portion.

The electric circuitry may comprise a sensor for detecting the presence of a liquid storage portion. The sensor is preferably able to distinguish one liquid storage portion from another liquid storage portion and hence ascertain how much liquid aerosol-forming substrate is contained in the liquid storage portion when full. The sensor may also be able to determine the composition of the liquid in the liquid storage portion based on indicia on the liquid storage portion or the shape or size of the liquid storage portion. This, coupled with the monitored activation, may allow the electric circuitry to predict the amount of liquid aerosol-forming substrate in the liquid storage portion during use.

In a preferred embodiment, the electric circuitry is arranged, when the amount of liquid aerosol-forming substrate in the liquid storage portion has decreased to a predetermined threshold, to deactivate the electric heater.

This is advantageous because the user can then no longer use the aerosol generating system once there is insufficient liquid aerosol-forming substrate. This will avoid creation of an aerosol which does not have the desired properties. This will avoid a poor experience for the user.

The electric circuitry may be arranged to deactivate the electric heater by blowing an electrical fuse between the electric heater and an electric power supply. The electric circuitry may be arranged to deactivate the electric heater by switching off a switch between the electric heater and an electric power supply. Alternative methods of deactivating the electric heater will be apparent to the skilled person.

In a preferred embodiment, the electric circuitry is arranged, when the amount of liquid aerosol-forming substrate in the liquid storage portion has decreased to a predetermined threshold, to indicate this to a user. This is advantageous because the indication enables the user to refill or replace the liquid storage portion.

The electrically operated aerosol generating system may comprise a user display. In that case, the indication may comprise an indication on the user display. Alternatively, the indication may comprise an audible indication, or any other suitable type of indication for a user.

The aerosol generating system may further comprise an electric power supply. Preferably, the aerosol generating system comprises a housing. Preferably, the housing is elongate. If the aerosol generating includes a capillary wick, the longitudinal axis of the capillary wick and the longitudinal axis of the housing may be substantially parallel. The housing may comprise a shell and a mouthpiece. In that case, all the components may be contained in either the shell or the mouthpiece. In one embodiment, the housing includes a removable insert comprising the liquid storage portion, the capillary wick and the heater. In that embodiment, those parts of the aerosol generating system may be removable from the housing as a single component. This may be useful for refilling or replacing the liquid storage portion, for example.

The housing may comprise any suitable material or combination of materials. Examples of suitable materials include metals, alloys, plastics or

composite materials containing one or more of those materials, or thermoplastics that are suitable for food or pharmaceutical applications, for example polypropylene, polyetheretherketone (PEEK) and polyethylene. Preferably, the material is light and non-brittle.

Preferably, the aerosol generating system is portable. The aerosol generating system may be a smoking system and may have a size comparable to a conventional cigar or cigarette. The smoking system may have a total length between approximately 30 mm and approximately 150 mm. The smoking system may have an external diameter between approximately 5 mm and approximately 30 mm.

Preferably, the electrically operated aerosol generating system is an electrically heated smoking system.

According to a second aspect of the invention, there is provided a method comprising: providing an electrically operated aerosol generating system comprising a liquid storage portion for storing liquid aerosol-forming substrate and an electric heater comprising at least one heating element for heating the liquid aerosol-forming substrate; and monitoring activation of the electric heater and estimating an amount of liquid aerosol-forming substrate remaining in the liquid storage portion based on the monitored activation.

Preferably, the step of monitoring activation of the electric heater comprises monitoring the temperature or resistance of the heating element over time to estimate a consumed amount of aerosol-forming substrate. Preferably, the estimate of a consumed amount of aerosol is based on a first equation relating heating element temperature or resistance to aerosol-forming substrate consumption up to a first threshold of temperature or resistance and based on a second equation relating heating element temperature or resistance to aerosol-forming substrate consumption above the first threshold of temperature or resistance.

Preferably, the second equation is a linear equation. The second equation preferably accounts for thermal diffusion through the aerosol forming substrate or an element holding the aerosol forming substrate.

Preferably, the first equation is a non-linear equation. The first equation preferably accounts for the enthalpy of vaporisation of the liquid aerosol-forming substrate.

According to a third aspect of the invention, there is provided electric

circuitry for an electrically operated aerosol generating system, the electric circuitry being arranged to perform the method of the second aspect of the invention.

According to a fourth aspect of the invention, there is provided a computer program which, when run on programmable electric circuitry for an electrically operated aerosol generating system, causes the programmable electric circuitry to perform the method of the second aspect of the invention.

According to a fifth aspect of the invention, there is provided a computer readable storage medium having stored thereon a computer program according to the fourth aspect of the invention.

Features described in relation to the aerosol generating system of the invention may also be applicable to the method of the invention. And, features described in relation to the method of the invention may also be applicable to the aerosol generating system of the invention.

The invention will be further described, by way of example only, with reference to the accompanying drawings, of which:

**Figure 1** shows one example of an electrically operated aerosol generating system having a liquid storage portion;

**Figure 2** is a plot of total particle mass versus power applied for two different liquid aerosol forming substrate compositions in a device of the type shown in Figure 1;

**Figure 3** is a plot of evaporation rate versus temperature of a liquid composition up to boiling point, together with a curve correlated to the plotted points;

**Figure 4** is a plot showing the evaporation rate of a liquid composition versus temperature in a device of the type shown in Figure 1, showing evaporation rate for two different power levels;

**Figure 5** is a plot showing the evolution of temperature of a heating element during a puff, with different plots shown for different stages in the consumption of the liquid aerosol forming substrate;

**Figure 6** is a plot showing the liquid evaporation rate during a puff and the corresponding temperature of the heating element;

**Figure 7** is a plot showing the cumulative evaporated mass for a puff;

**Figure 8** is a plot showing, on the y-axis, heating element resistance and, on the x-axis, heating element temperature of an electric heater of an electrically operated aerosol generating system; and

**Figure 9** is a schematic circuit diagram, which allows heating element resistance to be measured, according to one embodiment of the invention.

Figure 1 shows one example of an electrically operated aerosol generating system having a liquid storage portion. In Figure 1, the system is a smoking system. The smoking system 100 of Figure 1 comprises a housing 101 having a mouthpiece end 103 and a body end 105. In the body end, there is provided an electric power supply in the form of battery 107 and electric circuitry 109. A puff detection system 111 is also provided in cooperation with the electric circuitry 109. In the mouthpiece end, there is provided a liquid storage portion in the form of cartridge 113 containing liquid 115, a capillary wick 117 and a heater 119. Note that the heater is only shown schematically in Figure 1. In the exemplary embodiment shown in Figure 1, one end of capillary wick 117 extends into cartridge 113 and the other end of capillary wick 117 is surrounded by the heater 119. The heater is connected to the electric circuitry via connections 121, which may pass along the outside of cartridge 113 (not shown in Figure 1). The housing 101 also includes an air inlet 123, an air outlet 125 at the mouthpiece end, and an aerosol-forming chamber 127.

In use, operation is as follows. Liquid 115 is conveyed by capillary action from the cartridge 113 from the end of the wick 117 which extends into the cartridge to the other end of the wick which is surrounded by heater 119. When a user draws on the aerosol generating system at the air outlet 125, ambient air is drawn through air inlet 123. In the arrangement shown in Figure 1, the puff detection system 111 senses the puff and activates the heater 119. The battery 107 supplies electrical energy to the heater 119 to heat the end of the wick 117 surrounded by the heater. The liquid in that end of the wick 117 is vaporized by the heater 119 to create a supersaturated vapour. At the same time, the liquid being vaporized is replaced by further liquid moving along the wick 117 by capillary action. (This is sometimes referred to as "pumping action".) The supersaturated vapour created is mixed with and carried in the air flow from the air inlet 123. In the aerosol-forming chamber 127, the vapour condenses to form an inhalable aerosol, which is carried towards the outlet 125 and into the mouth of the user.

In the embodiment shown in Figure 1, the electric circuitry 109 and puff detection system 111 are preferably programmable. The electric circuitry 109 and puff detection system 111 can be used to manage operation of the aerosol generating system. This assists with control of the particle size in the aerosol.

Figure 1 shows one example of an electrically operated aerosol generating system according to the present invention. Many other examples are possible, however. In addition, note that Figure 1 is schematic in nature. In particular, the components shown are not to scale either individually or relative to one another. The electrically operated aerosol generating system needs to include or receive a liquid aerosol-forming substrate contained in a liquid storage portion. The electrically operated aerosol generating system requires some sort of electric heater having at least one heating element for heating the liquid aerosol-forming substrate. Finally, the electrically operated aerosol generating system requires electric circuitry for determining an amount of liquid aerosol-forming substrate in the liquid storage portion. This will be described below with reference to Figures 2 to 9. It is emphasized that the system does not need to be a smoking system and a puff detection system does not need to be provided. Instead, the system could operate by manual activation, for example the user operating a switch when a puff is taken. For example, the overall shape and size of the housing could be altered. Moreover, the system may not include a capillary wick. In that case, the system may include another mechanism for delivering liquid for vaporization.

However, in a preferred embodiment, the system does include a capillary wick for conveying the liquid from the liquid storage portion to the at least one heating element. The capillary wick can be made from a variety of porous or capillary materials and preferably has a known, pre-defined capillarity. Examples include ceramic- or graphite-based materials in the form of fibres or sintered powders. Wicks of different porosities can be used to accommodate different liquid physical properties such as density, viscosity, surface tension and vapour pressure. The wick must be suitable so that the required amount of liquid can be delivered to the heater. Preferably, the heater comprises at least one heating wire or filament extending around the capillary wick.

As discussed above, according to the invention, the electrically operated aerosol generating system includes electric circuitry for determining

an amount of liquid aerosol-forming substrate in the liquid storage portion. Embodiments of the invention will now be described with reference to Figures 2 to 9. The embodiments are based on the example shown in Figure 1, although they are applicable to other embodiments of electrically operated aerosol generating systems.

Figure 2 is a plot of the total particle mass (TPM) of aerosol generated in a user puff in a device as shown in Figure 1, for two different aerosol forming substrates. Plot 200, with the plotted points drawn as larger squares, shows the results for Liquid 1 and plot 210, with the plotted points shown as smaller squares, shows the results for Liquid 2 The plots show the effect on aerosol generation of increasing power to the heater. It can be seen that increasing the power to the heater broadly increases aerosol generation. At very high power aerosol mass reduces, and this can be explained by the evaporated mass remaining in the gaseous phase rather than forming droplets.

Figure 2 also illustrates that the mass of aerosol generated is also dependent on the composition of the liquid aerosol-forming substrate. For example, different compositions will have different boiling points and different viscosities. Any model to accurately estimate liquid aerosol-forming substrate consumption must therefore account for liquid composition and power applied to the heater.

The generation of aerosol requires supplying enough energy to the liquid to vaporise it. The energy required is called the enthalpy of vaporisation. The amount of energy supplied depends on the temperature of the heater element or elements: The higher the temperature the more energy is supplied to the liquid. So, up to the boiling point of the liquid, there is a relationship between the temperature of the heater elements and the evaporation rate. This is independent of the power supplied to the heater. Figure 3 is a plot showing the evaporation rate of a liquid aerosol-forming substrate versus temperature up to its boiling point. The experimental data is plotted as diamonds 220. Also shown is a curve 230, drawn with square points, that is fitted to the experimental data 220. The curve 230 is of the form $m = Ae^{BT}$, where m is the evaporated mass rate, A and B are calibration constants and T is the temperature of the heating element. The constants A and B depend on the liquid composition.

Once the temperature of the heating element reaches the boiling point of the liquid the rate of evaporation no longer increases in the same manner. At this point further energy from the heating element does not increase the temperature of the liquid. However, as the temperature of the heating element increases beyond the boiling point thermal diffusion through the liquid substrate and more particularly through any medium holding the substrate, in this embodiment the capillary wick, becomes a significant factor. As the heating element temperature rises there is a greater rate of thermal diffusion so more liquid substrate is vaporised.

Figure 4 is a plot of two different evaporation rate curves as a function of temperature using a wick system as shown in Figure 1. The two curves 240 and 250 correspond to two different amounts of power supplied to the heating element during a puff. In both curves 240 and 250, the first portion below the boiling point of the liquid corresponds to the curve 230 shown in Figure 3. Above the boiling point the two curves diverge. Curve 240, corresponds to a lower power than curve 250. Both curves show a linear increase in evaporation rate with temperature, but the rate of increase is clearly dependent on power. The portion of curves 240 and 250 above the boiling point of the liquid substrate are of the form $m = CT + D$, where m is the rate of evaporation, C and D are calibration constants and T is temperature. Constants C and D are dependent on liquid composition, the power applied to the heater as well as the physical properties of the device, such as the composition and dimensions of the wick and the configuration of the heater.

The curves of Figure 4 provide a model that can be used to calculate the evaporation rate of the liquid substrate if the temperature of the heating element and the power applied to the heating element are known. For each design of aerosol generating system the constants A, B, C and D need to be empirically derived and constants C and D must be derived for the different power levels that the system can operate at.

The temperature of the heating element changes during the course of each puff and changes as the amount of liquid in the liquid storage portion is reduced. Figure 5 is a plot showing five averaged temperature profiles during a puff. The temperature, T of the heating element is shown on the y-axis and the puff time t is shown on the x-axis. Curve 501 is the median of a first set of puffs, each puff having a 2-second puff duration. Similarly, curve 503 is the

median of a second set of puffs, curve 505 is the median of a third set of puffs curve 507 is the median of a fourth set of puffs and curve 509 is the median over a fifth set of puffs. In each curve, the vertical bars (for example shown at 511) indicate the standard deviation around the median for those puffs. Thus, the evolution of the measured temperature over the life of the liquid storage portion is shown. This behaviour was observed and confirmed for all liquid formulations vaporized and for all power levels used.

As can be seen from Figure 5, the temperature response of the heating element is reasonably stable over curves 501, 503 and 205. That is to say, the standard deviation around the median for the first three sets of puffs is reasonably small. The model illustrated in Figure 4 is most accurate during this period when the temperature response is stable. During this period there is always sufficient aerosol-forming substrate being delivered to the heater through the wick. Once the wick begins to dry a different behaviour is observed.

Figure 6 is an illustration of the temperature profile of a heating element during a puff (averaged over a set of puffs), shown as curve 600 together with the corresponding evaporation rate calculated using the model shown and described with reference to Figure 4, shown as curve 610.

The total mass of liquid aerosol-forming substrate evaporated during a puff can be calculated by integrating under the evaporation rate curve 610. This integral can be performed by the electric circuitry using the trapezium method for example. The result of the integral is shown in Figure 7. Figure 7 again shows the temperature profile 600 of a heating element during a puff but also shows the cumulative evaporated mass over the puff as curve 700.

The total amount of liquid aerosol-forming substrate consumed can be calculated by summing the totals calculated for each puff. This total consumed mass can be subtracted from a known initial mass of liquid in the liquid storage portion to provide an estimate of the amount of liquid aerosol-forming substrate remaining. The amount remaining can be indicated to the user as a meaningful quantity, such as an estimated number of puffs remaining or as a percentage value.

Determining the amount of liquid aerosol-forming substrate in the liquid storage portion is advantageous because, when the liquid storage portion is empty or nearly empty, insufficient liquid aerosol-forming substrate may be

supplied to the heater. This may mean that the aerosol created and inhaled by the user does not have the desired properties, for example, aerosol particle size. This may result in a poor experience for the user. In addition, it is advantageous to provide a mechanism whereby the user can be informed that the liquid storage portion is empty or nearly empty. Then the user can prepare to replace or refill the liquid storage portion.

The electric circuitry may include a sensor which is able to detect the presence of a liquid storage portion and, moreover, to determine the characteristics of the liquid storage portion including, for example, how much liquid aerosol-forming substrate is contained in the liquid storage portion and the composition of the liquid aerosol-forming substrate. As described in the applicant's pending International application PCT/IB2009/007969, this may be based on identification information provided on the liquid storage portion. This information, together with information derived from monitoring activation of the heater, allows the electric circuitry to predict the amount of liquid aerosol-forming substrate in the liquid storage portion. Alternatively, the electric circuitry does not need to include a sensor. For example, the amount of liquid aerosol-forming substrate in each liquid storage portion may simply be of only one kind and set at a standard amount.

A number of variations of the invention are possible. For example, the aerosol generating system does not need to include a puff detection system. Instead, the system could operate by manual activation, for example the user operating a switch when a puff is taken.

According to the first embodiment of the invention, a temperature sensor is provided in the aerosol generating system close to the heating element. The electric circuitry can monitor the temperature measured by the temperature sensor and hence determine an amount of liquid in the liquid storage portion as described. The advantage of this embodiment is that no calculation or derivation is required, since the temperature sensor directly measures the temperature close to the heating element.

According to the second embodiment of the invention, the amount of liquid in the liquid storage portion is determined by measuring the resistance of the electric heating element. If the heating element has suitable temperature coefficient of resistance characteristics (for example, see equation **(5)** below),

then the resistance may provide a measure of the temperature of the electric heating element.

Figure 8 is a plot showing the resistance, R of the heating element of the electric heater on the y-axis, versus the temperature, T of the heating element on the x-axis. As can be seen in Figure 8, as the temperature T of the heating element increases, so does the resistance R. Within a selected range (between temperatures T1 and T2 and resistances R1 and R2 in Figure 4), the temperature T and resistance R may be proportional to one another.

As discussed above in relation to the first embodiment of the invention, if the liquid storage portion is empty or nearly empty, insufficient liquid aerosol-forming substrate will be supplied to the heater. This will mean that any capillary wick will become dry, and the temperature of the heating element will increase. Figure 8 shows that such a temperature increase may be determined by measuring the resistance of the heating element because, as the temperature increases, the measured resistance will increase as well.

Figure 9 is a schematic electric circuit diagram showing how the heating element resistance may be measured according to the second embodiment of the invention. In Figure 9, the heater 901 is connected to a battery 903 which provides a voltage *V2*. The heater resistance to be measured at a particular temperature is $R_{heater}$. In series with the heater 901, an additional resistor 905, with known resistance *r* is inserted and connected to voltage *V1*. The voltage *V1* has an intermediate value between ground and voltage *V2*. In order for microprocessor 907 to measure the resistance $R_{heater}$ of the heater 901, the current through the heater 901 and the voltage across the heater 901 can both be determined. Then, the following well-known formula can be used to determine the resistance:

$$V = IR \quad \textbf{(1)}$$

In Figure 9, the voltage across the heater is *V2-V1* and the current through the heater is *I*. Thus:

$$R_{heater} = \frac{V2 - V1}{I} \quad \textbf{(2)}$$

The additional resistor 905, whose resistance r is known, is used to determine the current I, again using **(1)** above. The current through the resistor 905 is I and the voltage across the resistor 905 is V1. Thus:

$$I = \frac{V1}{r} \quad \textbf{(3)}$$

So, combining **(2)** and **(3)** gives:

$$R_{heater} = \frac{(V2 - V1)}{V1} r \quad \textbf{(4)}$$

Thus, the microprocessor 907 can measure *V2* and *V1*, as the aerosol generating system is being used and, knowing the value of *r*, can determine the heater's resistance at a particular temperature, $R_{heater}$.

Then, the following formula can be used to determine the temperature *T* from the measured resistance $R_{heater}$ at temperature *T*:

$$T = \frac{R_{heater}}{\alpha R_0} + T_0 - \frac{1}{\alpha} \quad \textbf{(5)}$$

where α is the thermal resistivity coefficient of the heating element material and $R_0$ is the resistance of the heating element at room temperature $T_0$.

An advantage of this embodiment is that no temperature sensor, which can be bulky and expensive, is required.

Thus, a measure of the temperature of the heating element can be derived. This can be used to determine when the amount of liquid in the liquid storage portion has decreased to a threshold and to estimate an absolute amount of aerosol-forming substrate remaining in the liquid storage portion.

In the embodiments described above, once it has been determined when the amount of liquid aerosol-forming substrate in the liquid storage portion has decreased to a threshold, one or more actions may be taken. The electric heater may be deactivated. For example, a system may be triggered to render the liquid storage portion unusable. For example, the electric circuitry, on determining that the amount of liquid aerosol-forming substrate in the liquid storage portion, has decreased to a threshold, may blow an electrical fuse

between the at least one heating element of the electric heater and an electric power supply. The electrical fuse may be provided as part of a removable component including the liquid storage portion. Alternatively, the electric circuitry, on determining that the amount of liquid aerosol-forming substrate in the liquid storage portion, has decreased to a threshold, may switch off a switch between the at least one heating element of the electric heater and an electric power supply. Alternative methods of deactivating the electric heater are, of course, possible. An advantage of deactivating the electric heater is that it is then impossible to use the aerosol generating system. This renders it impossible for a user to inhale an aerosol which does not have the desired properties.

Once it has been determined when the amount of liquid in the liquid storage portion has decreased to a threshold, the user may be advised. For example, the electric circuitry, on determining that the amount of liquid aerosol-forming substrate in the liquid storage portion, has decreased to a threshold, may indicate this to a user. For example, if the aerosol generating system includes a user display, it may be indicated to the user, via the user display, that the liquid storage portion is empty or nearly empty. Alternatively or additionally, an audible sound may indicate to the user that the liquid storage portion is empty or nearly empty. Alternative methods of indicating to the user that the liquid storage portion is empty or nearly empty are, of course, possible. An advantage of advising the user is that the user is then able to prepare to replace or refill the liquid storage portion.

Thus, according to the invention, the electrically operated aerosol generating system includes electric circuitry for determining when the amount of liquid aerosol-forming substrate in the liquid storage portion has decreased to a predetermined threshold. Features described in relation to one embodiment may also be applicable to another embodiment.

## CLAIMS

1. An electrically operated aerosol generating system for receiving an aerosol-forming substrate, the system comprising:

a liquid storage portion for storing liquid aerosol-forming substrate;

an electric heater comprising at least one heating element for heating the liquid aerosol-forming substrate; and

electric circuitry configured to monitor activation of the electric heater and estimate an amount of liquid aerosol-forming substrate remaining in the liquid storage portion based on the monitored activation.

2. An electrically operated aerosol generating system according to claim 1, wherein the electric circuitry is configured to estimate a consumed amount of liquid aerosol-forming substrate, and to subtract the consumed amount from a known initial amount to provide an estimate of liquid aerosol-forming substrate remaining in the liquid storage portion.

3. An electrically operated aerosol generating system according to claim 1 or 2, wherein the electric circuitry is configured to monitor activation of the electric heater by monitoring a temperature or resistance of the heating element over time to estimate a consumed amount of aerosol-forming substrate.

4. An electrically operated aerosol generating system according to claim 3, wherein the electric circuitry is configured to estimate a consumed amount of aerosol based on a first equation relating heating element temperature or resistance to aerosol-forming substrate consumption up to a first threshold of temperature or resistance and based on a second equation relating heating element temperature or resistance to aerosol-forming substrate consumption above the first threshold of temperature or resistance.

5. An electrically operated aerosol generating system according to claim 4, wherein the second equation is dependent on power applied to the heating element.

6. An electrically operated aerosol generating system according to claim 4 or 5, wherein the first equation is independent of power applied to the heating element.

7. An electrically operated aerosol generating system according to claim 4, 5 or 6, wherein the first threshold is the boiling point of the liquid aerosol-forming substrate.

8. An electrically operated aerosol generating system according to any one of claims 4 to 7, wherein the first and second equations are stored in the electric circuitry.

9. An electrically operated aerosol generating system according to claim 8, wherein a plurality of different first and second equations are stored in the electric circuitry for use with different compositions of liquid aerosol-forming substrate and for use at different power levels.

10. An electrically operated aerosol generating system according to any preceding claim, wherein the electric circuitry is arranged to measure the electrical resistance of the at least one heating element, to ascertain the temperature of the heating element from the measured electrical resistance

11. An electrically operated aerosol generating system according to any preceding claim, further comprising a capillary wick for conveying the liquid aerosol-forming substrate from the liquid storage portion to the electric heater.

12. A method comprising:

providing an electrically operated aerosol generating system comprising a liquid storage portion for storing liquid aerosol-forming substrate and an electric heater comprising at least one heating element for heating the liquid aerosol-forming substrate; and

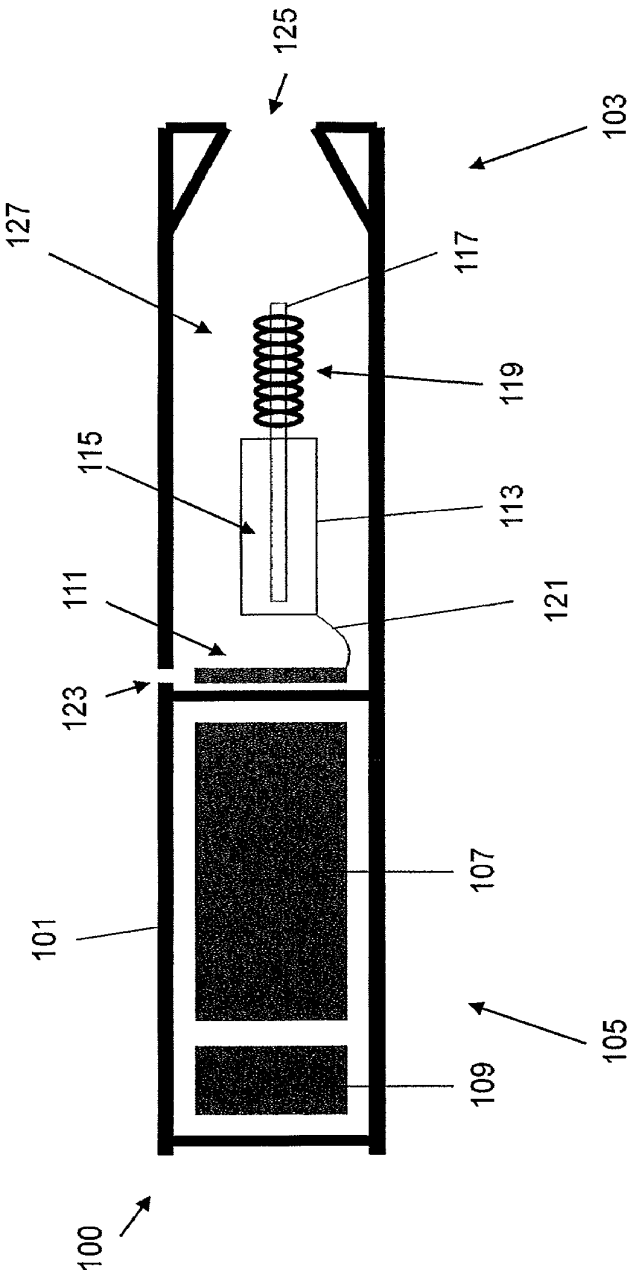
monitoring activation of the electric heater and estimating an amount of liquid aerosol-forming substrate remaining in the liquid storage portion based on the monitored activation.

13. Electric circuitry for an electrically operated aerosol generating system, the electric circuitry being arranged to perform the method of any of claim 12.

14. A computer program which, when run on programmable electric circuitry for an electrically operated aerosol generating system, causes the programmable electric circuitry to perform the method of claim 12.

15. A computer readable storage medium having stored thereon a computer program according to claim 14.

Figure 1




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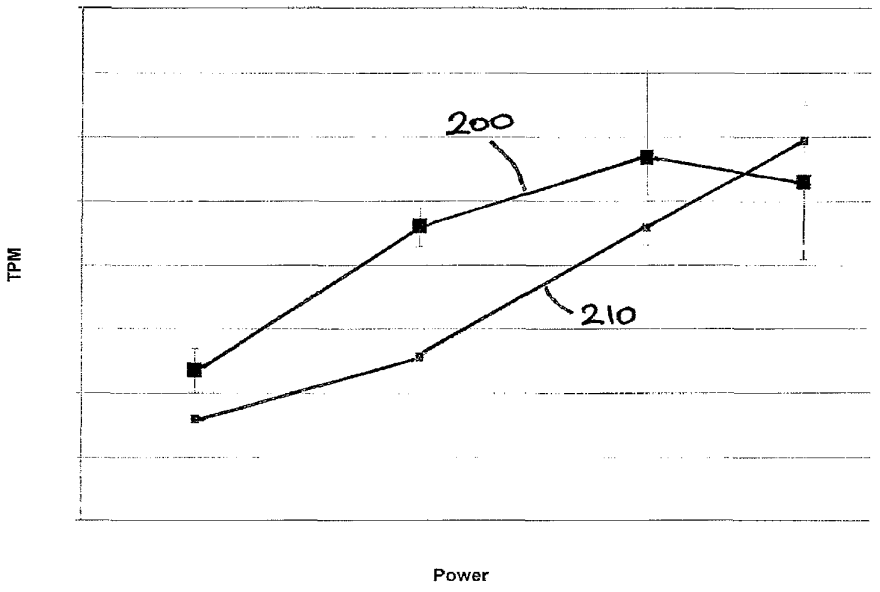



Figure 2

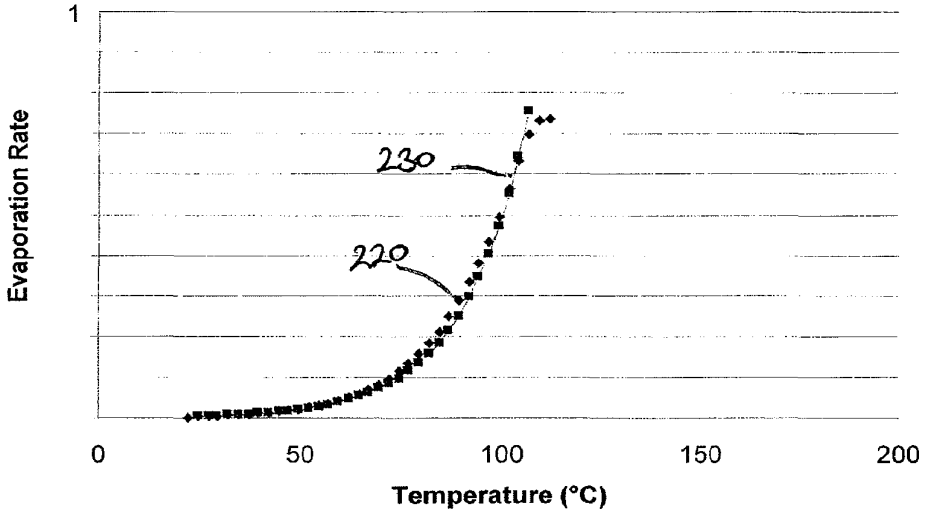



Figure 3

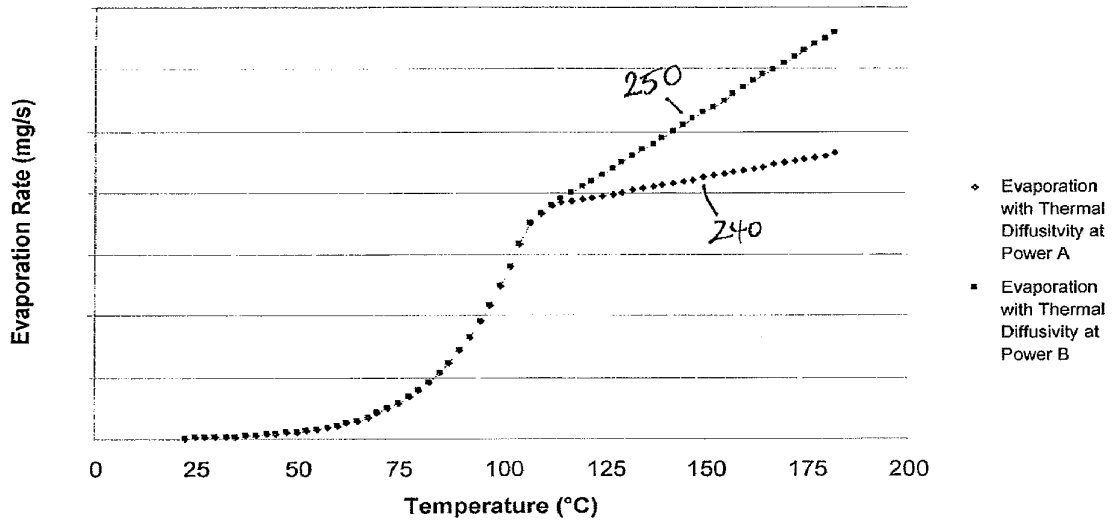



Figure 4

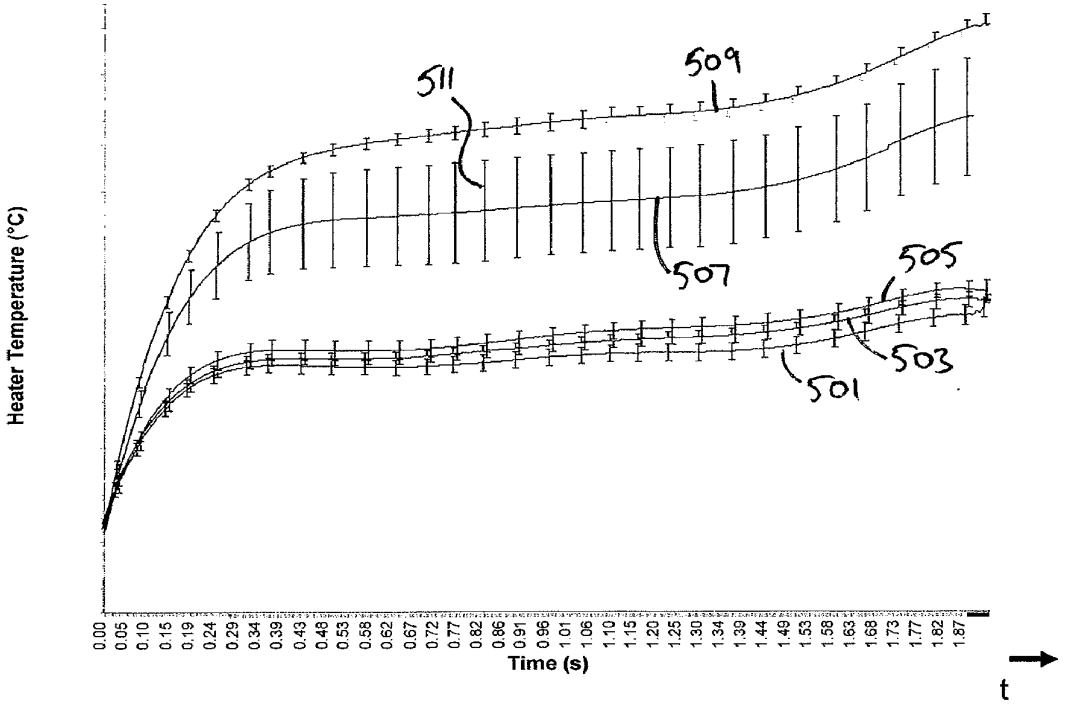



Figure 5

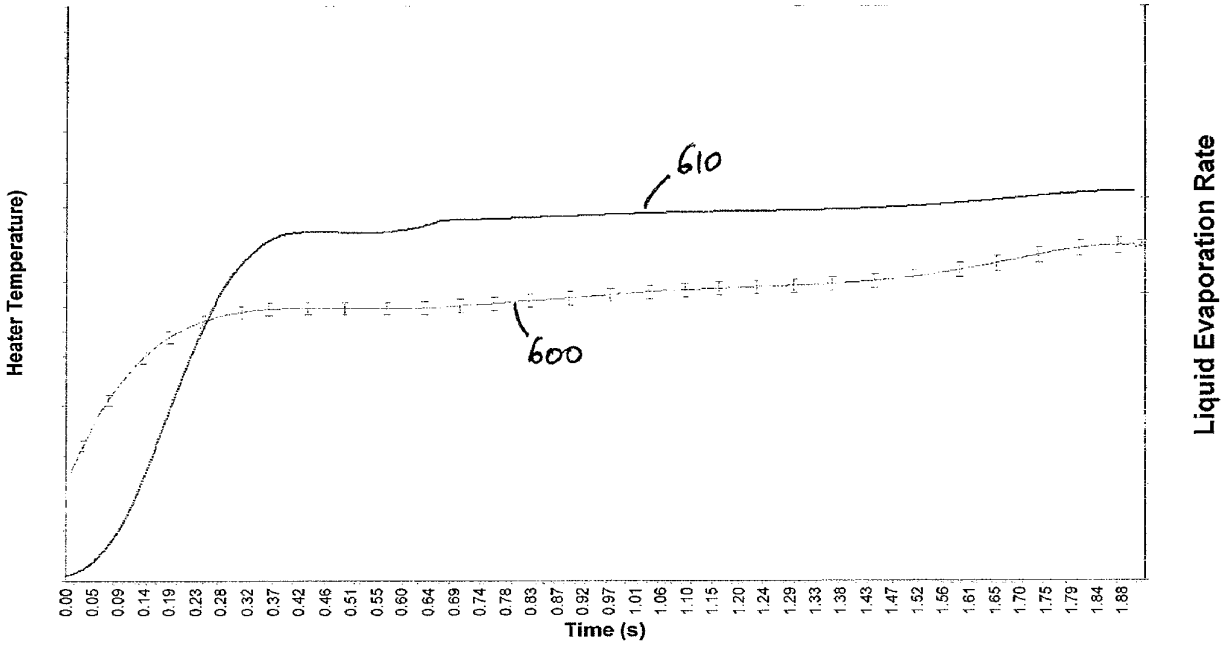



Figure 6

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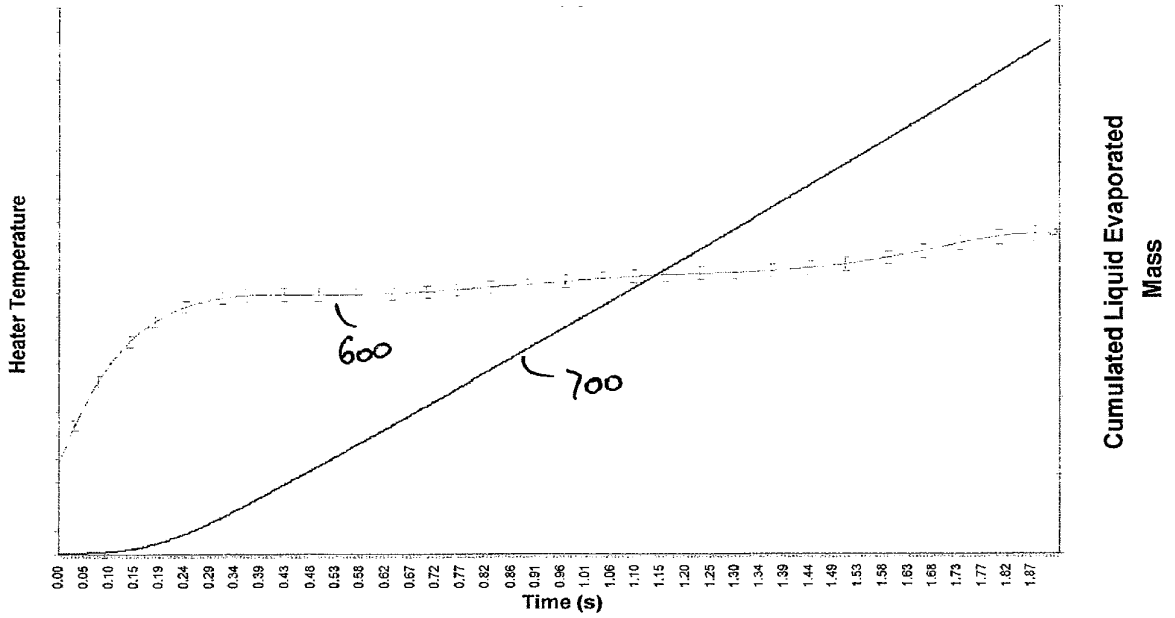



Figure 7

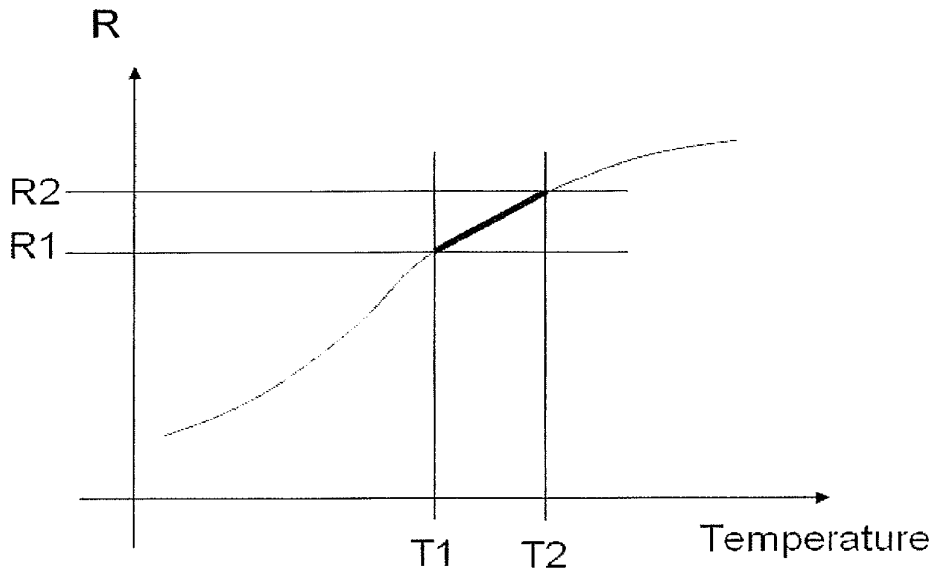



Figure 8

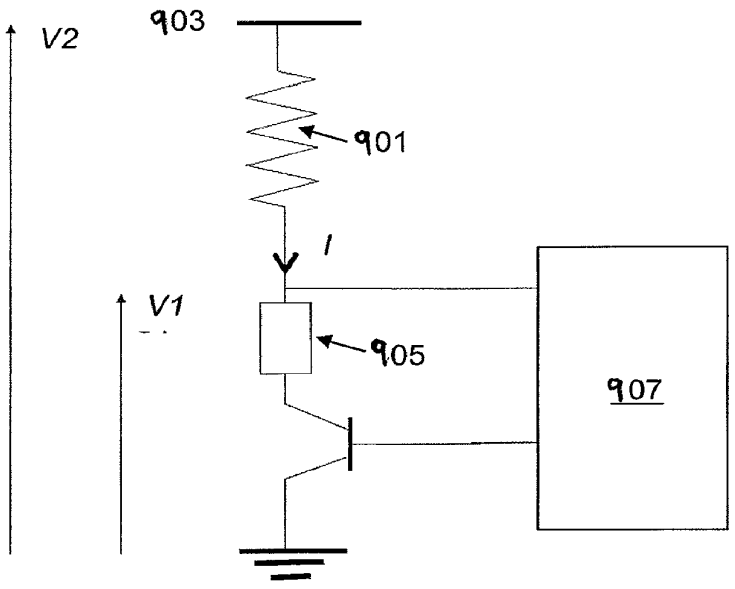



Figure 9

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/073795

A. CLASSIFICATION OF SUBJECT MATTER
INV. A24F47/00
ADD. A61M15/06

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)
A24F 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)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP 2 253 233 A1 (PHILIP MORRIS PROD [CH]) 24 November 2010 (2010-11-24) paragraph [0043] - paragraph [0068] | 1,12 |
| A | US 2009/283103 A1 (NIELSEN MICHAEL D [US] ET AL) 19 November 2009 (2009-11-19) paragraph [0030] - paragraph [0037] | 1,12 |
| A | WO 2007/078273 A1 (AUGITE INC [US]; LIU ZHEN [CN]) 12 July 2007 (2007-07-12) cited in the application page 3, lines 15-18 page 5, line 4 - page 7, line 19 | 1,12 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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 |
|---|---|
| 17 April 2012 | 24/04/2012 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Koob, Michael |

1

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/073795

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 13-15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 13-15

The subject-matter of claims 13-15 is unclear since the claims contain no features but merely a reference to a method which should be performed. There are also no detailed embodiments in the description or the drawings to support the computer program and the storage medium. The application therefore does not meet the requirements of Article 6 PCT, claims 13-15 are not clear and not supported by the description. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19). The search was based on the subject-matter of claims 1-12.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/073795

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 2253233 A1 | 24-11-2010 | AU 2010251453 A1 | 12-01-2012 |
| | | CA 2762919 A1 | 25-11-2010 |
| | | EP 2253233 A1 | 24-11-2010 |
| | | EP 2432339 A1 | 28-03-2012 |
| | | SG 176001 A1 | 29-12-2011 |
| | | US 2010313901 A1 | 16-12-2010 |
| | | WO 2010133342 A1 | 25-11-2010 |
| US 2009283103 A1 | 19-11-2009 | NONE | |
| WO 2007078273 A1 | 12-07-2007 | NONE | |

Form PCT/ISA/210 (patent family annex) (April 2005)

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3 October 2012 (03.10.2012)

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(74) Agent: **D. KLIGLER I.P. SERVICES LTD.**; P.O. Box 57651, 61576 Tel Aviv (IL).

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**Published**:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2013/050934 A1

(54) Title: SMOKING SYSTEM

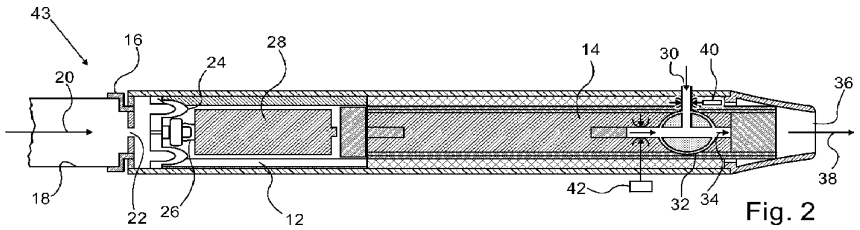



Fig. 2

(57) Abstract: In an electronic cigarette of the sort having a housing, a power section (12), and an atomizer (14), at least a portion of a first flow stream (25) passes through the atomizer (14). A mixing valve within the housing has a first input that receives the first flow stream (25), and a second input receiving a second flow stream (20) that avoids the atomizing element (14), and an output (34) connected in fluid continuity to the opening in the proximal end, wherein the output conducts a mixture of the first flow stream (25) and the second flow stream (20). The apparatus further includes a regulating element (42) for the mixing valve in order to control a composition of the mixture.

# Smoking System

## BACKGROUND OF THE INVENTION

1. Field of the Invention.

This invention relates to tobacco product alternatives More particularly, this invention relates to a smoking device for limiting exposure to smoke fumes produced through combustion, for example tobacco combustion.

2. Description of the Related Art.

Tobacco-containing smoking devices are known. For example from U.S. Patent No. 7,726,320, which is herein incorporated by reference, and which proposes a cigarette incorporated within an electrically powered aerosol generating device that acts as a holder for that cigarette. The smoking article possesses at least one form of tobacco. The smoking article also possesses a mouth-end piece that is used by the smoker to inhale components of tobacco that are generated by the action of heat upon components of the cigarette. A representative smoking article possesses an outer housing incorporating a source of electrical power (e.g., a battery), a sensing mechanism for powering the device at least during periods of draw, and a heating device (e.g., at least one electrical resistance heating element) for forming a thermally generated aerosol that incorporates components of tobacco. During use, the cigarette is positioned within the device, and after use, the used cigarette is removed from the device and replaced with another cigarette.

European patent document EP 1 736 065, herein incorporated by reference, proposes an electronic cigarette containing nicotine without tar, which includes a shell and a suction nozzle. On the exterior wall of the shell, there is an air orifice, while there is an electronic circuit board, a constant pressure cavity, a sensor, a gas liquid separator, an atomizer, and a supplying bottle orderly located in the interior of the shell, wherein the electronic circuit board consists of an electronic switching circuit and a high-frequency generator. At one side of the sensor there is an air duct. A negative pressure cavity is located in the sensor. The atomizer connects with the supplying bottle, and there is an atomizing cavity located in the atomizer.

SUMMARY OF THE INVENTION

There is provided according to embodiments of the invention a smoking apparatus, sometimes referred to as an electronic cigarette or e-cigarette. A distal opening of the apparatus admits a first flow stream, and a proximal end has an opening to allow egress of fluid flow therethrough into a mouth of a smoker. The apparatus further includes a power section in a housing, an atomizer section accepting an aerosol-forming material and an atomizing element. The atomizing element is energized by a power element in the power section, wherein at least a portion of the first flow stream passes through the atomizer section and acquires an aerosol from the atomizing element therein. A mixing valve within the housing has a first input that receives the first flow stream, a second input receiving a second flow stream that avoids the atomizing element, and an output connected in fluid continuity to the opening in the proximal end, wherein the output conducts a mixture of the first flow stream and the second flow stream. The apparatus further includes a regulating element for the mixing valve in order to control a composition of the mixture.

According to one aspect of the smoking apparatus, the distal opening is adapted to receive a cigarette therein and the first flow stream carries a flow of smoke of the cigarette. The housing has an external vent formed therethrough, and the second input of the mixing valve is connected to the vent. The second flow stream includes ambient air drawn through the vent.

In an aspect of the smoking apparatus the first flow stream comprises ambient air drawn through the distal opening and the body of the housing has an external vent formed therethrough. The smoking apparatus includes a mounting adapter for docking a portion of a cigarette alongside the housing, so that a proximal end of the cigarette is in fluid communication with the vent, and the second flow stream includes cigarette smoke of the docked cigarette that is drawn through the vent.

According to yet another aspect of the smoking apparatus, the mixing valve is disposed upstream from the atomizing element, and the mixture of the first flow stream and the second flow stream passes through the atomizer section.

According to still another aspect of the smoking apparatus, the mixing valve is disposed downstream from the atomizing element and only one of the first flow stream and the second flow stream passes through the atomizer.

According to a further aspect of the smoking apparatus, the power element includes a super-capacitor. The mixing valve may be a ball valve, a shutter valve, a diaphragm valve or a hinge valve.

There is further provided according to embodiments of the invention a smoking apparatus, having a housing, a proximal end and a distal opening that admits a first flow stream, the proximal end having an opening to allow egress of fluid flow therethrough into a mouth of a smoker. The apparatus further includes a power section in the housing, an atomizer section accepting an aerosol-forming material and an atomizing element. The atomizing element is energized by a power element in the power section, wherein at least a portion of the first flow stream passes through the atomizer section and acquires an aerosol from the atomizing element therein, and wherein a second flow stream divides from the first flow stream upstream from the atomizing element and bypasses the atomizing element. The apparatus further includes a mixing valve within the housing that is disposed downstream from the atomizing element, and which has a first input that receives the first flow stream, a second input that receives the second flow stream, an output connected in fluid continuity to the opening in the proximal end, wherein the output conducts a mixture of the first flow stream and the second flow stream, and a regulating element for the mixing valve to control a composition of the mixture.

According to one aspect of the smoking apparatus, the distal opening is adapted to receive a cigarette therein and the first flow stream carries a flow of smoke of the cigarette.

## BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

For a better understanding of the present invention, reference is made to the detailed description of the invention, by way of example, which is to be read in conjunction with the following drawings, wherein like elements are given like reference numerals, and wherein:

Fig. 1 is a semi-schematic diagram of a smoking device in accordance with an embodiment of the invention;

Fig. 2 is a semi-schematic diagram of a smoking device in accordance with an alternate embodiment of the invention;

Fig. 3 is a semi-schematic diagram of a smoking device showing a power supply element in accordance with an alternate embodiment of the invention;

Fig. 4 is a semi-schematic diagram of a smoking device in accordance with an alternate embodiment of the invention;

Fig. 5 is a semi-schematic diagram of a smoking device in accordance with an alternate embodiment of the invention;

Fig. 6 is a semi-schematic diagram of a smoking device in accordance with an alternate embodiment of the invention;

Fig. 7 is a schematic diagram of illustrating operation of a simplified ball valve that facilitates understanding of the embodiment shown in Fig. 6;

Fig. 8 is a semi-schematic diagram of a smoking device in accordance with an alternate embodiment of the invention;

Fig. 9 is a schematic diagram of a valve in accordance with an embodiment of the invention; and

Fig. 10 is a schematic diagram of a diaphragm valve, in accordance with an embodiment of the invention.

## DETAILED DESCRIPTION OF THE INVENTION

In the following description, numerous specific details are set forth in order to provide a thorough understanding of the various principles of the present invention. It will be apparent to one skilled in the art, however, that not all these details are necessarily always needed for practicing the present invention. In this instance, well-known circuits, control logic, and the details of computer program instructions for conventional algorithms and processes have not been shown in detail in order not to obscure the general concepts unnecessarily.

Turning now to the drawings, reference is initially made to Fig. 1, which is a semi-schematic diagram of a smoking device 10 in accordance with an embodiment of the invention. Device 10 has a battery section 12. The battery section 12 may include power controls. Suitable power controls are disclosed in U.S. Provisional Application No. 61/441,133, which is herein incorporated by reference. The device 10 includes a section 14, containing an atomizer and an aerosolizable liquid or gel, sometimes referred to herein as an "e-liquid", which typically contains a mixture of propylene glycol, vegetable glycerin, flavorings, and optionally contains nicotine. The atomizer is essentially a heating element, powered by a battery in the battery section 12. When powered, the atomizer acts on the liquid or gel. The components of the section 14 may be provided as separate components, or may be integral, as taught in U.S.

Provisional Application No. 61/474,569, which is herein incorporated by reference. In the latter case, the section 14 is known as a "cartomizer".

An adapter 16 for receiving a tobacco-containing unit 18 is disposed at one end of the device 10 in a longitudinal fashion, so that the device 10, when docked with the unit 18, may appear to observers as an actual cigarette. The unit 18 may be a cigarette, a nicotine pack or cartridge, a hookah, or other source of tobacco fumes. In any case, a first air intake for receiving tobacco fumes is represented by arrow 20. When smoke enters the device 10, an aperture 22 constricts the flow, thereby creating a pressure differential, which is sensed by an airflow sensor 24 of known type. It is desirable to minimize the flow resistance, for example by minimizing flow constriction, in order that that the user experiences a feeling of smoking an actual cigarette. There is a tradeoff, however, in that the energy transmitted by pressure differences resulting from the inhalation is used to create the atomizer action. For a given pressure difference and flow conditions the ability to release droplets is also dependent on the viscosity of e-liquid. E-cigarettes use a high viscosity liquid that is converted to a low viscosity by heating.

Electronic circuitry 26 linked to the sensor 24 activates a heating device that enable viscosity reduction and thus activation of the atomizer in the section 14. Part of this electronic circuitry is a pressure or flow sensor, which switches a power source when the smoker starts inhaling. The circuitry 26 is powered, typically by an electrical power source (single use or rechargeable), for example, a lithium ion battery 28, other known type of rechargeable battery, or alternatively by a super capacitor. Additionally or alternatively, the aperture 22 may be manually controlled by the user by pressing a button (not shown), which can be mounted on the shaft of the device 10. For convenience, the device 10 may be configured similarly to a pistol, the actuating button corresponding to the trigger.

A second air intake is formed through the device 10 as a side vent 30. The vent 30 may be created in several ways, for example as a longitudinal notch, a hole bored through the shaft of the device 10, or formed in an adapter connecting the section 14 and the battery section 12 as taught in the above noted U.S. Provisional Application No. 61/474,569.

A regulated three-way mixing valve 32 accepts air inflow via the first air intake (arrow 20) and from the second air intake (vent 30). Air exiting the valve 32 represented by arrow 34 contains a mixture of the two inflows in any desired proportion. The inflows may be

controlled at constriction points 45, 47. As a result the user inhales, through oral adaptor 36 (arrow 38) an air mixture containing from 0 – 100 percent tobacco fumes.

The valve 32 may be programmed by electronic circuitry 40 within the device 10. For example, initial puffs may contain 100% tobacco fumes. Thereafter the valve adjusts automatically to limit the proportion of smoke. Alternatively, a control 42 may be provided for the user to manually adjust the valve 32.

The circuitry 40 or the circuitry 26 may disable the atomizer in the section 14 when the proportion of tobacco fumes exceeds a predefined threshold.

The valve 32, vent 30, air flow sensor 24, and other components need not be positioned as shown. For example they may be relocated upstream in the first air flow, and be placed before the battery 28. Other locations are possible, but in any case the user inhales a desired proportion of air and tobacco fumes. In some embodiments, a conventional cigarette may be smoked in combination with or in alternation with the e-cigarette. In such cases the air stream resulting from the conventional cigarette should be diverted to bypass the atomizer, as explained below.

Alternate Embodiment 1.

Reference is now made to Fig. 2, which is a semi-schematic diagram of a smoking device 64 in accordance with an alternate embodiment of the invention. The general construction of the smoking device 64 is similar to the device 10 (Fig. 1). However the valve 32 is disposed downstream (in the direction of inhaled airflow) from the atomizer in the section 14.

Alternate Embodiment 2.

The battery 28, particularly when realized as a lithium ion battery, has several disadvantages. Charging and discharging must be carefully regulated. In addition, precautions must be taken to prevent contact with liquid in the section 14, should leakage occur. Indeed, under some circumstances the battery 28 could be a fire hazard. In addition, charging times limit the utility of the device 10, or may require the user to carry duplicates of the battery section 12 or the battery 28.

Reference is now made to Fig. 3, which is a schematic diagram of a smoking device 46 in accordance with an alternate embodiment of the invention. In this embodiment, the battery 28 is replaced by a super capacitor 44, which can be charged within seconds by connection to ordinary house power. The device 46 is provided with intakes 58, 60 for air and tobac-

co fumes. The capacitance of the capacitor 44 is sufficient to power the atomizer for a desired number of usages before it discharges.

Alternate Embodiment 3.

Reference is now made to Fig. 4, which is a schematic diagram of a smoking device 48 in accordance with an alternate embodiment of the invention. In this embodiment, the device 48 has a mounting adapter 49 for docking a portion of a conventional cigarette 50 or other source of tobacco fumes longitudinally alongside the housing. The smoke enters through a side vent as described above (arrow 52). Ambient air enters through a distal end intake (arrow 54), both reaching mixing valve 56. It will be noted that an air stream represented by arrow 54 passes through an atomizer 57, while the air stream from the cigarette 50 does not enter the atomizer 57.

Alternate Embodiment 4.

In this embodiment the air intake is regulated by valves at the intakes, or alternatively, by a mixing valve located at the intake, which can be an electronically controlled valve, or any other type of valve as explained elsewhere herein. Reference is now made to Fig. 5, which is a semi-schematic diagram of a smoking device 66 in accordance with an alternate embodiment of the invention. In this embodiment, the aperture 22 (Fig. 1) has been replaced by a shutter valve 68. The vent 30 is guarded by another shutter valve 70. The shutter valves 68, 70 have the same construction, as best seen in balloons 72, 74. Alternatively, the two shutter valves may differ in construction. In any case, the combined flows exit toward the oral adaptor 36 via outlet tube 76 as shown by the arrow 34.

In the shutter valves 68, 70, an air shutter 62 is slidable over intake 58 to restrict air flow therethrough. The shutter 62 may be controlled manually by the user, or automatically by a controller 78 to adjust the relative flows through inlet tubes 80, 82. The shutters shown in Fig. 5 are exemplary. Other closure arrangements, e.g., hinged valves, electronically controlled valves, cam driven piston valves, can be substituted for the shutter valves 68, 70. Several such alternatives are described in the embodiments below. Indeed the shutter valves 68, 70 can be used as regulatory elements in the valve 32 (Fig. 1).

Alternate Embodiment 5.

Reference is now made to Fig. 6, which is a semi-schematic diagram of a smoking device 84, in accordance with an alternate embodiment of the invention. In this embodiment the valve 32 (Fig. 1) is realized as a ball valve 64, in which air outflow may be allocated in any desired proportion between an outlet 86 leading to a vent 88 and an outlet 90 leading toward the oral adaptor 36. Ball valves typically have low maintenance costs. In addition to affording quick, quarter-turn on-off operation, ball valves are compact, require no lubrication, and give tight sealing with low torque. However, they have relatively poor throttling characteristics. In a throttling position, the partially exposed seat is vulnerable to erosion because of the impingement of high velocity flow.

A first air stream, represented by arrows 20, is diverted from the atomizer by shutter valve 23, and reaches the ball valve 64. A second air stream, represented by arrows 25 enters via aperture 21, passes through the atomizer 57 and thence to the ball valve 64. Thus mixing occurs in the ball valve 64 downstream from the atomizer 57, after it has acted on the second air stream.

Reference is now made to Fig. 7, which is a schematic diagram of illustrating operation of a simplified ball valve 92 that facilitates understanding of the ball valve 64 (Fig. 6), in accordance with an embodiment of the invention. Fluid flow direction is indicated by the arrows in Fig. 7. From left to right, the ball valve 92 is shown in open, throttled, and closed positions, respectively.

The ball valve 92 has a body 94 and a ball 96, an inlet 98 and a single outlet 100. In this respect the ball valve 92 is unlike the ball valve 64, which has two outlets 86, 90. The ball 96 rotates about an axis 102, under control of an actuator 104.

Alternate Embodiment 6.

Reference is now made to Fig. 8, which is a semi-schematic diagram of a smoking device, in accordance with an alternate embodiment of the invention. In this embodiment, mixing occurs after a portion of the airflow has passed through the atomizer. A bypass tube 106 transmits a proportion of the air flow, the proportion being regulated by the control 42 at a constriction point 108, while the remainder of the airflow passes through the atomizer via tube 110, as shown by arrow 112. When the constriction point 108 is fully open, the atomizer offers greater flow resistance than the bypass tube 106, and most of the flow passes through

the bypass tube 106. Actuating the control 42 constrains flow through the bypass tube 106 at the constriction point 108, so that a greater proportion of the flow arrives at the vent 30 by passing through the atomizer and the tube 110. Providing a parallel flow circuit via the bypass tube 106 allows the total flow resistance to be lowered. The arrangement shown schematically in Fig. 8 may be applied, *mutatis mutandis*, to any of the other embodiments disclosed herein.

Alternate Embodiment 7.

Reference is now made to Fig. 9, which is a schematic diagram of a valve 114 in accordance with an embodiment of the invention. The valve 114 can be employed in the various embodiments herein, for example at the constriction points 108, 45 (Fig. 8). Movement of a ball (or cylinder) 116 against the wall of a tube 118 produces compression and increases flow resistance.

Alternate Embodiment 8.

Reference is now made to Fig. 10, which is a schematic diagram of a diaphragm valve 120, in accordance with an embodiment of the invention, wherein displacement a diaphragm 122 by an actuator 124 into the flow throttles or obstructs the flow entirely. From left to right the diaphragm valve 120 is shown in open, throttled, and closed positions, respectively. The diaphragm valve 120 can be used in the various embodiments herein, for example at the constriction points 108, 45 (Fig. 8).

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and sub-combinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.

Claims.

1. A smoking apparatus, comprising:

a housing having a body, a proximal end and a distal opening that admits a first flow stream, the proximal end having an opening to allow egress of fluid flow therethrough into a mouth of a smoker;

a power section in the housing;

an atomizer section accepting an aerosol-forming material and an atomizing element, the atomizing element being energized by a power element in the power section, wherein at least a portion of the first flow stream passes through the atomizer section and acquires an aerosol from the atomizing element therein;

a mixing valve within the housing having a first input that receives the first flow stream, a second input receiving a second flow stream that avoids the atomizing element, and an output connected in fluid continuity to the opening in the proximal end, wherein the output conducts a mixture of the first flow stream and the second flow stream; and

a regulating element for the mixing valve to control a composition of the mixture.

2. The smoking apparatus according to claim 1, wherein the distal opening is adapted to receive a cigarette therein and the first flow stream carries a flow of smoke of the cigarette, and wherein the body of the housing has an external vent formed therethrough, the second input of the mixing valve being connected to the vent, and the second flow stream comprises ambient air drawn through the vent.

3. The smoking apparatus according to claim 1, wherein the first flow stream comprises ambient air drawn through the distal opening and the body of the housing has an external vent formed therethrough, the smoking apparatus further comprising:

a mounting adapter for docking a portion of a cigarette alongside the housing, so that a proximal end of the cigarette is in fluid communication with the vent, so that the second flow stream comprises cigarette smoke drawn through the vent.

4. The smoking apparatus according to claim 1, wherein the mixing valve is disposed upstream from the atomizing element, and the mixture of the first flow stream and the second flow stream passes through the atomizer section.

5. The smoking apparatus according to claim 1, wherein the mixing valve is disposed downstream from the atomizing element and only one of the first flow stream and the second flow stream passes through the atomizer section.

6. The smoking apparatus according to claim 1, wherein the power element comprises a super-capacitor.

7. The smoking apparatus according to claim 1, wherein the mixing valve comprises a ball valve.

8. The smoking apparatus according to claim 1, wherein the mixing valve comprises a shutter valve.

9. The smoking apparatus according to claim 1, wherein the mixing valve comprises a diaphragm valve.

10. The smoking apparatus according to claim 1, wherein the mixing valve comprises a hinge valve.

11. A smoking apparatus, comprising:

a housing having a body, a proximal end and a distal opening that admits a first flow stream, the proximal end having an opening to allow egress of fluid flow therethrough into a mouth of a smoker;

a power section in the housing;

an atomizer section accepting an aerosol-forming material and an atomizing element, the atomizing element being energized by a power element in the power section, wherein at least a portion of the first flow stream passes through the atomizer section and acquires an

aerosol from the atomizing element therein, and wherein a second flow stream divides from the first flow stream upstream from the atomizing element and bypasses the atomizing element;

a mixing valve within the housing disposed downstream from the atomizing element and having a first input that receives the first flow stream, a second input receiving the second flow stream, and an output connected in fluid continuity to the opening in the proximal end, wherein the output conducts a mixture of the first flow stream and the second flow stream; and

a regulating element for the mixing valve to control a composition of the mixture.

12. The smoking apparatus according to claim 11, wherein the distal opening is adapted to receive a cigarette therein and the first flow stream carries a flow of smoke of the cigarette.

13. The smoking apparatus according to claim 11, wherein the power element comprises a super-capacitor.

14. The smoking apparatus according to claim 11, wherein the mixing valve comprises a ball valve.

15. The smoking apparatus according to claim 11, wherein the mixing valve comprises a shutter valve.

16. The smoking apparatus according to claim 11, wherein the mixing valve comprises a diaphragm valve.

17. The smoking apparatus according to claim 11, wherein the mixing valve comprises a hinge valve.

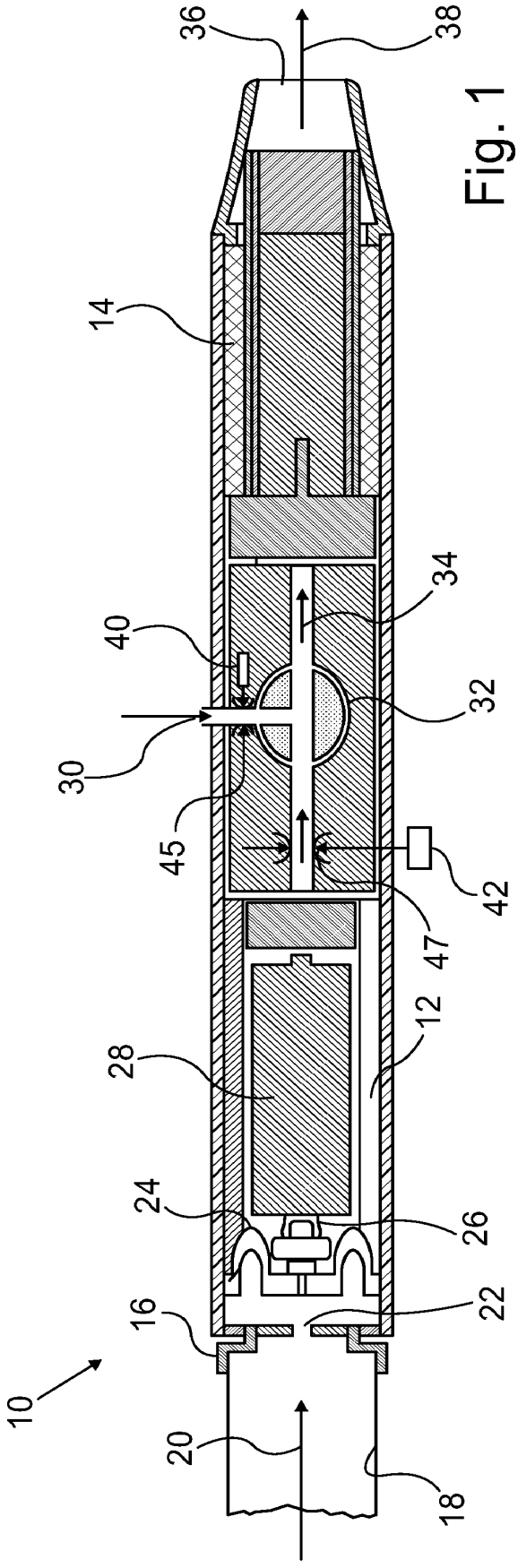

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Fig. 1

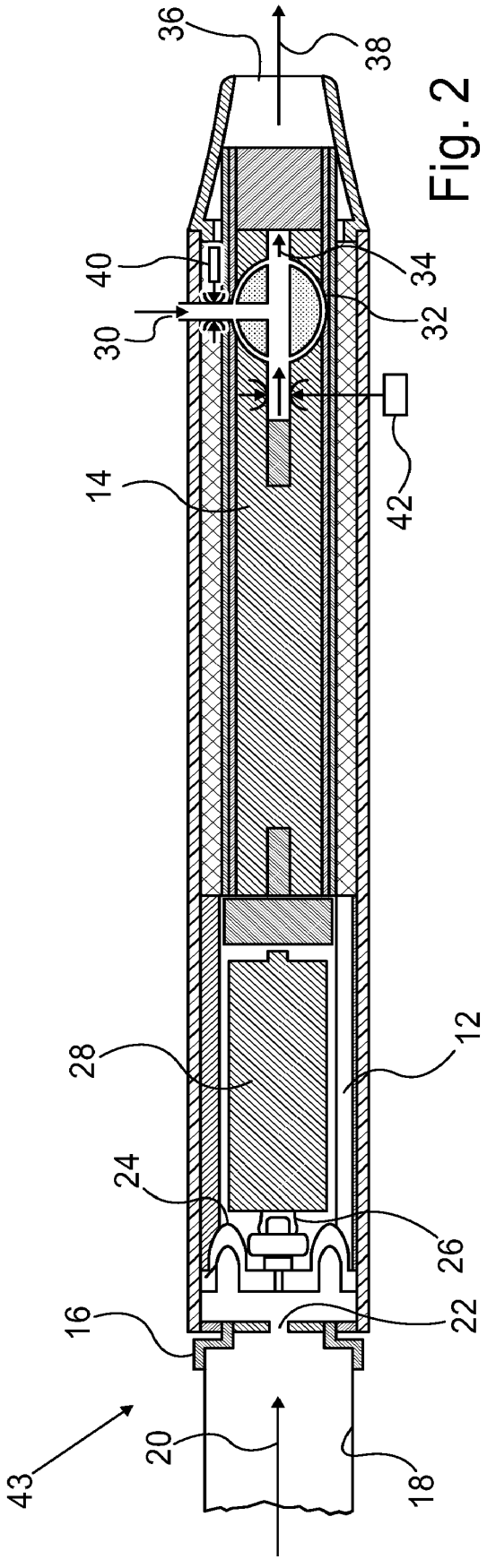

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Fig. 2

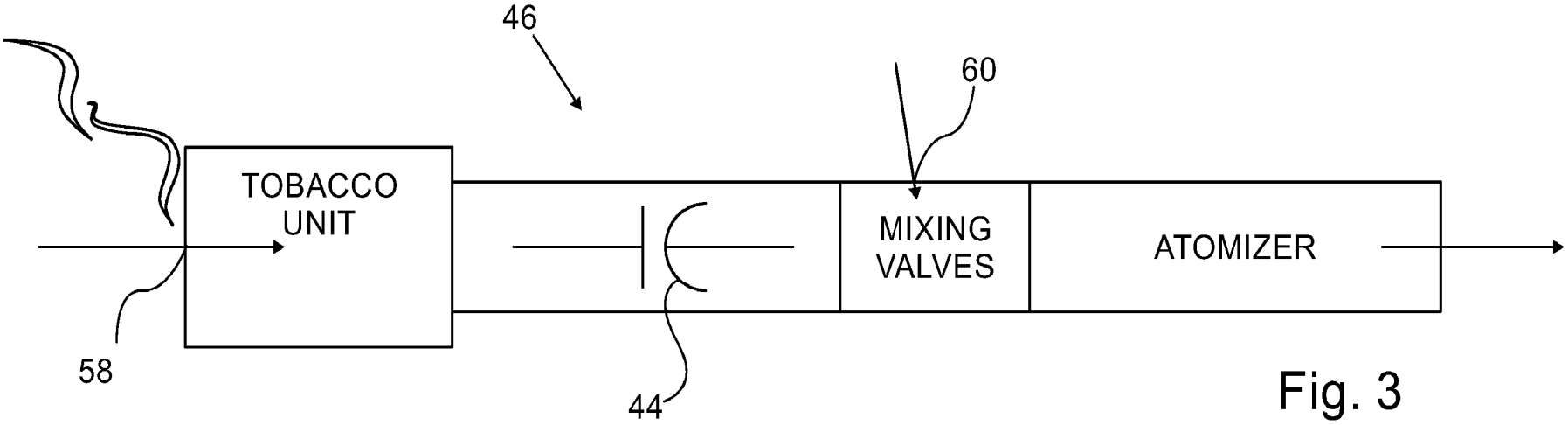

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TOBACCO UNIT
MIXING VALVES
ATOMIZER
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Fig. 3



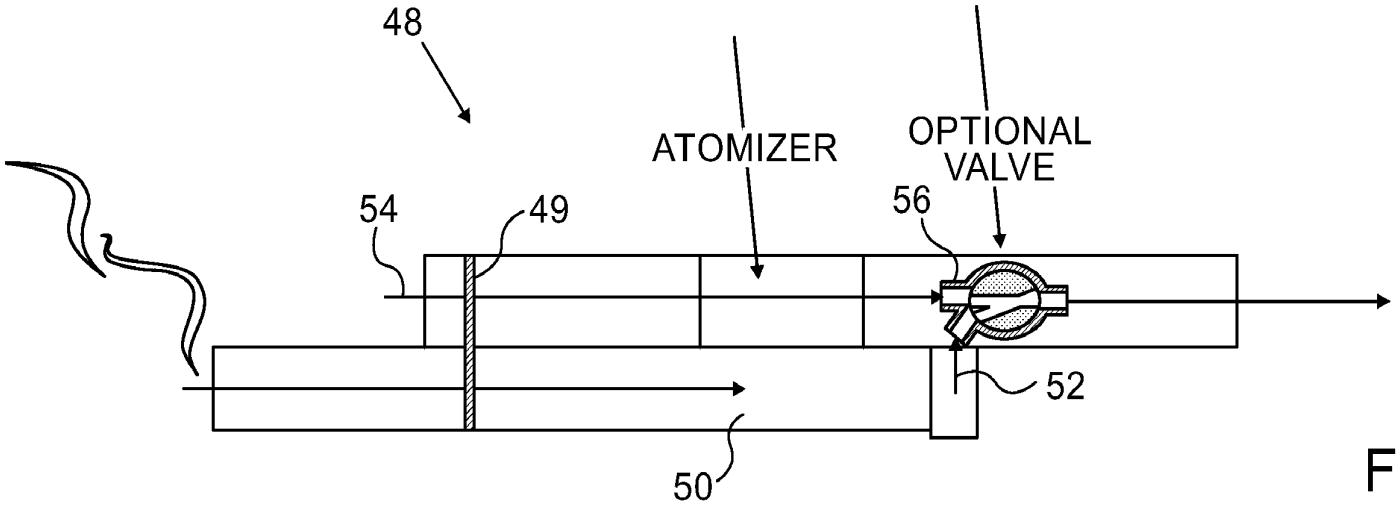

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ATOMIZER
OPTIONAL VALVE
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Fig. 4

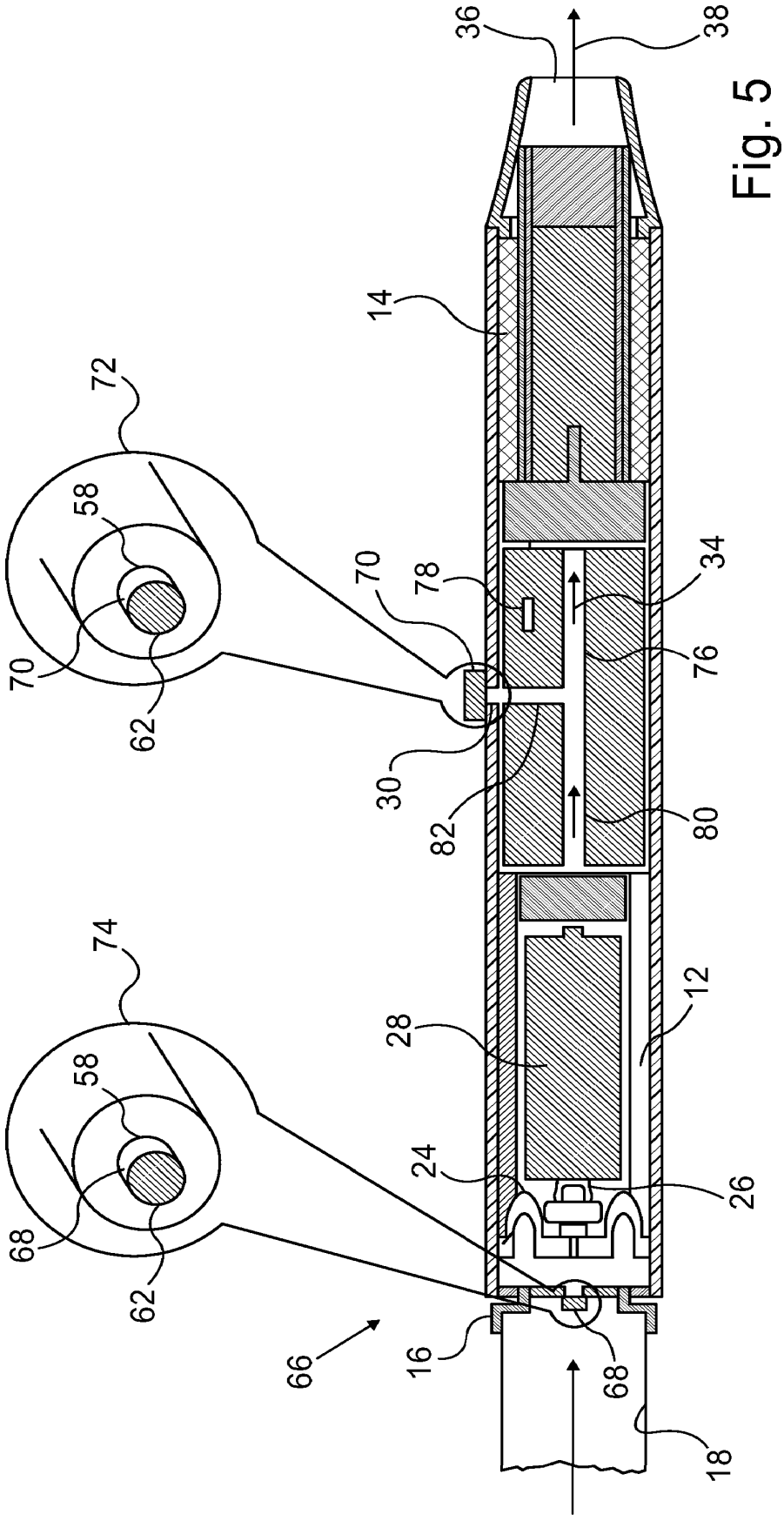

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Fig. 5

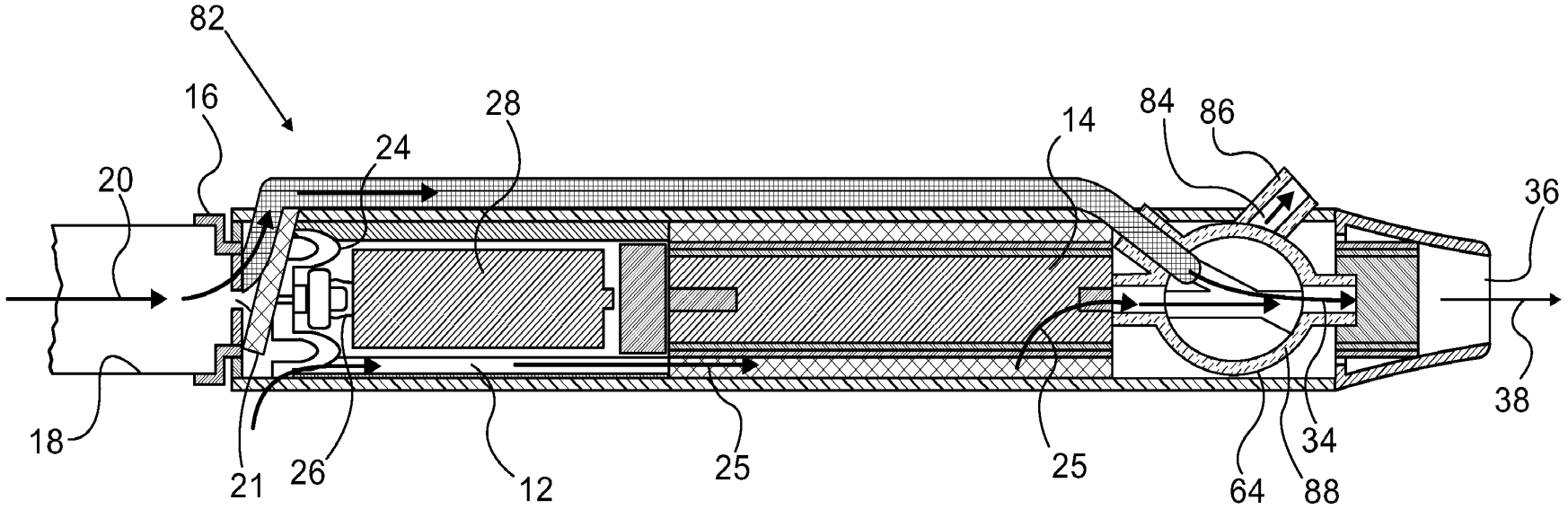

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Fig. 6

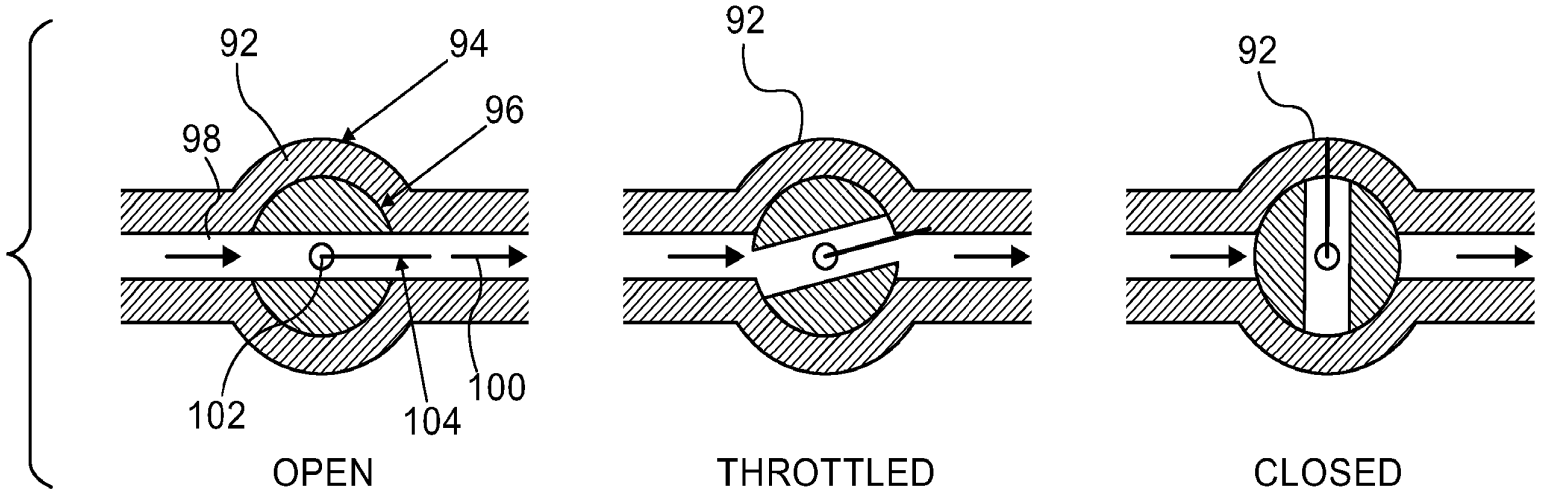

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Fig. 7

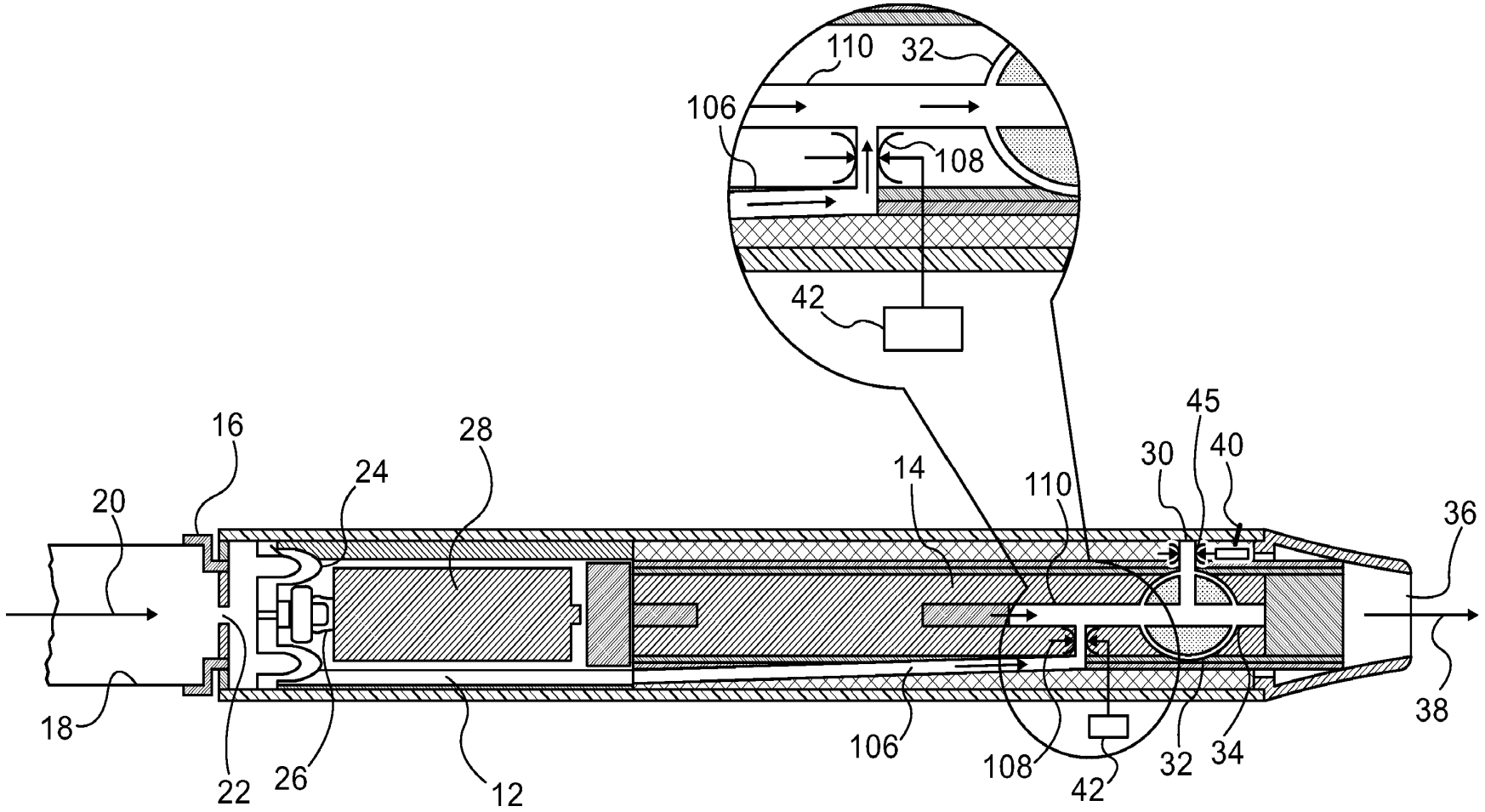

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Fig. 8

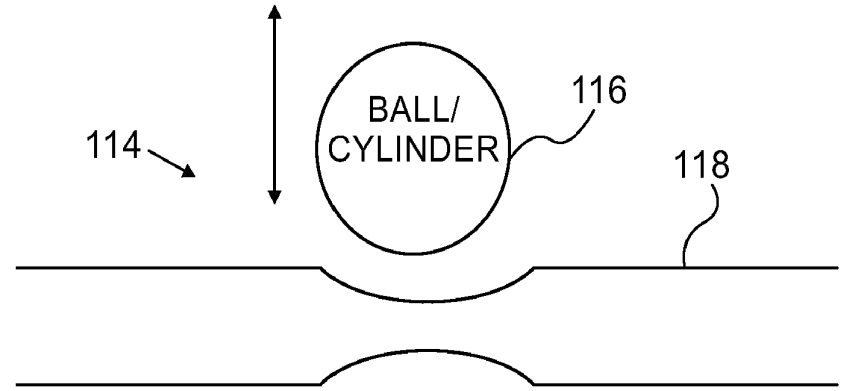



Fig. 9



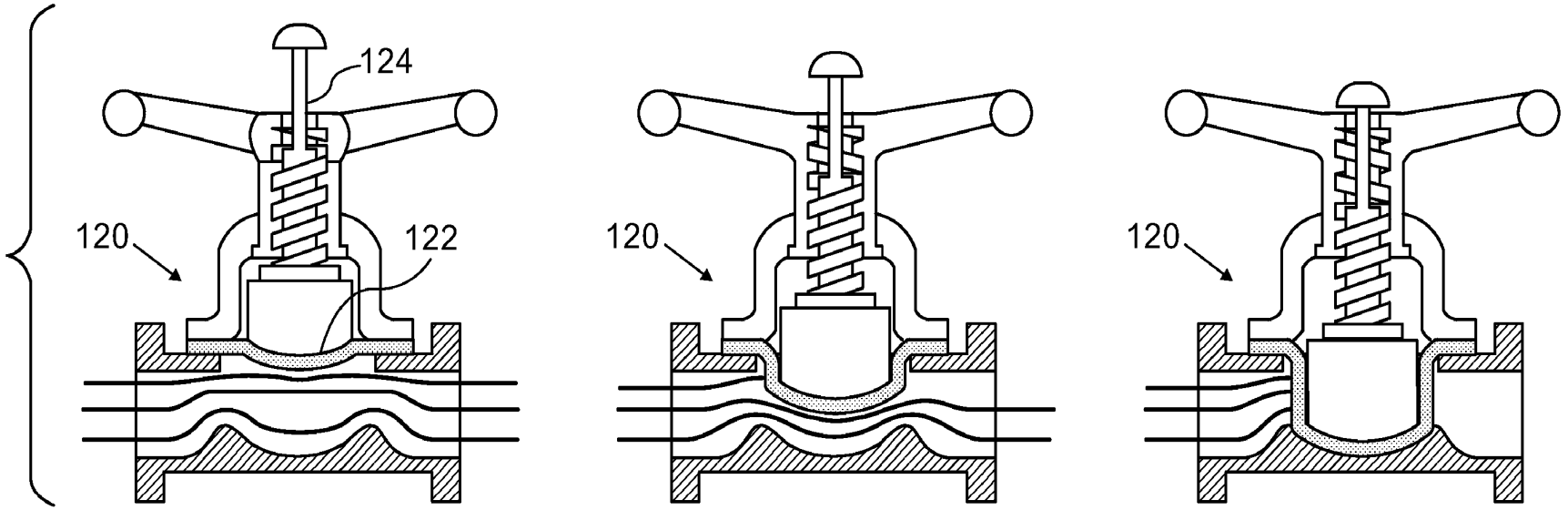



Fig. 10

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/055287

A. CLASSIFICATION OF SUBJECT MATTER
IPC (2013.01) A24F 47/00, A24F 5/04

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 (2013.01) A24F

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 practicable, search terms used)
Databases consulted: THOMSON INNOVATION

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 7726320 B2 John Howard Robinson<br>01 Jun 2010 (2010/06/01)<br>the whole document | 1-17 |
| Y | US 3601131 A Eugene T. Reggio<br>24 Aug 1971 (1971/08/24)<br>the whole document | 1-17 |
| Y | US 3519000 A Roy W. Houser<br>07 Jul 1970 (1970/07/07)<br>the whole document | 1-17 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"E" earlier application or patent but published on or after the international filing date
"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
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"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
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 Jan 2013 | 31 Jan 2013 |

| Name and mailing address of the ISA: | Authorized officer |
|---|---|
| Israel Patent Office<br>The Technology Park, Bldg.5, Malcha, Jerusalem, 9695101,<br>Facsimile No. 972-2-5651616 | NARGASI Ayelet<br>AyeletN@justice.gov.il<br>Telephone No. 972-2-5651620 |

Form PCT/ISA/210 (second sheet) (July 2009)

International application No.
PCT/IB2012/055287

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(19) World Intellectual Property Organization
International Bureau

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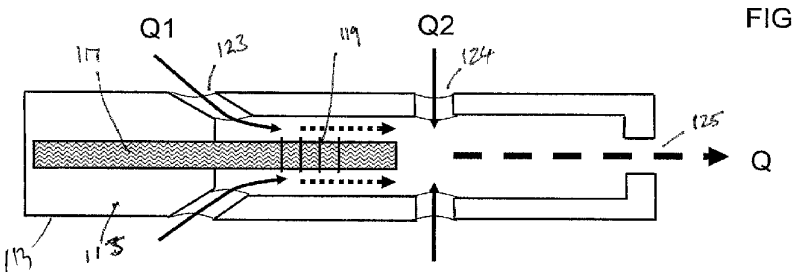



FIG 2

(57) Abstract: There is provided an aerosol generating device comprising: a housing having a first air inlet (123) and an air outlet (125), the housing defining an air flow channel between the first air inlet (123) and the air outlet (125), and a heater (119) configured to heat an aerosol-forming substrate (117) positioned within or adjacent to the air flow channel, wherein the housing further comprises a second air inlet (124), the second air inlet (124) positioned between the heater (119) and the air outlet (125), the second air inlet (124) configured to allow air into the air flow channel, and wherein the second air inlet (124) is larger than the first air inlet (123).

# AN AEROSOL GENERATING DEVICE HAVING AIRFLOW INLETS

The present invention relates to an aerosol generating device for heating an aerosol-forming substrate. Particularly, but not exclusively, the present invention relates to an electrically operated aerosol generating device for heating a liquid aerosol-forming substrate.

WO-A-2009/132793 discloses an electrically heated smoking system. A liquid is stored in a liquid storage portion, and a capillary wick has a first end which extends into the liquid storage portion for contact with the liquid therein, and a second end which extends out of the liquid storage portion. A heating element heats the second end of the capillary wick. The heating element is in the form of a spirally wound electric heating element in electrical connection with a power supply, and surrounding the second end of the capillary wick. In use, the heating element may be activated by the user to switch on the power supply. Suction on a mouthpiece by the user causes air to be drawn into the electrically heated smoking device over the capillary wick and heating element and subsequently into the mouth of the user.

It is an objective of the present invention to improve the generation of aerosol in such an electrically heated aerosol generating system.

The generation of aerosol in an aerosol generating device requires two processes. First, the aerosol forming substrate must be vaporized. Then, the resulting vapour must condense to form the droplets of the aerosol. Typically, in aerosol generating devices such as electric smoking devices, only a single air inlet is provided upstream of the heater to allow air into the device, flow past a heater (or other substrate vaporizing element) to pick up the vapour and then out of an air outlet of the device, such as a mouthpiece. In this context “upstream” and “downstream” refer to the air flow through the device from air inlet to air outlet. Condensation of the vaporized substrate occurs around and downstream of the heater (that is, between the heater and the air outlet in the direction of airflow), within the device. There is only a limited ability to control the condensation process in such devices in order to optimise the aerosol quantity and aerosol properties.

According to one aspect of the invention, there is provided an aerosol generating device comprising: a housing having a first air inlet and an air outlet, the housing defining an air flow channel between the first air inlet and the air outlet; and a heater configured to heat an aerosol-forming substrate positioned within or adjacent to the air flow channel; wherein the housing further comprises a second air inlet, the second air inlet positioned between the heater and the air outlet, the second air inlet configured to allow ambient air into the air flow channel, and wherein the second air inlet is larger than the first air inlet.

The provision of a second air inlet between the heater and the air outlet, in accordance with the present invention, allows a vaporized substrate to be rapidly cooled before it leaves the device through the air outlet. This cooling through the provision of the second air inlet allows the

outlet temperature to be controlled. The cooling process through the provision of the second air inlet also allows the optimal conversion of vapour into aerosol.

The second air inlet is larger than the first air inlet (that is, allows in more air). A larger inlet in this context means that for a given suction on the air outlet a greater flow of air is drawn through that inlet. So, for a given suction on the air outlet a greater flow of air is drawn through the second air inlet than the first air inlet. Preferably, the second air inlet allows an air flow at least five times larger than the air flow provided by the first air inlet. That is, for a given suction on the air outlet at least five times more air is drawn through the second air inlet than the first air inlet. This could be accomplished by forming the second air inlet from a greater number of apertures. This could also be accomplished by making apertures that make up the second air inlet larger than apertures that make up the first air inlet. This could also be acheived by a combination of more apertures that make up the second air inlet and larger apertures that make up the second air inlet. More preferably, the second air inlet is more than eight times larger than the first air inlet and may be fourteen times larger than the first air inlet.

The airflow past the heater or substrate need only be sufficient to move the vaporized substrate towards the second air inlet. The first air inlet and the air flow channel are preferably configured to provide for substantially laminar air flow between the first air inlet and the second air inlet when suction is applied to the air inlet. This provides efficient transport of vaporized substrate away from the heater. The second air inlet provides cooling air into the device to cool the vapour and control the condensation of the vapour. The second air inlet and the air flow channel are preferably configured to provide for turbulent air flow between the second air inlet and the air output in order to efficiently cool the air and condense the vapour.

The relative dimensions of the first and second air inlets can be selected to optimise the properties of the aerosol delivered to the user, or the total mass flow rate through the outlet. The mass flow rate is the mass flow rate through the first inlet and the mass flow rate through the second inlet. The total mass flow rate directly depends on the relative number and sizes of the apertures forming the first and second air inlets and can be altered to optimise the delivered aerosol for a given demanded temperature at the outlet. The number and sizes of the apertures forming the first and second air inlets can be found to maximise aerosol mass flow rate. The number and sizes of the apertures forming the first and second air inlets depends on the substrate composition. Different geometries will also exhibit different behaviours. The device may be configured to automatically alter the size of the first air inlet or second air inlet based on the composition of the aerosol-forming substrate, the temperature of the heater or a detected flow rate through a portion of the device

The device may comprise a main body part and a cartridge. The cartridge may contain the aerosol forming substrate. The consumable cartridge may be replaced when the supply of aerosol-forming substrate is exhausted. A portion of the housing of the device is preferably

formed by the consumable cartridge and includes the second air inlet or the first air inlet, or both the first and second air inlets. The heater may also be part of the cartridge. Preferably the capillary wick is also part of the cartridge. The consumable cartridge may also include a mouthpiece. An aerosol generating device, wherein the device comprises a cartridge, the cartridge comprising the aerosol forming substrate and wherein a portion of the housing is formed by the cartridge and includes the second air inlet or the first air inlet, or both the first and second air inlets.

The device housing may include a mouthpiece portion surrounding the air outlet, the device being configured such that suction by a user on the mouthpiece portion draws air through the first and second air inlets into the air flow channel. The device is preferably passive with respect to air flow, and so includes no fan or blower. However, it is possible to include a fan or other active airflow management component in the device if desired.

Preferably, the housing of the device is elongate. The housing may comprise any suitable material or combination of materials. Examples of suitable materials include metals, alloys, plastics or composite materials containing one or more of those materials, or thermoplastics that are suitable for food or pharmaceutical applications, for example polypropylene, polyetheretherketone (PEEK) and polyethylene. Preferably, the material is light and non-brittle.

The first air inlet may comprise a plurality of first apertures in the housing. The second air inlet may comprise a plurality of second apertures in the housing. The plurality of first and second apertures can be symmetrically disposed around the airflow channel. Preferably there are between one and five first apertures and between one and five second air apertures. More preferably there are between two and four first air inlets and between two and four second air inlets. Even more preferably, there are three first air inlets and three second air inlets. However, there may be 10 or more first and second air inlets and there may be an equal or unequal number of first air inlets and second air inlets, in any combination of numbers. .

The airflow channel may be configured in a number of ways. For example a heater may form part of a wall of the airflow channel. The airflow channel may surround the heater or may be formed only on one side of the heater. The airflow channel may not include a heater, but the wall or walls of the airflow channel could be the aerosol forming substrate. The airflow channel may have a substantially circular cross-section, or may have a substantially oval or substantially elliptical cross-section.

The vaporiser may be a heater. The heater may heat the aerosol-forming substrate means by one or more of conduction, convection and radiation. The heater may be an electric heater powered by an electric power supply. The heater may alternatively be powered by a non-electric power supply, such as a combustible fuel: for example, the heater may comprise a thermally conductive element that is heated by combustion of a gas fuel.

The heater is preferably an electric heater. The electric heater may comprise a single heating element. Alternatively, the electric heater may comprise more than one heating element for example two, or three, or four, or five, or six or more heating elements. The heating element or heating elements may be arranged appropriately so as to most effectively heat the aerosol-forming substrate.

The at least one electric heating element preferably comprises an electrically resistive material. Suitable electrically resistive materials include but are not limited to: semiconductors such as doped ceramics, electrically "conductive" ceramics (such as, for example, molybdenum disilicide), carbon, graphite, metals, metal alloys and composite materials made of a ceramic material and a metallic material. Such composite materials may comprise doped or undoped ceramics. Examples of suitable doped ceramics include doped silicon carbides. Examples of suitable metals include titanium, zirconium, tantalum and metals from the platinum group. Examples of suitable metal alloys include stainless steel, Constantan, nickel-, cobalt-, chromium-, aluminium- titanium- zirconium-, hafnium-, niobium-, molybdenum-, tantalum-, tungsten-, tin-, gallium-, manganese- and iron-containing alloys, and super-alloys based on nickel, iron, cobalt, stainless steel, Timetal®, iron-aluminium based alloys and iron-manganese-aluminium based alloys. Timetal® is a registered trade mark of Titanium Metals Corporation, 1999 Broadway Suite 4300, Denver Colorado. In composite materials, the electrically resistive material may optionally be embedded in, encapsulated or coated with an insulating material or vice-versa, depending on the kinetics of energy transfer and the external physicochemical properties required. The heating element may comprise a metallic etched foil insulated between two layers of an inert material. In that case, the inert material may comprise Kapton®, all-polyimide or mica foil. Kapton® is a registered trade mark of E.I. du Pont de Nemours and Company, 1007 Market Street, Wilmington, Delaware 19898, United States of America.

Alternatively, the at least one electric heating element may comprise an infra-red heating element, a photonic source or an inductive heating element.

The at least one electric heating element may take any suitable form. For example, the at least one electric heating element may take the form of a heating blade. Alternatively, the at least one electric heating element may take the form of a casing or substrate having different electro-conductive portions, or an electrically resistive metallic tube. The liquid storage portion may incorporate a disposable heating element. Alternatively, if the aerosol-forming substrate is liquid, one or more heating needles or rods that run through the liquid aerosol-forming substrate may also be suitable. Alternatively, the at least one electric heating element may be a disk (end) heater or a combination of a disk heater with heating needles or rods. Alternatively, the at least one electric heating element may comprise a flexible sheet of material. Other alternatives include a heating wire or filament, for example a nickel-chromium (Ni-Cr), platinum, tungsten or alloy wire, or a heating plate. Optionally, the heating element may be deposited in or on a rigid

carrier material.

The at least one electric heating element may comprise a heat sink, or heat reservoir comprising a material capable of absorbing and storing heat and subsequently releasing the heat over time to heat the aerosol-forming substrate. The heat sink may be formed of any suitable material, such as a suitable metal or ceramic material. Preferably, the material has a high heat capacity (sensible heat storage material), or is a material capable of absorbing and subsequently releasing heat via a reversible process, such as a high temperature phase change. Suitable sensible heat storage materials include, for example, silica gel, alumina, carbon, glass mat, glass fibre, minerals, a metal or alloy such as aluminium, silver or lead, and a cellulose material. Other suitable materials which release heat via a reversible phase change include paraffin, sodium acetate, naphthalene, wax, polyethylene oxide, a metal, metal salt, a mixture of eutectic salts or an alloy.

The heat sink may be arranged such that it is directly in contact with the aerosol-forming substrate and can transfer the stored heat directly to the substrate. Alternatively, the heat stored in the heat sink or heat reservoir may be transferred to the aerosol-forming substrate by means of a heat conductor, such as a metallic tube.

The at least one heating element may heat the aerosol-forming substrate by means of conduction. The heating element may be at least partially in contact with the substrate. Alternatively, the heat from the heating element may be conducted to the substrate by means of a heat conductor.

In addition, or alternatively, the at least one heating element may transfer heat to the incoming ambient air that is drawn through the aerosol generating device during use, which in turn heats the aerosol-forming substrate by convection. The ambient air may be heated before passing through the aerosol-forming substrate. Alternatively, the ambient air may be first drawn through the liquid substrate and then heated.

The aerosol-forming substrate may be a solid aerosol-forming substrate. The aerosol-forming substrate preferably comprises a tobacco material comprising volatile tobacco flavour compounds which are released from the substrate upon heating. The aerosol-forming substrate may comprise a non-tobacco material. The aerosol-forming substrate may comprise tobacco material and non-tobacco containing material. Preferably, the aerosol-forming substrate further comprises an aerosol former that facilitates the formation of a dense and stable aerosol. Examples of suitable aerosol formers are glycerine and propylene glycol.

However, in a preferred embodiment, the aerosol-forming substrate is a liquid aerosol-forming substrate. The liquid aerosol-forming substrate preferably has physical properties, for example boiling point and vapour pressure, suitable for use in the aerosol generating device. If the boiling point is too high, it may not be possible to vaporize the liquid but, if the boiling point is too low, the liquid may vaporize too readily. The liquid preferably comprises a tobacco

material comprising volatile tobacco flavour compounds which are released from the liquid upon heating. Alternatively, or in addition, the liquid may comprise a non-tobacco material. The liquid may include aqueous solutions, non-aqueous solvents such as ethanol, plant extracts, nicotine, natural or artificial flavours or any combination of these. Preferably, the liquid further comprises an aerosol former. Examples of suitable aerosol formers are glycerine and propylene glycol.

If the aerosol-forming substrate is a liquid substrate, the aerosol generating device may further comprise a liquid storage portion for storing the liquid aerosol-forming substrate. An advantage of providing a liquid storage portion is that the liquid in the liquid storage portion is protected from ambient air (because air cannot generally enter the liquid storage portion). It can also be protected from light. By protecting the liquid from air and light, the risk of degradation of the liquid is significantly reduced. Moreover, a high level of hygiene can be maintained. The liquid storage portion may not be refillable. Thus, when the liquid in the liquid storage portion has been used up, the aerosol generating device is replaced. Alternatively, the liquid storage portion may be refillable. In that case, the aerosol generating device may be replaced after a certain number of refills of the liquid storage portion. Preferably, the liquid storage portion is arranged to hold liquid for a pre-determined number of puffs. If the aerosol generating device comprises a first portion having a mouthpiece and a second portion opposite the first portion, the liquid storage portion may be contained in the first portion or in the second portion.

The aerosol-forming substrate may alternatively be any other sort of substrate, for example, a gas substrate, or any combination of the various types of substrate.

If the aerosol-forming substrate is a liquid aerosol-forming substrate, the heater of the aerosol generating device may comprise a capillary wick for conveying the liquid aerosol-forming substrate by capillary action. Preferably, the capillary wick is arranged to be in contact with liquid in the liquid storage portion. Preferably, the capillary wick extends into the liquid storage portion. In that case, in use, liquid is transferred from the liquid storage portion by capillary action in the capillary wick. In one embodiment, liquid in one end of the capillary wick is vaporized to form a supersaturated vapour. The supersaturated vapour is mixed with and carried in the air flow. During the flow, the vapour condenses to form the aerosol and the aerosol is carried towards the mouth of a user. The liquid aerosol-forming substrate has physical properties, including surface tension and viscosity, which allow the liquid to be transported through the capillary wick by capillary action.

The capillary wick may have a fibrous or spongy structure. The capillary wick preferably comprises a bundle of capillaries. For example, the capillary wick may comprise a plurality of fibres or threads or other fine bore tubes. The fibres or threads may be generally aligned in the longitudinal direction of the aerosol generating device. Alternatively, the capillary wick may comprise sponge-like or foam-like material formed into a rod shape. The rod shape may extend along the longitudinal direction of the aerosol generating device. The structure of the wick forms

a plurality of small bores or tubes, through which the liquid can be transported by capillary action. The capillary wick may comprise any suitable material or combination of materials. Examples of suitable materials are capillary materials, for example a sponge or foam material, ceramic- or graphite-based materials in the form of fibres or sintered powders, foamed metal or plastics material, a fibrous material, for example made of spun or extruded fibres, such as cellulose acetate, polyester, or bonded polyolefin, polyethylene, terylene or polypropylene fibres, nylon fibres or ceramic. The capillary wick may have any suitable capillarity and porosity so as to be used with different liquid physical properties. The liquid has physical properties, including but not limited to viscosity, surface tension, density, thermal conductivity, boiling point and vapour pressure, which allow the liquid to be transported through the capillary system by capillary action. The capillary wick must be suitable so that the required amount of liquid can be delivered to the heater.

Alternatively, instead of a capillary wick, the aerosol generating device may comprise any suitable capillary or porous interface between the liquid aerosol-forming substrate and the heater, for conveying the desired amount of liquid to the heater.

The liquid storage portion is preferably a container. The liquid storage portion may not be refillable. Thus, when the liquid in the liquid storage portion has been used up, the aerosol generating device is replaced. Alternatively, the liquid storage portion may be refillable. In that case, the aerosol generating device may be replaced after a certain number of refills of the liquid storage portion. Preferably, the liquid storage portion is arranged to hold liquid for a pre-determined number of puffs.

In one preferred embodiment, the aerosol-forming substrate is a liquid aerosol-forming substrate, the aerosol generating device comprises a liquid storage portion for storing the liquid aerosol-forming substrate, an electric heater and a capillary wick. In that embodiment, preferably the capillary wick is arranged to be in contact with liquid in the liquid storage portion. In use, liquid is transferred from the liquid storage portion towards the electric heater by capillary action in the capillary wick. In one embodiment, the capillary wick has a first end and a second end, the first end extending into or next to the liquid storage portion for contact with liquid therein and the electric heater being arranged to heat liquid in the second end. When the heater is activated, the liquid at the second end of the capillary wick is vaporized by the heater to form the supersaturated vapour. The supersaturated vapour is mixed with and carried in the air flow. Air from the second air inlet then mixes with the vapour and the vapour condenses to form the aerosol and the aerosol is carried towards the mouth of a user.

In another aspect of the invention, there is provided a cartridge comprising:

an aerosol-forming substrate;

a heater configured to heat the aerosol-forming substrate, the heater positioned within or adjacent to an air flow channel through the cartridge;

the air flow channel terminating at an outlet through which, in use, aerosol is delivered to a user;

and an air inlet in an external surface of the cartridge, the air inlet configured to allow air into the air flow channel at a position between the heater and the outlet, wherein the air inlet and the air flow channel are configured to give rise to turbulent air flow through the air flow channel when suction is applied to the outlet.

The cartridge may include a mouthpiece. The cartridge may be configured to be connected to a main body of an aerosol generating device comprising a power source for providing power to the heater. The cartridge may also include a further air inlet or set of air inlets upstream of the air inlet.

Preferably, the device further includes means for dynamically controlling air flow rate through either the first air inlet or the second air inlet by changing the size of either first or second air inlet. This may comprise means for partially blocking the first or second inlet, such as a mechanical shutter element. The partial blocking may take the form of completely blocking some of a plurality of apertures that comprise either the first or second inlet. It may be desirable to dynamically control the flow rate of air through the first air inlet or second air inlet based on, for example, the composition of the aerosol-forming substrate, the temperature of the heater or a detected flow rate through a portion of the device. It may be feasible to impact the mass air flow rate with a restrictor valve.

The aerosol generating device may be electrically operated and may further comprise an electric power supply. If the aerosol generating device comprises a consumable cartridge and a main body, the electric power supply may be contained in the cartridge or the main body. Preferably, the electric power supply is contained in the main body.

The aerosol generating device may further comprise electric circuitry. In one embodiment, the electric circuitry comprises a sensor to detect air flow indicative of a user taking a puff on the air outlet. In that case, preferably, the electric circuitry is arranged to provide an electric current pulse to the electric heater when the sensor senses a user taking a puff. Preferably, the time-period of the electric current pulse is pre-set, depending on the amount of liquid desired to be vaporized. The electric circuitry is preferably programmable for this purpose. Alternatively, the electric circuitry may comprise a manually operable switch for a user to initiate a puff. The time-period of the electric current pulse is preferably pre-set depending on the amount of liquid desired to be vaporized. The electric circuitry is preferably programmable for this purpose. If the aerosol generating device comprises a consumable cartridge and a main body, the electric circuitry may be contained in the cartridge or the main body. Preferably, the electric circuitry is contained in the main body.

Preferably, the aerosol generating device is portable. The aerosol generating device may be a smoking device. The aerosol generation device may have a size comparable to a

conventional cigar or cigarette. The smoking device may have a total length between approximately 30 mm and approximately 150 mm. The smoking device may have an external diameter between approximately 5 mm and approximately 30 mm.

Preferably, the aerosol generating device is an electrically operated smoking device.

In a further aspect of the invention, there is provided a method of delivering an aerosol from an aerosol-forming substrate comprising the steps of:

vaporizing the aerosol-forming substrate in a first chamber through which air is flowing towards a second chamber,

condensing the vaporized substrate in the second chamber, including the step of supplying ambient air to the second chamber through an ambient air inlet, to generate an aerosol; and

delivering the aerosol from the second chamber through an outlet in the second chamber. The rate of supply of ambient air may be selected to provide a maximum aerosol mass flow rate from the second chamber.

Features described in relation to one aspect of the invention may be applicable to another aspect of the invention. In particular, features described in relation to the aerosol generating device may also be applicable to the cartridge.

The invention will be further described, by way of example only, with reference to the accompanying drawings, of which:

Figure 1 shows an embodiment of an aerosol generating device according to the invention;

Figure 2 is a schematic illustration of the air flow paths in a device of the type shown in Figure 1;

Figure 3 is a schematic illustration of the air flow paths in an alternative design in accordance with the invention; and

Figure 4 is a plot of the mass of aerosol delivered to a user versus A, a parameter relating the size of the first and second inlets.

Figure 1 is a schematic illustration of one example of an aerosol generating device according to the invention. In Figure 1, the device is an electrically operated smoking device having a liquid storage portion. The smoking device 100 of Figure 1 comprises a first end which is the mouthpiece end 103 and a second end which is the body end 105. In the body end 105, there is provided an electric power supply in the form of battery 107 and electric circuitry in the form of hardware 109 and puff detection system 111. In the mouthpiece end 103, there is provided a liquid storage portion in the form of cartridge 113 containing liquid 115, a capillary wick 117 and a heater 119. Note that the heater is only shown schematically in Figure 1. In the exemplary embodiment shown in Figure 1, one end of capillary wick 117 extends into liquid storage portion 113 and the other end of capillary wick 117 is surrounded by the heater 119.

The heater is connected to the electric circuitry via connections 121, which may pass along the outside of liquid storage portion 113 (not shown in Figure 1). The housing is formed in two parts with the portion of the housing including the mouthpiece end and the liquid storage portion 113 being a consumable cartridge and the body end of the housing being a reusable main body portion of the device. The position of the join between the cartridge and the main body of the device is not shown in Figure 1 and may be selected by the designer. The housing 101 includes two air inlets 123 and 124 and an air outlet 125. In use, air flow through the device is provided by a user inhaling at the air outlet to draw air through the first and second inlets. The first air inlet 123 is positioned upstream of the heater, that is with the heater positioned between the first inlet and the air outlet 125. The second air inlet is positioned downstream of the heater i.e. between the heater and the air outlet.

In use, operation is as follows. Liquid 115 is conveyed by capillary action from the cartridge 113 from the end of the wick 117 which extends into the cartridge to the other end of the wick which is surrounded by heater 119. When a user draws on the aerosol generating device at the air outlet 125, ambient air is drawn through air inlet 123. In the arrangement shown in Figure 1, the puff detection system 111 senses the puff and activates the heater 119. The battery 107 supplies electrical energy to the heater 119 to heat the end of the wick 117 surrounded by the heater. The liquid in that end of the wick 117 is vaporized by the heater 119 to create a supersaturated vapour. At the same time, the liquid being vaporized is replaced by further liquid moving along the wick 117 by capillary action. The supersaturated vapour created is mixed with and carried in the air flow from the air inlet 123 towards the outlet 125. In the aerosol forming chamber 127, the vapour condenses to form an inhalable aerosol, which is carried towards the outlet 125 and into the mouth of the user. Ambient air is drawn into the aerosol forming chamber 127 through the second air inlet 124 when a user inhales. This ambient air mixes with the vapour to cool it and accelerate condensation. This cooling air provides aerosol with a desirable droplet size and density as well as ensuring a desirable temperature for the air aerosol entering the user's mouth.

In the embodiment shown in Figure 1, the hardware 109 and puff detection system 111 are preferably programmable. The hardware 109 and puff detection system 111 can be used to manage the aerosol generating device operation.

Figure 1 shows one example of an aerosol generating device according to the present invention. Many other examples are possible, however. The aerosol generating device simply needs to include a heater for vaporizing the aerosol-forming substrate, at least one air outlet, and at least two air inlets, one of which is between the heater and the outlet. For example, the device need not be electrically operated. For example, the device need not be a smoking device. For example, the aerosol-forming substrate need not be a liquid aerosol-forming substrate. Moreover, even if the aerosol-forming substrate is a liquid aerosol-forming substrate,

the device may not include a capillary wick. In that case, the device may include another mechanism for delivering liquid for vaporization. For example, a puff detection system need not be provided. Instead, the device could operate by manual activation, for example the user operating a switch when a puff is taken. For example, the overall shape and size of the aerosol generating device could be altered. For example, the consumable cartridge may comprise only internal elements or only the liquid storage portion 113 and may form no part of the housing 101. Alternatively there may be no consumable cartridge and the device may be refillable or non-refillable.

As discussed above, according to the invention, the aerosol generating device includes at least two air inlets, one of which is positioned between the heater and the outlet in the direction of gas flow through the device. An embodiment of the invention will now be described with reference to Figure 2. The embodiment is based on the example shown in Figure 1, although is applicable to other embodiments of aerosol generating devices. Note that Figures 1, 2 and 3 are schematic in nature. In particular, the components shown are not necessarily to scale either individually or relative to one another.

Figure 2 is an illustration of the air flow paths in a device of the type shown in Figure 1. Figure 2 illustrates a liquid storage portion 113 containing liquid aerosol-forming substrate 115. A wick 117 delivers the liquid to heater 119. Air is drawn into the housing through first apertures forming the first inlet 123 when a user inhales at outlet 125. The first air apertures 123 are configured to provide a laminar flow of air past the heater to transport vaporized substrate away from the vicinity of the heater towards the outlet and are arranged symmetrically around the housing. The first apertures and the air flow channel are shaped to encourage laminar air flow past the heaters. Ambient air is also drawn into the housing through second air apertures forming second air inlet 124 provided downstream of the heater 119. The ambient air is cooler that the mixture of air and vapour that has been heated by the heater and so the ambient air from the second air inlets cool the air and vapour travelling towards the outlet. Second air apertures are configured to provide an air flow that mixes with the air and vapours travelling towards the outlet and to create a turbulent flow in order to maximise the cooling effect. In Figure 2, they are shown as defining second air inlet channels transverse to the laminar flow of air past the heater.

The cooling effect of the air from the second air inlet means that the vaporized substrate condenses more rapidly than it would in the absence of the second air inlets. The design of the first air inlets and second air inlets, in particular both their absolute and relative sizes, affects the properties and amount of aerosol delivered to the user at the outlet 125. The more ambient air that is drawn through the second air inlets, the more of the vaporized aerosol is condensed and an aerosol with better physical attributes can be provided to the user.

Figure 3 shows an alternative design for the air flow through the device. In Figure 3 the substrate 115 is provided within the housing 301 in a hollow cylindrical carrier material that surrounds the air flow channel. The heater 119 is provided within the airflow channel. The first air inlet 323 is positioned upstream of the heater and the second air inlets 324 positioned downstream of the heater closer to the outlet 325. Again the second air inlet provides an incoming flow of air transverse to the flow of air past the heater in order to ensure good mixing. It should be clear that many alternative geometries are possible using the same separation of an initial air flow to transport vapour and a second air flow to provide cooling.

The relative dimensions of the first and second air inlets can be selected to optimise the properties of the aerosol delivered to the user. As shown in Figures 2 and 3 the total mass flow rate through the outlet 125 is Q. The mass flow rate through the first inlet is $Q_1$ and the mass flow rate through the second inlet 124 is $Q_2$. The relationship between the flow rates is:

$$Q = Q_1 + Q_2 = AQ + (1-A)Q$$

The parameter A directly depends on the relative number and sizes of the apertures forming the first and second air inlets and can be altered to optimise the delivered aerosol for a given demanded temperature at the outlet. Figure 4 is a plot of the mass flow rate versus A for three different substrate materials, water, glycerine (G) and propylene glycol (PG) flowing through a device with a diameter of 8.4 mm at a velocity of 0.5m/s with a room temperature of 20 °C and an outlet temperature of 40°C. It can be clearly seen that a value of A can be found to maximise aerosol mass flow rate and that that value depends on the substrate composition. Different geometries will also exhibit different behaviours.

It can also be seen that the maximum aerosol mass flow rate is found when the second air inlets are larger than the first air inlet. In the case of glycerine, the second air inlet needs to be about 10 times larger than the first air inlet. This can be understood by considering that the airflow past the heater and/or substrate from the first inlet need only be sufficient to move the vaporized substrate towards the second air inlet. If the first air inlet and air flow channel is configured to provide for substantially laminar air flow between the first air inlet and the second air inlet, the air flow required to efficiently transport vaporized substrate away from the heater is very small. In contrast, the second air inlet provides cooling air into the device to control the condensation of the vapour and for rapid cooling requires relatively large flow rate through the second air inlet. The second air inlet and air flow channel is preferably configured to provide for turbulent air flow between the second air inlet and the air output in order to efficiently cool the air and condense the vapour.

If the device allows for cartridges containing different substrate compositions to be used, then the cartridges can be designed to include either or both of the first and second air inlets, optimised for the particular composition that they contain.

It is also possible to include a mechanically movable shutter or sleeve to selectively block one or more apertures forming the first or second air inlet, so as to alter the parameter Alpha. This alteration may be achieved manually or automatically under the control of the electric circuitry. Furthermore, the geometry of the airflow channel and of the first and second air inlets may take many forms. The optimal geometry for a particular device and application may be determined empirically or theoretically.

**CLAIMS**

1. An aerosol generating device comprising:

a housing having a first air inlet and an air outlet, the housing defining an air flow channel between the first air inlet and the air outlet; and

a heater configured to heat an aerosol-forming substrate positioned within or adjacent to the air flow channel;

wherein the housing further comprises a second air inlet, the second air inlet positioned between the heater and the air outlet, the second air inlet configured to allow air into the air flow channel and wherein the second air inlet is larger than the first air inlet.

2. An aerosol generating device according to claim 1, wherein the second air inlet is at least five times larger than the first inlet.

3. An aerosol generating element according to claim 1 or 2 wherein the second air inlet and the air channel are configured to give rise to turbulent air flow through the air flow channel between the second air inlet and the air outlet when suction is applied to the air outlet.

4. An aerosol generating device according to any preceding claim, wherein the second air inlet comprises a plurality of second apertures in the housing.

5. An aerosol generating device according to any preceding claim, wherein the first air inlet comprises a plurality of first apertures in the housing.

6. An aerosol generating device according to any preceding claim, wherein the housing comprises a mouthpiece portion surrounding the air outlet, such that suction on the mouthpiece draws air into the air flow channel through the first and second air inlets.

7. An aerosol generating device according to any preceding claim, wherein the device comprises a cartridge, the cartridge comprising the aerosol forming substrate and wherein a portion of the housing is formed by the cartridge and includes the second air inlet or the first air inlet, or both the first and second air inlets.

8. An aerosol generating element according to any preceding claim wherein the first air inlet and the air channel are configured to give rise to laminar air flow through the air flow channel when suction is applied to the air outlet.

9. An aerosol generating device according to any preceding claim wherein the aerosol-forming substrate is a liquid substrate.

10. An aerosol generating device according to any preceding claim further including means for altering the size of either the first air inlet or the second air inlet.

11. An aerosol generating device according to claim 10 wherein the device is configured to automatically alter the size of the first air inlet or second air inlet based on the composition of the aerosol-forming substrate, the temperature of the heater or a detected flow rate through a portion of the device.

12. An aerosol generating device according to any preceding claim wherein the device is an electrically operated smoking device.

13. A cartridge comprising:

an aerosol-forming substrate;

a heater configured to heat the aerosol-forming substrate, the heater positioned within or adjacent to an air flow channel through the cartridge;

the air flow channel terminating at an outlet through which, in use, aerosol is delivered to a user; and

an air inlet in an external surface of the cartridge, the air inlet configured to allow air into the air flow channel at a position between the heater and the outlet, wherein the air inlet and the air flow channel are configured to give rise to turbulent air flow through the air flow channel when suction is applied to the outlet.

14. A consumable cartridge according to claim 13, wherein the cartridge is configured to be connected to a main body of an aerosol generating device comprising a power source for providing power to the heater.

15. A method of delivering an aerosol from an aerosol-forming substrate comprising the steps of:

vaporizing the aerosol-forming substrate in a first chamber through which air is flowing towards a second chamber,

condensing the vaporized substrate in the second chamber, including the step of supplying ambient air to the second chamber through an ambient air inlet, to generate an aerosol, at a rate selected to provide a maximum aerosol mass flow rate from the second chamber, and

delivering the aerosol from the second chamber through an outlet in the second chamber.

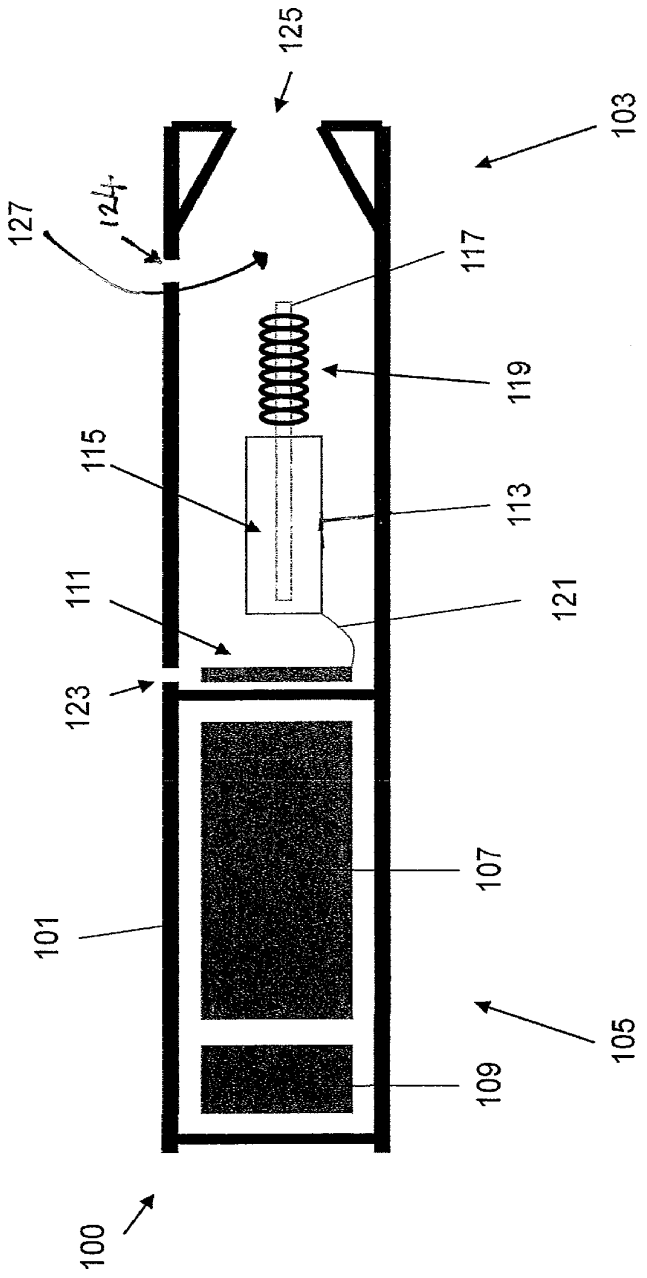



Figure 1

FIG 2

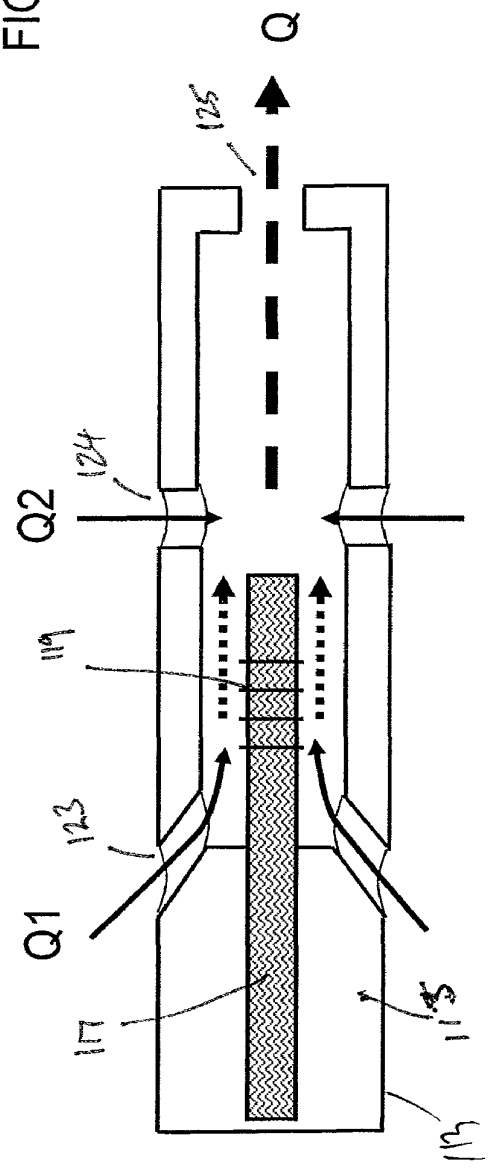


FIG 3

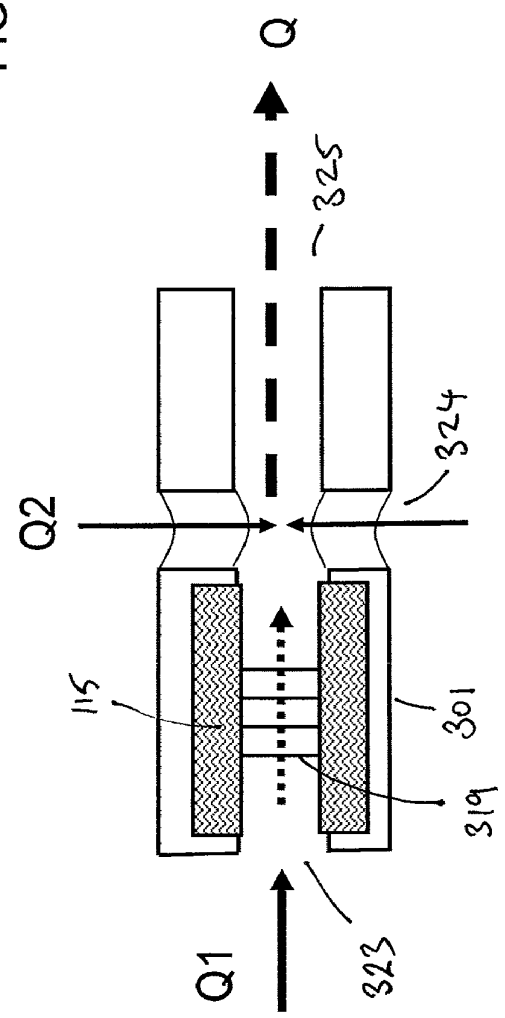
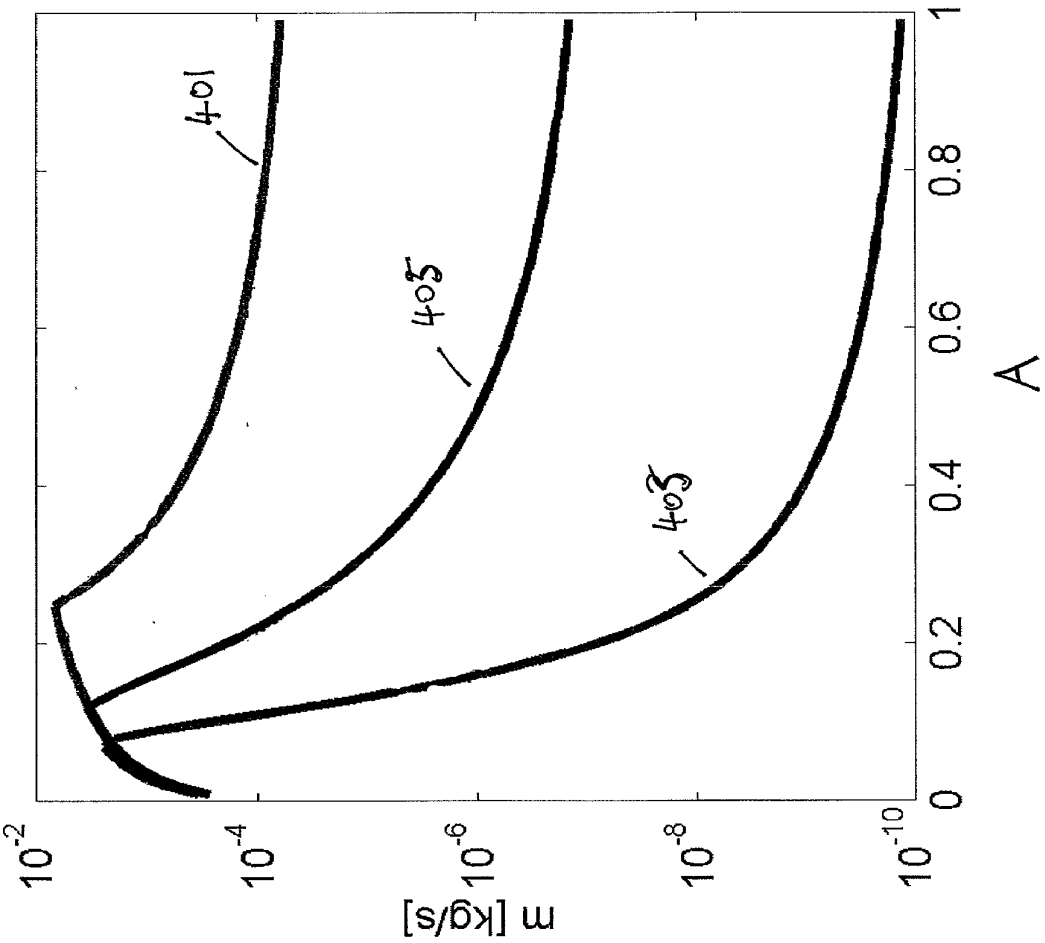


FIG 4



# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/074514

A. CLASSIFICATION OF SUBJECT MATTER
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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)
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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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X | WO 2007/098337 A2 (BRENNEISE JAKE [US]) 30 August 2007 (2007-08-30) page 5, line 6 - page 12, line 20; claims; figures | 13-15 |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Marzano Monterosso |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No
PCT/EP2012/074514

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(54) Title: AEROSOL GENERATING SYSTEM WITH CONSUMPTION MONITORING AND FEEDBACK

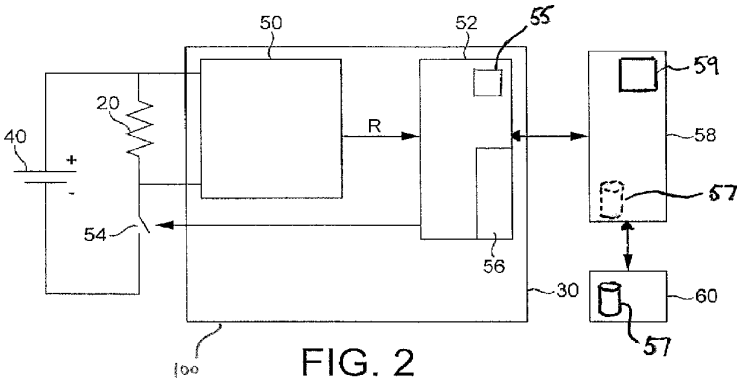



FIG. 2

(57) Abstract: There is provided an aerosol-generating system configured for oral or nasal delivery of a generated aerosol to a user, the system comprising: a heater element configured to heat an aerosol-forming substrate to generate an aerosol; a power source connected to the heater element; a controller connected to the heater element and to the power source, wherein the controller is configured to control operation of the heater element, the controller including or being connected to a means to detect a change in air flow past the heater element; first data storage means connected to the controller for recording detected changes in airflow past the heater element and data relating to the operation of the heater element; second data storage means comprising a database relating changes in airflow and data relating to the operation of the heater element to the properties of the aerosol delivered to the user; and an indication means, such as a display, coupled to the second data storage means for indicating to the user a property of the aerosol delivered to the user. The property or properties of the aerosol delivered to the user may comprise amounts of particular chemical compounds.

WO 2013/098398 A2

# AEROSOL-GENERATING SYSTEM WITH CONSUMPTION MONITORING AND FEEDBACK

This specification relates to aerosol-generating systems and in particular to systems including aerosol-generating devices for user inhalation, such as smoking devices. The specification relates to a device and method for monitoring the use of the device and providing to the user an indication of their aerosol consumption or their consumption of a particular constituent or constituents of the aerosol.

Conventional lit end cigarettes deliver smoke as a result of combustion of the tobacco and a wrapper which occurs at temperatures which may exceed 800 degrees Celsius during a puff. At these temperatures, the tobacco is thermally degraded by pyrolysis and combustion. The heat of combustion releases and generates various gaseous combustion products and distillates from the tobacco. The products are drawn through the cigarette and cool and condense to form a smoke containing the tastes and aromas associated with smoking. At combustion temperatures, not only tastes and aromas are generated but also a number of undesirable compounds.

Electrically heated smoking devices are known, which are essentially aerosol-generating devices, which operate at lower temperatures than conventional lit end cigarettes. An example of such an electrical smoking device is disclosed in WO2009/118085. WO2009/118085 discloses an electrical smoking device in which an aerosol-forming substrate is heated by a heater element to generate an aerosol. The temperature of the heater element is controlled to be within a particular range of temperatures in order to ensure that undesirable volatile compounds are not generated and released from the substrate while other, desired volatile compounds are released.

It is desirable to provide an aerosol-generating system which can provide the user with information about his or her consumption of aerosol or particular compounds in the aerosol, such as nicotine. This allows the use to better understand and regulate their consumption. It is also desirable to be able to collect system usage and aerosol consumption data for clinical studies and population level statistics.

In an aspect of the disclosure of this specification, there is provided an aerosol-generating system configured for oral or nasal delivery of a generated aerosol to a user, the system comprising:

a heater element configured to heat an aerosol-forming substrate to generate an aerosol;

a power source connected to the heater element;

a controller connected to the heater element and to the power source, wherein the controller is configured to control operation of the heater element, the controller including or being connected to a means to detect a change in air flow past the heater element;

first data storage means connected to the controller for recording detected changes in airflow past the heater element and data relating to the operation of the heater element; and

second data storage means comprising a database relating changes in airflow and data relating to the operation of the heater element to the properties of the aerosol delivered to the user; and

an indication means, such as a display, coupled to the second data storage means for indicating to the user a property of the aerosol delivered to the user.

The indication means may be a display that is able to display detailed information about the properties of the aerosol delivered to the user, such as amounts of particular compounds delivered to the user within a particular time period. However, the indication means may be more basic and may be an audible or visual alarm that is activated when consumption of a particular compound with a given time period exceeds a threshold level. The threshold level may be set by the user. As will be described, the indication means may be provided on an aerosol-generating device containing the heater element or may be provided on a secondary device to which data from an aerosol-generating device is sent.

As used herein aerosol "delivered" to a user means aerosol that is inhaled by the user during use. Inhaled as used herein, means drawn into the body through the mouth or nose and includes the situation where an aerosol is drawn into the user's lungs, and also the situation where an aerosol is only drawn into the user's mouth or nasal cavity before being expelled from the user's body.

The first data storage means may be configured to record detected changes in airflow or user puffs or inhalations. The first data storage means may record a count of user puffs or the time of each puff. The first data storage means may also be configured to record the temperature of the heater element and the power supplied during each puff. The first data storage means may record any available data from the controller, as desired.

The database may comprise data specific to a particular type of aerosol-forming substrate. The system may then comprise identifying means for identifying the aerosol-forming substrate received in the device. Identifying means may include an optical scanner for

reading indicia on the aerosol-forming substrate or electronic circuitry configured to detect an electrical characteristic of the aerosol-forming substrate, such as a characteristic resistance. Alternatively, or in addition, the system may include a user interface configured to allow a consumer to input data identifying the aerosol-forming substrate received in the device.

The data relating to the operation of the aerosol-generating element may comprise the temperature of heater element or power supplied to the heater element. This information, together with airflow data, and optionally the identity of the substrate can be compared to stored data in the second data storage means to extract data describing properties of the aerosol delivered to the user. The properties of aerosol delivered to the user may comprise amounts of particular chemical compounds.

The database may include amounts of specific compounds delivered by the system under particular conditions, for particular substrates. The database may include formulas relating particular parameters of the operation of the aerosol-generating device, such as temperature and airflow, to amounts of specific compounds delivered by the system. The amounts and the formulas may be derived or extrapolated from experimental data.

The system may be an electrical smoking system. In the case of an electrical smoking system, the second data storage means may store information derived from smoking sessions using a standardized smoking machine under various smoking regimes and under controlled environment for smoking and controlled humidity for particular aerosol-forming substrates. This experimentally derived data can be used to extrapolate likely inhaled volume of mainstream smoke from the changes in airflow and operation of the heater. The smoking regimes using a standardized smoking machine may be, for example, the standard ISO regime or the Canadian intense regime.

In the case of a smoking system, the data stored in the second data storage means may include, but is not limited to amounts of the following compounds contained within the aerosol delivered: Acetaldehyde, Acetamide, Acetone, Acrolein, Acrylamide, Acrylonitrile, 4-Aminobiphenyl, 1-Aminonaphthalene, 2-Aminonaphthalene, Ammonia, Anabasine, o-Anisidine, Arsenic, A-α-C (2-Amino-9H-pyrido[2,3-b]indole), Benz[a]anthracene, Benz[j]aceanthrylene, Benzene, Benzo[b]fluoranthene, Benzo[k]fluoranthene, Benzo[b]furan, Benzo[a]pyrene, Benzo[c]phenanthrene, Beryllium, 1,3-Butadiene, Cadmium, Caffeic acid, Carbon monoxide, Catechol, Chlorinated dioxins/furans, Chromium, Chrysene, Cobalt, Cresols (o-, m-, and p-cresol), Crotonaldehyde,

Cyclopenta[c,d]pyrene, Dibenz[a,h]anthracene, Dibenzo[a,e]pyrene, Dibenzo[a,h]pyrene, Dibenzo[a,i]pyrene, Dibenzo[a,l]pyrene, 2,6-Dimethylaniline, Ethyl carbamate (urethane), Ethylbenzene, Ethylene oxide, Formaldehyde, Furan, Glu-P-1 (2-Amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole), Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole), Hydrazine, Hydrogen cyanide, Indeno[1,2,3-cd]pyrene, IQ (2-Amino-3-methylimidazo[4,5-f]quinoline), Isoprene, Lead, MeA-α-C (2-Amino-3-methyl)-9H-pyrido[2,3-b]indole), Mercury, Methyl ethyl ketone, 5-Methylchrysene, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), Naphthalene, Nickel, Nicotine, Nitrobenzene, Nitromethane, 2-Nitropropane, N-Nitrosodiethanolamine (NDELA), N-Nitrosodiethylamine, N-Nitrosodimethylamine (NDMA), N-Nitrosomethylethylamine, N-Nitrosomorpholine (NMOR), N-Nitrosonornicotine (NNN), N-Nitrosopiperidine (NPIP), N-Nitrosopyrrolidine (NPYR), N-Nitrososarcosine (NSAR), Nornicotine, Phenol, PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine), Polonium-210, Propionaldehyde, Propylene oxide, Quinoline, Selenium, Styrene, o-Toluidine, Toluene, Trp-P-1 (3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole), Trp-P-2 (1-Methyl-3-amino-5H-pyrido[4,3-b]indole), Uranium-235, Uranium-238, Vinyl acetate, or Vinyl chloride.

The system may comprise a single aerosol-generating device containing all of the components of the system. Alternatively, the system may comprise an aerosol-generating device and one or more secondary devices to which the aerosol-generating device may directly or indirectly couple or connect, with the one or more secondary devices comprising some of the components of the system. So, in the case of the system comprising a single device, the second data storage means or the display, or both the second data storage means and the display are contained within a single housing together with the heater element and the power source. The first data storage means and the second data storage means may be parts of a single physical memory. In alternative embodiments, the second data storage means or the display, or both the second data storage means and the display may be part of the one or more secondary devices. For example, a laptop computer may be part of the system and connectable to the aerosol-generating device. The laptop computer may contain the second data storage means and the display and may perform a comparison of the data from the first data storage means with data in the second data storage means.

As used herein, aerosol-generating device means a device that interacts with an aerosol-forming substrate to generate an aerosol. An aerosol-generating device may comprise a power supply which may be an external power supply or an on-board power supply forming part of the aerosol-generating device.

The one or more secondary devices may be a charging device configured to replenish the power source in the aerosol-generating device. Alternatively, or in addition, the one or more secondary devices may comprise a laptop, desktop computer, mobile phone or other consumer electronic device. In one embodiment the second data storage means may comprise a remote server to which the aerosol-generating device or another secondary device can connect over a communications network. The user may be required to send the detected changes in airflow past the heater element and the data relating to the operation of the heater element (herein referred to as usage data) to the remote server in order to receive from the server the properties of the aerosol delivered to the user. This allows for central storage of usage data which can be used for population level statistics, may be used to improve system design and may be used in clinical studies.

Data may be transferred between different devices within the system by any suitable means. For example, a wired connection may used, such as a USB connection. Alternatively a wireless connection may be used. Data may also be transferred over a communications network, such as the Internet. In one embodiment, an aerosol-generating device may be configured to transfer data from the first data storage means to the second data storage means in a battery charging device every time the aerosol-generating device is recharged, through suitable data connections.

Any suitable type of memory may be used for the first and second data storage means, such as RAM or flash memory.

The identity or one of more characteristics of the aerosol-forming substrate may be provided before or after the recording of usage data. As described, the identity or one of more characteristics of the aerosol-forming substrate may be provided by a data input from the user of the system or may be provided as a result of an automated substrate detection process.

The system may be configured to provide an alert when a user is estimated to have been delivered a threshold amount of one or more compounds by the system within a predetermined time period. A plurality of thresholds may be set for different compounds and different time periods. The alert may be provided on an aerosol-generating device containing the heater element, or on one or more secondary devices. The alert may be a simple visual or audible signal or may be the presentation of more detailed information on a

display screen. The alert may be provided to warn the user that their consumption of a particular compound has reached a desired limit or predetermined dose.

A user password or user name may be entered into a user interface in the system to ensure that recorded data is matched to previously recorded data from the same user. Alternatively, if the system includes one or more secondary devices in which the second data storage means is located, an assumption may be made that each aerosol-generating device is used by a unique user and a device identifier may be contained in usage data or in other data transferred from the aerosol-generating device.

In a second aspect of the disclosure of the specification, there is provided a method of providing aerosol delivery data to an end user of an electrically heated aerosol-generating device, the device comprising a heater element and a power supply for supplying power to the heater element, and means to detect a change in air flow past the heater element comprising:

recording detected changes in airflow past the heater element and data relating to the operation of the heater element; and

extracting from a database, based on the detected changes in airflow and data relating to the operation of the heater element, properties of the aerosol delivered to the user; and

indicating, for example displaying, the extracted properties of the aerosol delivered to the user.

The method may further comprise the step of detecting or providing at least one characteristic of the aerosol-forming substrate received in the device, wherein the step of extracting is also based on the at least one characteristic of the aerosol-forming substrate received in the device.

The extracted properties of the aerosol delivered to the user may comprise amounts of particular chemical compounds. The aerosol-generating device may be a smoking device.

In a third aspect of the disclosure of the specification, there is provided a computer program that when executed on a computer or other suitable processing device, carries out the method of second aspect or at least the steps of extracting and indicating.

In a fourth aspect of the disclosure of the specification, there is provided a computer readable storage medium carrying computer executable instructions that when executed on

a computer or other suitable processing device, carry out the method of second aspect or at least the steps of extracting and indicating.

The computer executable instructions may be provided as an app or computer program for a personal computer or portable computing device such as a mobile phone or other processing device to which the aerosol-generating device could be connected. The app or computer program may downloadable by a user over a communications network, such as the Internet. The computer executable instructions may include the database or may include means to access the database stored on a remote device.

In a fifth aspect of the disclosure there is provided an aerosol-generating device configured for oral or nasal delivery of a generated aerosol to a user, the device comprising:

a heater element configured to heat an aerosol-forming substrate to generate an aerosol;

a power source connected to the heater element;

a controller connected to the heater element and to the power source, wherein the controller is configured to control operation of the heater element, the controller including or being connected to a means to detect a change in air flow past the heater element;

first data storage means connected to the controller for recording detected changes in airflow past the heater element and data relating to the operation of the heater element; and

a data output means configured to allow data from the first data storage means to be output to an external device.

In a sixth aspect of the disclosure, there is provided a kit comprising: an electrically heated aerosol-generating device, the device comprising a heater element and a power supply for supplying power to the heater element, and means to detect a change in air flow past the heater element; and a computer readable storage medium carrying computer executable instructions or a code allowing for the download of computer executable instructions from a remote device, the computer executable instructions, when executed on a computer or other suitable processing device, carrying out the method of second aspect, or at least the steps of extracting and indicating.

In all aspects of the disclosure, the means to detect a change in airflow past the heater may be a dedicated flow sensor, such as a microphone or a thermocouple, connected to the controller. Alternatively, the controller may be configured to control power supplied to the heater element from the power source to maintain the heater element at a target

temperature and may be configured to monitor changes in a temperature of the heater element or changes in the power supplied to the heater element to detect a change in air flow past the heater element.

The controller may judge, based on predetermined thresholds or based on a control loop, such as a Schmitt trigger, whether the detected changes in airflow are the result of a user puff. For example, in one embodiment the controller may be configured to monitor if a difference between the temperature of the heater element and the target temperature exceeds a threshold in order to detect a change in air flow past the heater element indicative of a user inhalation. The controller may be configured to monitor whether a difference between the temperature of the heater element and the target temperature exceeds a threshold for a predetermined time period or for a predetermined number of measurement cycles to detect a change in air flow past the heater element indicative of a user inhalation. This ensures that very short term fluctuations in temperature do not lead to false detection of a user inhalation.

In another embodiment the controller may be configured to monitor a difference between the power supplied to the heater element and an expected power level to detect a change in air flow past the heater element indicative of a user inhalation. Alternatively, or in addition, the controller may be configured to compare a rate of change of temperature or a rate of change of power supplied with a threshold level to detect a change in air flow past the heater element indicative of a user inhalation.

The controller may be configured to adjust the target temperature when a change in airflow past the heater is detected. Increased airflow brings more oxygen into contact with the substrate. This increases the likelihood of combustion of the substrate at a given temperature. Combustion of the substrate is undesirable. So the target temperature may be lowered when an increase in airflow is detected in order to reduce the likelihood of combustion of the substrate. Alternatively, or in addition, the controller may be configured to adjust the power supplied to the heater element when a change in airflow past the heater element is detected. Airflow past the heater element typically has a cooling effect on the heater element. The power to the heater element may be temporarily increased to compensate for this cooling.

In one embodiment, the controller may be configured to monitor the temperature of the heater element based on a measure of the electrical resistance of the heater element. This

allows the temperature of the heater element to be detected without the need for additional sensing hardware.

The temperature of the heater element may be monitored at predetermined time intervals, such as every few milliseconds. This may be done continuously or only during periods when power is being supplied to the heater element.

The controller may be configured to reset, ready to detect the next user puff when the difference between the detected temperature and the target temperature is less than a threshold amount. The controller may be configured to require that the difference between the detected temperature and the target temperature is less than a threshold amount for a predetermined time or number of measurement cycles.

In some embodiments, the controller may be configured to compare a measure of power supplied to the heater element or energy supplied to the heater element from the power source to a threshold measure of power or energy to detect the presence of an aerosol-forming substrate close to the heater element or a material property of an aerosol-forming substrate close to the heater element.

The measure of power or energy can be any measure of power or energy, including average power over a predetermined time period or over a predetermined number of measurement cycles, a rate of change of power or energy or a cumulative measure of the power or energy supplied over a predetermined time period or over a predetermined number of measurement cycles.

In one embodiment, the measure of energy is normalised energy over a predetermined time period. In another embodiment, the measure of energy is a rate of decrease of normalised energy over a predetermined time period.

The amount of power or energy required to reach and maintain the heater element at a target temperature depends on the rate of heat loss from the heater element. This is strongly dependent on the environment surrounding the heater element. If a substrate is close to or contacts the heater element it will affect the rate of heat loss from the heater element compared to the situation in which there is no substrate close to the heater element. In one embodiment, the device is configured to receive an aerosol- forming substrate into contact with the heater element. The heater element then loses heat to the

substrate by conduction. The device may be configured so that the substrate surrounds the heater element in use.

The controller may be configured to reduce to zero the supply of power to the heater element from the power source if the measure of power or energy is less than the threshold measure of power or energy. If the amount of energy needed to maintain the heater element temperature at a target temperature is less than expected, it may be because an aerosol-forming substrate is not present in the device or it may be that an unsuitable substrate, such as a previously used substrate, is in the device. A previously used substrate will typically have lower water content and lower aerosol former content than a new substrate and therefore draws less energy from the heater element. In either case it is usually desirable to stop the supply of power to the heater.

In all aspects of the disclosure, the power source may be any suitable power supply, such as a gas, chemical or electrical power supply. The power supply may be battery. In one embodiment, the power supply is a Lithium-ion battery. Alternatively, the power supply may be a Nickel-metal hydride battery, a Nickel cadmium battery, or a Lithium based battery, for example a Lithium-Cobalt, a Lithium-Iron-Phosphate or a Lithium-Polymer battery. Power may be supplied to the heater element as a pulsed signal. The amount of power delivered to the heater element may be adjusted by altering the duty cycle or the pulse width of the power signal.

The heater element may comprise a single heater element. Alternatively, the heater element may comprise more than one heater element. The heater element or heater elements may be arranged appropriately so as to most effectively heat the aerosol-forming substrate.

The heater element may comprise an electrically resistive material. Suitable electrically resistive materials include but are not limited to: semiconductors such as doped ceramics, electrically "conductive" ceramics (such as, for example, molybdenum disilicide), carbon, graphite, metals, metal alloys and composite materials made of a ceramic material and a metallic material. Such composite materials may comprise doped or undoped ceramics. Examples of suitable doped ceramics include doped silicon carbides. Examples of suitable metals include titanium, zirconium, tantalum, gold, silver and metals from the platinum group. Examples of suitable metal alloys include stainless steel, nickel-, cobalt-, chromium-, aluminium- titanium- zirconium-, hafnium-, niobium-, molybdenum-, tantalum-, tungsten-, tin-, gallium-, manganese-, gold- and iron-containing alloys, and super-alloys

based on nickel, iron, cobalt, stainless steel, Timetal® and iron-manganese-aluminium based alloys. In composite materials, the electrically resistive material may optionally be embedded in, encapsulated or coated with an insulating material or vice-versa, depending on the kinetics of energy transfer and the external physicochemical properties required. Ceramic and/or insulating materials may include, for example, aluminium oxide or zirconia oxide ($ZrO_2$). Alternatively, the electric heater may comprise an infra-red heater element, a photonic source, or an inductive heater element.

The heater element may take any suitable form. For example, the heater element may take the form of a heating blade. Alternatively, the heater element may take the form of a casing or substrate having different electro-conductive portions, or an electrically resistive metallic tube. Alternatively, one or more heating needles or rods that run through the centre of the aerosol-forming substrate may be as already described. Alternatively, the heater element may be a disk (end) heater or a combination of a disk heater with heating needles or rods. Other alternatives include a heating wire or filament, for example a Ni-Cr (Nickel-Chromium), platinum, tungsten or alloy wire or a heating plate. Optionally, the heater element may be deposited in or on a rigid carrier material. In one such embodiment, the heater element may be formed using a metal having a defined relationship between temperature and resistivity. In such an exemplary device, the metal may be formed as a track on a suitable insulating material, such as ceramic material, and then sandwiched in another insulating material, such as a glass. Heater elements formed in this manner may be used to both heat and monitor the temperature of the heaters during operation.

The heater element may heat the aerosol-forming substrate by means of conduction. The heater element may be at least partially in contact with the substrate, or the carrier on which the substrate is deposited. Alternatively, the heat from the heater element may be conducted to the substrate by means of a heat conductive element.

Alternatively, the heater element may transfer heat to the incoming ambient air that is drawn through the system during use, which in turn heats the aerosol-forming substrate by convection. The ambient air may be heated before passing through the aerosol-forming substrate.

In one embodiment, power is supplied to the heater element until the heater element reaches a temperature of between approximately 250 °C and 440 °C in order to produce an aerosol from the aerosol-forming substrate. Any suitable temperature sensor and control circuitry may be used in order to control heating of the heater element to reach the

temperature of between approximately 250 °C and 440 °C, including the use of one or more additional heater elements. This is in contrast to conventional cigarettes in which the combustion of tobacco and cigarette wrapper may reach 800 °C.

The aerosol-forming substrate may be contained in a smoking article. During operation, the smoking article containing the aerosol-forming substrate may be completely contained within the aerosol-generating system. In that case, a user may puff on a mouthpiece of the aerosol-generating system. Alternatively, during operation the smoking article containing the aerosol-forming substrate may be partially contained within the aerosol-generating system. In that case, the user may puff directly on the smoking article.

The smoking article may be substantially cylindrical in shape. The smoking article may be substantially elongate. The smoking article may have a length and a circumference substantially perpendicular to the length. The aerosol-forming substrate may be substantially cylindrical in shape. The aerosol-forming substrate may be substantially elongate. The aerosol-forming substrate may also have a length and a circumference substantially perpendicular to the length. The aerosol-forming substrate may be received in the sliding receptacle of the aerosol-generating device such that the length of the aerosol-forming substrate is substantially parallel to the airflow direction in the aerosol-generating device.

The smoking article may have a total length between approximately 30 mm and approximately 100 mm. The smoking article may have an external diameter between approximately 5 mm and approximately 12 mm. The smoking article may comprise a filter plug. The filter plug may be located at the downstream end of the smoking article. The filter plug may be a cellulose acetate filter plug. The filter plug is approximately 7 mm in length in one embodiment, but may have a length of between approximately 5 mm to approximately 10 mm.

In one embodiment, the smoking article has a total length of approximately 45 mm. The smoking article may have an external diameter of approximately 7.2 mm. Further, the aerosol-forming substrate may have a length of approximately 10 mm. Alternatively, the aerosol-forming substrate may have a length of approximately 12 mm. Further, the diameter of the aerosol-forming substrate may be between approximately 5 mm and approximately 12 mm. The smoking article may comprise an outer paper wrapper. Further, the smoking article may comprise a separation between the aerosol-forming substrate and the filter plug. The separation may be approximately 18 mm, but may be in the range of

approximately 5 mm to approximately 25 mm.

As used herein, the term "aerosol-forming substrate" means a substrate capable of releasing volatile compounds that can form an aerosol. The volatile compounds may be released by heating or combusting the aerosol-forming substrate. The aerosol-forming substrate may comprise nicotine.

The aerosol-forming substrate may be a solid aerosol-forming substrate. Alternatively, the aerosol-forming substrate may comprise both solid and liquid components. The aerosol-forming substrate may comprise a tobacco-containing material containing volatile tobacco flavour compounds which are released from the substrate upon heating. Alternatively, the aerosol-forming substrate may comprise a non-tobacco material. The aerosol-forming substrate may further comprise an aerosol former that facilitates the formation of a dense and stable aerosol. Examples of suitable aerosol formers are glycerine and propylene glycol.

If the aerosol-forming substrate is a solid aerosol-forming substrate, the solid aerosol-forming substrate may comprise, for example, one or more of: powder, granules, pellets, shreds, spaghettis, strips or sheets containing one or more of: herb leaf, tobacco leaf, fragments of tobacco ribs, reconstituted tobacco, homogenised tobacco, extruded tobacco and expanded tobacco. The solid aerosol-forming substrate may be in loose form, or may be provided in a suitable container or cartridge. Optionally, the solid aerosol-forming substrate may contain additional tobacco or non-tobacco volatile flavour compounds, to be released upon heating of the substrate. The solid aerosol-forming substrate may also contain capsules that, for example, include the additional tobacco or non-tobacco volatile flavour compounds and such capsules may melt during heating of the solid aerosol-forming substrate.

As used herein, homogenised tobacco comprises material formed by agglomerating particulate tobacco and may be in the form of a sheet. Homogenised tobacco material may have an aerosol-former content of greater than 5% on a dry weight basis. Homogenised tobacco material may alternatively have an aerosol former content of between 5% and 30% by weight on a dry weight basis. Sheets of homogenised tobacco material may be formed by agglomerating particulate tobacco obtained by grinding or otherwise comminuting one or both of tobacco leaf lamina and tobacco leaf stems; alternatively, or in addition, sheets of homogenised tobacco material may comprise one or more of tobacco dust, tobacco fines and other particulate tobacco by-products formed during, for example, the treating,

handling and shipping of tobacco. Sheets of homogenised tobacco material may comprise one or more intrinsic binders, that is tobacco endogenous binders, one or more extrinsic binders, that is tobacco exogenous binders, or a combination thereof to help agglomerate the particulate tobacco; alternatively, or in addition, sheets of homogenised tobacco material may comprise other additives including, but not limited to, tobacco and non-tobacco fibres, aerosol-formers, humectants, plasticisers, flavourants, fillers, aqueous and non-aqueous solvents and combinations thereof.

In a particularly preferred embodiment, the aerosol-forming substrate comprises a gathered crimpled sheet of homogenised tobacco material. As used herein, the term 'crimped sheet' denotes a sheet having a plurality of substantially parallel ridges or corrugations. Preferably, when the aerosol-generating article has been assembled, the substantially parallel ridges or corrugations extend along or parallel to the longitudinal axis of the aerosol-generating article. This advantageously facilitates gathering of the crimped sheet of homogenised tobacco material to form the aerosol-forming substrate. However, it will be appreciated that crimped sheets of homogenised tobacco material for inclusion in the aerosol-generating article may alternatively or in addition have a plurality of substantially parallel ridges or corrugations that are disposed at an acute or obtuse angle to the longitudinal axis of the aerosol-generating article when the aerosol-generating article has been assembled. In certain embodiments, the aerosol-forming substrate may comprise a gathered sheet of homogenised tobacco material that is substantially evenly textured over substantially its entire surface. For example, the aerosol-forming substrate may comprise a gathered crimped sheet of homogenised tobacco material comprising a plurality of substantially parallel ridges or corrugations that are substantially evenly spaced-apart across the width of the sheet.

Optionally, the solid aerosol-forming substrate may be provided on or embedded in a thermally stable carrier. The carrier may take the form of powder, granules, pellets, shreds, spaghettis, strips or sheets. Alternatively, the carrier may be a tubular carrier having a thin layer of the solid substrate deposited on its inner surface, or on its outer surface, or on both its inner and outer surfaces. Such a tubular carrier may be formed of, for example, a paper, or paper like material, a non-woven carbon fibre mat, a low mass open mesh metallic screen, or a perforated metallic foil or any other thermally stable polymer matrix.

The solid aerosol-forming substrate may be deposited on the surface of the carrier in the form of, for example, a sheet, foam, gel or slurry. The solid aerosol-forming substrate may be deposited on the entire surface of the carrier, or alternatively, may be deposited in a

pattern in order to provide a non-uniform flavour delivery during use.

Although reference is made to solid aerosol-forming substrates above, it will be clear to one of ordinary skill in the art that other forms of aerosol-forming substrate may be used with other embodiments. For example, the aerosol-forming substrate may be a liquid aerosol-forming substrate. If a liquid aerosol-forming substrate is provided, the aerosol-generating device preferably comprises means for retaining the liquid. For example, the liquid aerosol-forming substrate may be retained in a container. Alternatively or in addition, the liquid aerosol-forming substrate may be absorbed into a porous carrier material. The porous carrier material may be made from any suitable absorbent plug or body, for example, a foamed metal or plastics material, polypropylene, terylene, nylon fibres or ceramic. The liquid aerosol-forming substrate may be retained in the porous carrier material prior to use of the aerosol-generating system or alternatively, the liquid aerosol-forming substrate material may be released into the porous carrier material during, or immediately prior to use. For example, the liquid aerosol-forming substrate may be provided in a capsule. The shell of the capsule preferably melts upon heating and releases the liquid aerosol-forming substrate into the porous carrier material. The capsule may optionally contain a solid in combination with the liquid.

Alternatively, the carrier may be a non-woven fabric or fibre bundle into which tobacco components have been incorporated. The non-woven fabric or fibre bundle may comprise, for example, carbon fibres, natural cellulose fibres, or cellulose derivative fibres.

The aerosol-generating system may comprise an air inlet. The aerosol-generating system may comprise an air outlet. The aerosol-generating system may comprise a condensation chamber for allowing the aerosol having the desired characteristics to form.

Embodiments will now be described in detail, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is a schematic drawing showing the basic elements of an aerosol-generating device in accordance with one embodiment;
Figure 2 is a schematic diagram illustrating the control elements of one embodiment;
Figure 3 is a graph illustrating changes in heater temperature and supplied power during user puffs in accordance with another embodiment;
Figure 4 illustrates a control sequence for determining if a user puff is taking place in accordance with an yet another embodiment;

Figure 5 is a graph illustrating the different the normalised energy required to be supplied to a heater element to maintain the temperature at a target level for new, old and no substrate next to the heater element; and

Figure 6 illustrates a control sequence for determining if an appropriate substrate is in the device.

In Figure 1, the inside of an embodiment of an aerosol-generating device 100 is shown in a simplified manner. Particularly, the elements of the aerosol-generating device 100 are not drawn to scale. Elements that are not relevant for the understanding of the embodiment discussed herein have been omitted to simplify Figure 1.

The aerosol-generating device 100 comprises a housing 10 and an aerosol-forming substrate 2, for example a cigarette. The aerosol-forming substrate 2 is pushed inside the housing 10 to come into thermal proximity with the heater element 20. The aerosol-forming substrate 2 will release a range of volatile compounds at different temperatures. Some of the volatile compounds released from the aerosol-forming substrate 2 are only formed through the heating process. Each volatile compound will be released above a characteristic release temperature. By controlling the maximum operation temperature of the aerosol-generating device 100 to be below the release temperature of some of the volatile compounds, the release or formation of these smoke constituents can be avoided.

Additionally, the aerosol-generating device 100 includes an electrical energy supply 40, for example a rechargeable lithium ion battery, provided within the housing 10. The aerosol-generating device 100 further includes a controller 30 that is connected to the heater element 20, the electrical energy supply 40, an aerosol-forming substrate detector 32 and a user interface 36, for example a graphical display or a combination of LED indicator lights that convey information regarding device 100 to a user.

The aerosol-forming substrate detector 32 may detect the presence and identity of an aerosol-forming substrate 2 in thermal proximity with the heater element 20 and signals the presence of an aerosol-forming substrate 2 to the controller 30. The provision of a substrate detector is optional.

The controller 30 controls the user interface 36 to display system information, for example, battery power, temperature, status of aerosol-forming substrate 2, other messages or combinations thereof.

The controller 30 further controls the maximum operation temperature of the heater element 20. The temperature of the heater element can be detected by a dedicated temperature sensor. Alternatively, in another embodiment the temperature of the heater element is determined by monitoring its electrical resistivity. The electrical resistivity of a length of wire is dependent on its temperature. Resistivity $\rho$ increases with increasing temperature. The actual resistivity $\rho$ characteristic will vary depending on the exact composition of the alloy and the geometrical configuration of the heater element 20, and an empirically determined relationship can be used in the controller. Thus, knowledge of resistivity $\rho$ at any given time can be used to deduce the actual operation temperature of the heater element 20.

The resistance of the heater element R = V/I; where V is the voltage across the heater element and I is the current passing through the heater element 20. The resistance R depends on the configuration of the heater element 20 as well as the temperature and is expressed by the following relationship:

$$R = \rho (T) * L/S \qquad \text{equation 1}$$

Where $\rho$ (T) is the temperature dependent resistivity, L is length and S the cross-sectional area of the heater element 20. L and S are fixed for a given heater element 20 configuration and can be measured. Thus, for a given heater element design R is proportional to $\rho$ (T).

The resistivity $\rho(T)$ of the heater element can be expressed in polynomial form as follows:

$$\rho (T) = \rho_o * (1 + \alpha_1 T + \alpha_2 T^2) \qquad \text{equation 2}$$

Where $\rho_o$ is the resistivity at a reference temperature $T_o$ and $\alpha_1$ and $\alpha_2$ are the polynominal coefficients.

Thus, knowing the length and cross-section of the heater element 20, it is possible to determine the resistance R, and therefore the resistivity $\rho$ at a given temperature by measuring the heater element voltage V and current I. The temperature can be obtained simply from a look-up table of the characteristic resistivity versus temperature relationship for the heater element being used or by evaluating the polynomial of equation (2) above. In

one embodiment, the process may be simplified by representing the resistivity ρ versus temperature curve in one or more, preferably two, linear approximations in the temperature range applicable to tobacco. This simplifies evaluation of temperature which is desirable in a controller 30 having limited computational resources.

Figure 2 is a block diagram illustrating the control elements of a system including the device of Figure 1 together with other system components. The system includes aerosol-generating device 100, secondary device 58 and optionally one or more remote devices 60. The aerosol-generating device 100 is as illustrated in Figure 1, but only the control elements of the aerosol-generating device are shown in Figure 2. As will be described, the secondary device 58 and one or more remote devices 60 operate to compare usage data from the aerosol-generating device with experimental usage data held within a database 57 that relates aerosol-generating device usage to the properties of the aerosol delivered to the user. The properties of the aerosol delivered to the user can then be displayed on a display 59 on the secondary device 58, or on a display on the aerosol-generating device or on an external device 60.

Referring to Figure 2, the controller 30 includes a measurement unit 50 and a control unit 52. The measurement unit is configured to determine the resistance R of the heater element 20. The measurement unit 50 passes resistance measurements to the control unit 52. The control unit 52 then controls the provision of power from the battery 40 to the heater element 20 by toggling switch 54. The controller may comprise a microprocessor as well as separate electronic control circuitry. In one embodiment, the microprocessor may include standard functionality such as an internal clock in addition to other functionality.

In a preparation of the controlling of the temperature, a value for the target operation temperature of the aerosol-generating device 100 is selected. The selection is based on the release temperatures of the volatile compounds that should and should not be released. This predetermined value is then stored in the control unit 52. The control unit 52 includes a non-volatile memory 56.

The controller 30 controls the heating of the heater element 20 by controlling the supply electrical energy from the battery to the heater element 20. The controller 30 only allows for the supply of power to the heater element 20 if the aerosol-forming substrate detector 32 has detected an aerosol-forming substrate 20 and the user has activated the device. By the switching of switch 54, power is provided as a pulsed signal. The pulse width or duty cycle

of the signal can be modulated by the control unit 52 to alter the amount of energy supplied to the heater element. In one embodiment, the duty cycle may be limited to 60-80%. This may provide additional safety and prevent a user from inadvertently raising the compensated temperature of the heater such that the substrate reaches a temperature above a combustion temperature.

In use, the controller 30 measures the resistivity $\rho$ of the heater element 20. The controller 30 then converts the resistivity of the heater element 20 into a value for the actual operation temperature of the heater element, by comparing the measured resistivity $\rho$ with the look-up table. This may be done within the measurement unit 50 or by the control unit 52. In the next step, the controller 30 compares the actual derived operation temperature with the target operation temperature. Alternatively, temperature values in the heating profile are pre-converted to resistance values so the controller regulates resistance instead of temperature, this avoids real-time computations to convert resistance to temperature during the smoking experience.

If the actual operation temperature is below the target operation temperature, then the control unit 52 supplies the heater element 20 with additional electrical energy in order to raise the actual operation temperature of the heater element 20. If the actual operation temperature is above the target operation temperature, the control unit 52 reduces the electrical energy supplied to the heater element 20 in order to lower the actual operation temperature back to the target operation temperature.

The control unit may implement any suitable control technique to regulate the temperature, such as a simple thermostatic feedback loop or a proportional, integral, derivative (PID) control technique.

The temperature of the heater element 20 is not only affected by the power being supplied to it. Airflow past the heater element 20 cools the heater element, reducing its temperature. This cooling effect can be exploited to detect changes in air flow through the device. The temperature of the heater element, and also its electrical resistance, will drop when air flow increases before the control unit 52 brings the heater element back to the target temperature.

Figure 3 shows a typical evolution of heater element temperature and applied power during use of an aerosol-generating device of the type shown in Figure 1. The level of supplied

power is shown as line 61 and the temperature of the heater element as line 62. The target temperature is shown as dotted line 64.

An initial period of high power is required at the start of use in order to bring the heater element up to the target temperature as quickly as possible. Once the target temperature has been reached the applied power drops to the level required to maintain the heater element at the target temperature. However, when a user puffs on the substrate 2, air is drawn past the heater element and cools it below the target temperature. This is shown as feature 66 in Figure 3. In order to return the heater element 20 to the target temperature there is a corresponding spike in the applied power, shown as feature 68 in Figure 3. This pattern is repeated throughout the use of the device, in this example a smoking session, in which four puffs are taken.

By detecting temporary changes in temperature or power, or in the rate of change of temperature or power, user puffs or other airflow events can be detected. Figure 4 illustrates an example of a control process, using a Schmitt trigger debounce approach, which can be used within control unit 52 to determine when a puff is taking place. The process in Figure 4 is based on detecting changes in heater element temperature. In step 400 an arbitrary state variable, which is initially set as 0, is modified to three quarters of its original value. In step 410 a delta value is determined that is the difference between a measured temperature of the heater element and the target temperature. Steps 400 and 410 can be performed in reverse order or in parallel. In step 415 the delta value is compared with a delta threshold value. If the delta value is greater than the delta threshold then the state variable is increased by one quarter before passing to step 425. This is shown as step 420. If the delta value is less that the threshold the state variable is unchanged and the process moves to step 425. The state variable is then compared with a state threshold. The value of the state threshold used is different depending on whether the device is determined at that time to be in a puffing or not-puffing state. In step 430 the control unit determines whether the device is in a puffing or not-puffing state. Initially, i.e. in a first control cycle, the device is assumed to be in a not-puffing state.

If the device is in a not-puffing state the state variable is compared to a HIGH state threshold in step 440. If the state variable is higher than the HIGH state threshold then the device is determined to be in a puffing state. If not, it is determined to remain in a not-puffing state. In both cases, the process then passes to step 460 and then returns to 400.

If the device is in a puffing state the state variable is compared to a LOW state threshold in step 450. If the state variable is lower than the LOW state threshold then the device is determined to be in a not-puffing state. If not, it is determined to remain in a puffing state. In both cases, the process then passes to step 460 and then returns step to 400.

The value of the HIGH and LOW threshold values directly influence the number of cycles through the process are required to transition between not-puffing and puffing states, and vice versa. In this way very short term fluctuations in temperature and noise in the system, which are not the result of a user puff, can be prevented from being detected as a puff. Short fluctuations are effectively filtered out. However, the number of cycles required is desirably chosen so that the puff detection transition can take place before the device compensates for the drop in temperature by increasing the power delivered to the heater element. Alternatively the controller could suspend the compensation process while making the decision of whether a puff is taken or not. In one example LOW = 0.06 and HIGH = 0.94, which means that the system would need to go through at least 10 iterations when the delta value was greater than the delta threshold to go from not puffing to puffing.

The system illustrated in Figure 4 can be used to provide a puff count and, if the controller includes a clock, an indication of the time at which each puff takes place. The puffing and not-puffing states can also be used to dynamically control the target temperature. Increased airflow brings more oxygen into contact with the substrate. This increases the likelihood of combustion of the substrate at a given temperature. Combustion of the substrate is undesirable. So the target temperature may be lowered when a puffing state is determined in order to reduce the likelihood of combustion of the substrate. The target temperature can then be returned to its original value when a not-puffing state is determined.

The process shown in Figure 4 is just one example of a puff detection process. For example, similar processes to that illustrate in Figure 4 could be carried out using applied power as a measure or using rate of change of temperature or rate of change of applied power. It is also possible to use a process similar to that shown in Figure 4, but using only a single state threshold instead of different HIGH and LOW thresholds.

The system can also automatically detect if an expected substrate is present or not. The amount of energy required to reach the target temperature and maintain the heater element at the target temperature depends on the presence or absence of a substrate material 2

close to the heater element 20, and on the properties of the substrate. Figure 5 shows the evolution of normalised energy supplied to the heater element as a function of time. Curve 70 is the normalised energy when a new substrate is in the device and curve 72 is the normalised energy when no substrate is in the device. The normalised energy is the energy supplied during a fixed time interval normalised against an initial energy measurement. A normalised measure of energy minimises the influence of environmental conditions such as ambient temperature, airflow and humidity.

It can be seen that in both cases the power delivered to heater element monotonically decreases with time following an initial high power period to bring the heater element up to the target temperature. However, Figure 5 shows that at T= 10 seconds the amount of energy supplied with a new substrate in the device is about twice the amount of energy supplied when no substrate is present in the device. The difference in energy supplied between a new and a previously heated substrate is smaller but still detectable. In one embodiment, the difference in the normalized energy may be measured at T=5 seconds and accurately determine if a substrate is present or not.

The controller is able to calculate the normalised energy supplied to the heater element up to a predetermined time, and from that is able to determine if an expected or proper substrate is in the device.

Figure 6 illustrates an example of a control process that can be carried out by the control unit 52 to determine if a substrate is in the device or not. The process is a loop process and starts at step 600. In step 610 the round number is incremented. At the start of the process the round number is set to zero. Each time the control loop is passed through, the round number is incremented in step 610. At step 620 the process branches depending on the value of the round number. In the initial loop, when the round number equals one, the process passes to step 630. At step 630 the initial energy, i.e. the energy supplied to the heater so far, is set as the energy. This initial energy is used to normalise subsequent energy measurements. The process then passes to step 640 and back to step 610. Subsequent rounds pass directly from step 620 to step 640 until a decision round is reached. Each round may be carried out at a fixed time interval, for example every two seconds. The decision round corresponds to the time at which the controller is configured to compare the normalised energy with an expected or threshold value to determine if a substrate is present or not. The threshold value of normalised energy is illustrated by dotted line 74 in Figure 3. In this example the decision round is round five, and occurs 10

seconds after the device is switched on. In the decision round, the process passes from step 620 to step 650. In step 650 the normalised energy is calculated as the energy supplied since the device was switched on divided by the product of the initial energy and the decision round number (in this example five). The calculated normalised energy is then compared to a threshold value in step 660. If the normalised energy exceeds the threshold value then the control unit determines that an appropriate substrate is present and the device can continue to be used. If the normalised energy does not exceed the threshold, the control unit determines that no substrate (or an inappropriate substrate) is present and the control unit then prevents the supply of power to the heater element by holding switch 54 open.

The process illustrated in Figure 6 is just one example of a process for determining if an appropriate substrate is present in an aerosol-generating device. Other measures of power or energy supplied to the heater element may be used and normalised or non-normalised data may be used. The time at which the determination is made is also a matter of choice. The advantage of an early determination in order to take early action if necessary must be balanced against the need to obtain a reliable result.

The measure of power or energy can be compared to a plurality of thresholds. This may be useful to distinguish between different types of substrate or between an inappropriate substrate and the absence of any substrate.

As well as being useful for dynamic control of the aerosol-generating device, the puff detection data and substrate detection data determined by the controller 30 may be useful for analysis purposes. In particular, the puff detection data together with data relating to the temperature of the heater element and/or the power supplied to the heater element (collectively referred to as usage data herein) can be compared with stored, experimentally derived data relating usage data to properties of the aerosol delivered by the device under different usage scenarios. The properties of the aerosol delivered can be provided to the user as feedback on his or her consumption of aerosol and of key constituents of the aerosol. The properties of the aerosol can also be collected over time and from several different users to provide a population level data set that can be subsequently analysed.

The stored, experimentally derived data relating usage data to properties of the aerosol delivered by the device under different usage scenarios can be contained in a database and can be held on the aerosol-generating device or on a secondary device to which the

aerosol-generating device can be connected. The secondary device may be any processing device, such as a laptop computer or a mobile phone. In one embodiment the secondary device is a charging device for recharging the battery in the aerosol-generating device.

It will be apparent to one of ordinary skill that, to the extent that additional environment data is required to accurately compare actual user data and the experimentally derived data, the control unit 52 may include additional sensing functionality to provide such environmental data. For example, the control unit 52 may include a humidity sensor 55 and humidity data may be included as part of the data eventually provided to the external device 58. Alternatively, or in addition, sensor 55 may be an ambient temperature sensor.

The usage of the device may also be analysed by an external device 58, 60 to determine which experimentally derived data most closely matches the usage behaviour, for example in terms of length and frequency of inhalation and number of inhalations. The experimentally derived data with the most closely matching usage behaviour may then be used as the basis for further analysis and display.

Figure 2 illustrates connection of the controller 30 to an external secondary device 58 including a display 59. The puff count and time data can be exported to the external device 58 together with other captured usage data and may be further relayed from the secondary device 58 to other external processing or data storage devices 60. The aerosol-generating device may include any suitable data output means. For example the aerosol-generating device may include a wireless radio connected to the controller 30 or memory 56, or a universal serial bus (USB) socket connected to the controller 30 or memory 56. Alternatively, the aerosol-generating device may be configured to transfer data from the memory to an external memory in a battery charging device every time the aerosol-generating device is recharged through suitable data connections. The battery charging device can provide a larger memory for longer term storage of the puff data and can be subsequently connected to a suitable data processing device or to a communications network. In addition, data as well as instructions for controller 30 may be uploaded, for example, to control unit 52 when controller 30 is connected to the external device 58.

Additional data may also be collected during operation of aerosol-generating device 100 and transferred to the external device 58. Such data may include, for example, a serial number or other identifying information of the aerosol-generating device; the time at start of

smoking session; the time of the end of smoking session; and information related to the reason for ending a smoking session.

In one embodiment, a serial number or other identifying information, or tracking information, associated with the aerosol-generating device 100 may be stored within controller 30. For example, such tracking information may be stored in memory 56. Because the aerosol-generating device 100 may be not always be connected to the same external device 58 for charging or data transfer purposes, this tracking information can be exported to external processing or data storage devices 60 and gathered to provide a more complete picture of the user's behaviour. A serial number or other identifying information allows the usage data from the device to be associated with previously stored usage data from the same device.

It will now be apparent to one of ordinary skill in the art that knowledge of the time of the operation of the aerosol-generating device, such as a start and stop of the smoking session, may also be captured using the methods and apparatuses described herein. For example, using the clock functionality of the controller 30 or the control unit 52, a start time of the smoking session may be captured and stored by controller 30. Similarly, a stop time may be recorded when the user or the aerosol-generating device 100 ends the session by stopping power to the heater element 20. The accuracy of such start and stop times may further be enhanced if a more accurate time is uploaded to the controller 30 by the external device 58 to correct any loss or inaccuracy. For example, during a connection of the controller 30 to the external device 58, device 58 may interrogate the internal clock function of the controller 30, compare the received time value with a clock provided within external device 58 or one or more of external processing or data storage devices 60, and provide an updated clock signal to controller 30.

The reason for terminating a smoking session or operation of the aerosol-generating device 100 may also be identified and captured. For example, control unit 52 may contain a look up table that includes various reasons for the end of the smoking session or operation. An exemplary listing of such reasons is provided here.

| Session code | Reason for session ending | Description of reason |
|---|---|---|
| 0 | (normal end) | End of session reached |
| 1 | (stop by user) | The user aborted the experience (by pushing power button to end session, by |

| | | |
|---|---|---|
| | | inserting aerosol-generating device into the external device 58, or via a remote control command |
| 2 | (heater broken) | Suspected heater damage in view of temperature measurements outside of a predetermined range during heating |
| 3 | (incorrect heating level) | Malfunction occurs where heater element temperature overshoots or undershoots a predetermined operating temperature outside of an acceptable tolerance range |
| 4 | (external heating) | Heater element temperature remains higher than the target even if the supplied power is reduced |

The above table provides a number of exemplary reasons why operation or a smoking session may be terminated. It will now be apparent to one of ordinary skill in the art, by using various indications provided by the measurement unit 50 and the control unit 52 provided in the controller 30, either alone or in combination with recorded indications in response to the controller 30 control of the heating of the heater element 20, controller 30 may assign session codes with a reason for ending the operation of aerosol-generating device 100 or a smoking session using such a device. Other reasons that may be determined from available data using the above described methods and apparatuses will now be apparent to one of ordinary skill in the art and may also be implemented using the methods and apparatuses described herein without deviating from the scope or spirit of this specification and the exemplary embodiments described herein.

The user's consumption of aerosol deliverables may be accurately approximated because the aerosol-generating device 100 described herein may accurately control the temperature of the heater element 20, and because data may be gathered by the controller 30, as well as the units 50 and 52 provided within the controller 30, and an accurate profile of the actual use of the device 100 during a session can be obtained.

In one exemplary embodiment, the usage data captured by the controller 30 can be compared to data determined during controlled sessions to even further enhance the understanding of the user use of the device 100. For example, by first collecting data using a smoking machine under controlled environmental conditions and measuring data such as

the puff number, puffing volume, puff interval, and resistivity of heater element, a database 57 can be constructed that provides, for examples, levels of nicotine or other deliverables provided under the experimental conditions. Such experimental data can then be compared to data collected by the controller 30 during actual use and be used to determine, for example, information on how much of a deliverable the user has inhaled. In one embodiment, as illustrated in Figure 2, such a database 57 containing experimental data may be stored in one or more of remote devices 60 and additional comparison and processing of the data may take place in one or more of devices 60. For example, remote devices 60 may be one or more servers operated by a manufacturer of aerosol-generating devices connected to and accessible from the Internet. Alternatively, database 57 may be located within external device 58, as illustrated in dotted line in Figure 2.

The database 57 may comprise data for a plurality of different types of aerosol-forming substrate and for a plurality of different types of aerosol-generating device. An indication of the type of substrate and the type of device may be provided by the user either before a smoking session or after a smoking session and may be input into the aerosol-generating device or into one of the secondary devices. Alternatively an indication of the type of substrate and the type of device may be provided automatically by the aerosol-generating device as part of the usage data.

The data stored in the database 57 may include amounts of the following compounds contained within the aerosol delivered under particular operating conditions: Acetaldehyde, Acetamide, Acetone, Acrolein, Acrylamide, Acrylonitrile, 4-Aminobiphenyl, 1-Aminonaphthalene, 2-Aminonaphthalene, Ammonia, Anabasine, o-Anisidine, Arsenic, A-α-C (2-Amino-9H-pyrido[2,3-b]indole), Benz[a]anthracene, Benz[j]aceanthrylene, Benzene, Benzo[b]fluoranthene, Benzo[k]fluoranthene, Benzo[b]furan, Benzo[a]pyrene, Benzo[c]phenanthrene, Beryllium, 1,3-Butadiene, Cadmium, Caffeic acid, Carbon monoxide, Catechol, Chlorinated dioxins/furans, Chromium, Chrysene, Cobalt, Cresols (o-, m-, and p-cresol), Crotonaldehyde, Cyclopenta[c,d]pyrene, Dibenz[a,h]anthracene, Dibenzo[a,e]pyrene, Dibenzo[a,h]pyrene, Dibenzo[a,i]pyrene, Dibenzo[a,l]pyrene, 2,6-Dimethylaniline, Ethyl carbamate (urethane), Ethylbenzene, Ethylene oxide, Formaldehyde, Furan, Glu-P-1 (2-Amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole), Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole), Hydrazine, Hydrogen cyanide, Indeno[1,2,3-cd]pyrene, IQ (2-Amino-3-methylimidazo[4,5-f]quinoline), Isoprene, Lead, MeA-α-C (2-Amino-3-methyl)-9H-pyrido[2,3-b]indole), Mercury, Methyl ethyl ketone, 5-Methylchrysene, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), Naphthalene, Nickel, Nicotine,

Nitrobenzene, Nitromethane, 2-Nitropropane, N-Nitrosodiethanolamine (NDELA), N-Nitrosodiethylamine, N-Nitrosodimethylamine (NDMA), N-Nitrosomethylethylamine, N-Nitrosomorpholine (NMOR), N-Nitrosonornicotine (NNN), N-Nitrosopiperidine (NPIP), N-Nitrosopyrrolidine (NPYR), N-Nitrososarcosine (NSAR), Nornicotine, Phenol, PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine), Polonium-210, Propionaldehyde, Propylene oxide, Quinoline, Selenium, Styrene, o-Toluidine, Toluene, Trp-P-1 (3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole), Trp-P-2 (1-Methyl-3-amino-5H-pyrido[4,3-b]indole), Uranium-235, Uranium-238, Vinyl acetate, or Vinyl chloride.

The information about the properties of the aerosol delivered to the user may displayed on the aerosol-generating device 100 or may be displayed on the display 59 of a secondary device 58, such as a mobile phone or charging device, or on a remote, external device 60.

It will now be apparent to one of ordinary skill in the art, that using the methods and apparatuses discussed herein, nearly any desired information may be captured by such that comparison to experimental data is possible and various attributes associated with a user's operation of the aerosol-generating device 100 be accurately approximated.

The exemplary embodiments described above illustrate but are not limiting. In view of the above discussed exemplary embodiments, other embodiments consistent with the above exemplary embodiments will now be apparent to one of ordinary skill in the art.

**Claims**

1. An aerosol-generating system configured for oral or nasal delivery of a generated aerosol to a user, the system comprising:

a heater element configured to heat an aerosol-forming substrate to generate an aerosol;

a power source connected to the heater element;

a controller connected to the heater element and to the power source, wherein the controller is configured to control operation of the heater element, the controller including or being connected to a means to detect a change in air flow past the heater element;

first data storage means connected to the controller for recording detected changes in airflow past the heater element and data relating to the operation of the heater element; and

second data storage means comprising a database relating changes in airflow and data relating to the operation of the heater element to the properties of the aerosol delivered to the user; and

an indication means coupled to the second data storage means for indicating properties of the aerosol delivered to the user.

2. An aerosol system according to claim 1, wherein the controller is configured to control power supplied to the heater element from the power source to maintain the heater element at a target temperature and is configured to monitor changes in a temperature of the heater element or changes in the power supplied to the heater element to detect a change in air flow past the heater element.

3. An aerosol-generating system according to claim 1 or 2, wherein the controller is configured to compare a measure of power supplied to the heater element or energy supplied to the heater element from the power source to a threshold measure of power or energy to detect the presence of an aerosol-forming substrate close to the heater element or a material property of an aerosol-forming substrate close to the heater element.

4. An aerosol-generating system according to any preceding claim, wherein the database comprises data specific to a particular type of aerosol-forming substrate.

5. An aerosol-generating system according to claim 4, further comprising identifying means for identifying the aerosol-forming substrate received in the device or a user

interface configured to allow a consumer to input data identifying the aerosol-forming substrate received in the device.

6. An aerosol-generating system according to any preceding claim, wherein the data relating to the operation of the aerosol-generating element comprises the temperature of heater element or power supplied to the heater element.

7. An aerosol-generating system according to any preceding claim, comprising a housing, wherein the second data storage means or the display, or both the second data storage means and the display are contained within the housing together with at least one of the heater element and the power source.

8. An aerosol-generating system according to any one of claims 1 to 6, wherein the system comprises an aerosol-generating device and one or more secondary devices to which the aerosol-generating device may directly or indirectly coupled, and wherein the second data storage means and the display are part of the one or more secondary devices.

9. An aerosol-generating system according to claim 8, wherein the secondary device is a charging device configured to replenish the power source in the aerosol-generating device.

10. An aerosol-generating system according to any one of claims 1 to 9, wherein the properties of aerosol delivered to the user comprise amounts of particular chemical compounds.

11. An aerosol-generating system according to any preceding claim, wherein the system is an electrical smoking device.

12. A method of providing aerosol delivery data to an end user of an electrically heated aerosol-generating device, the device comprising a heater element and a power supply for supplying power to the heater element, and means to detect a change in air flow past the heater element comprising:

recording detected changes in airflow past the heater element and data relating to the operation of the heater element; and

extracting from a database, based on the detected changes in airflow and data relating to the operation of the heater element, properties of the aerosol delivered to the user; and

indicating the extracted properties of the aerosol delivered to the user.

13. A method according to claim 12, further comprising the step of detecting or providing at least one characteristic of the aerosol-forming substrate received in the device, wherein the step of extracting is also based on the at least one characteristic of the aerosol-forming substrate received in the device.

14. A method according to claim 12 or 13, wherein the extracted properties of the aerosol delivered to the user comprise amounts of particular chemical compounds.

15. A computer program that when executed on a computer or other suitable processing device, carries out the method of any one of claims 12 to 14.

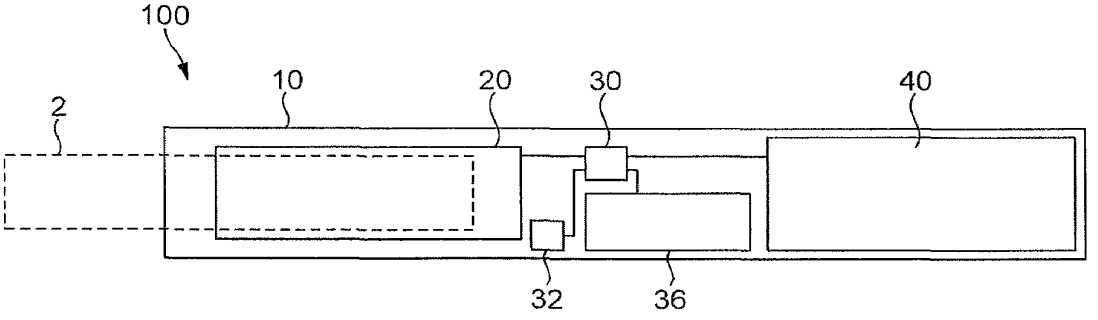



FIG. 1

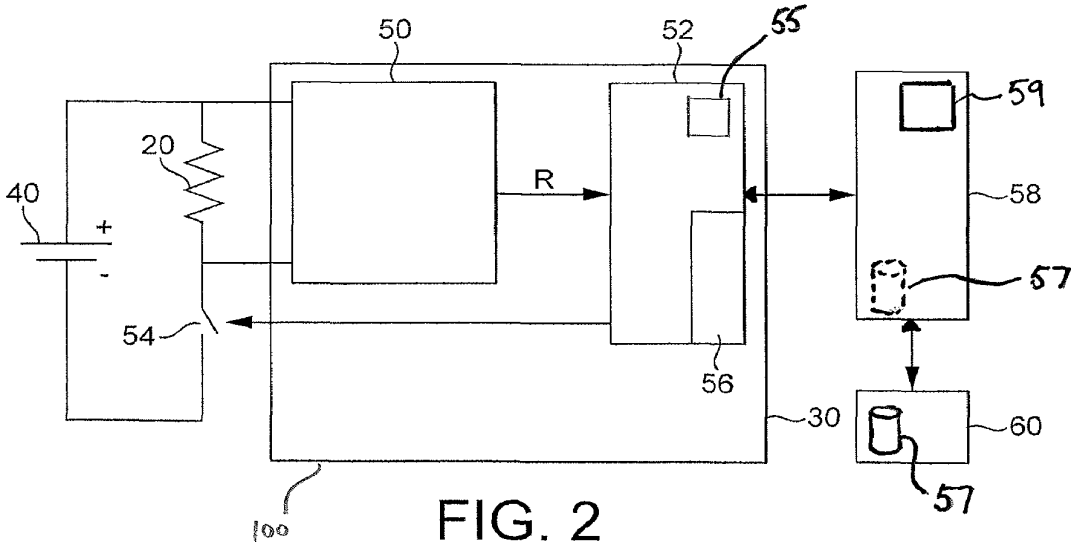



FIG. 2

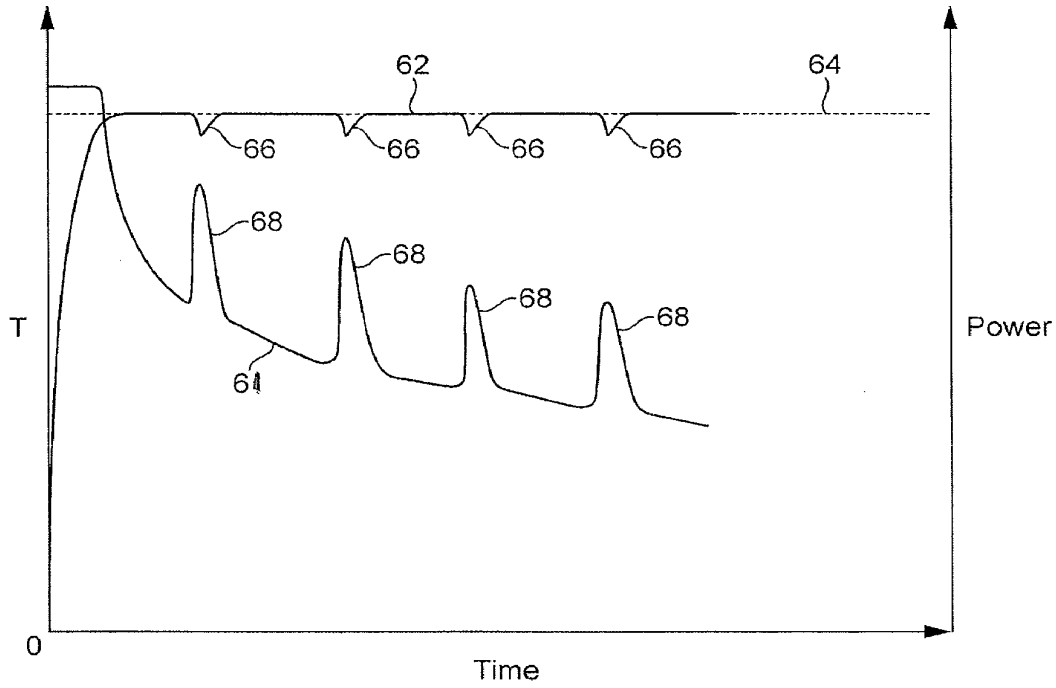



FIG. 3

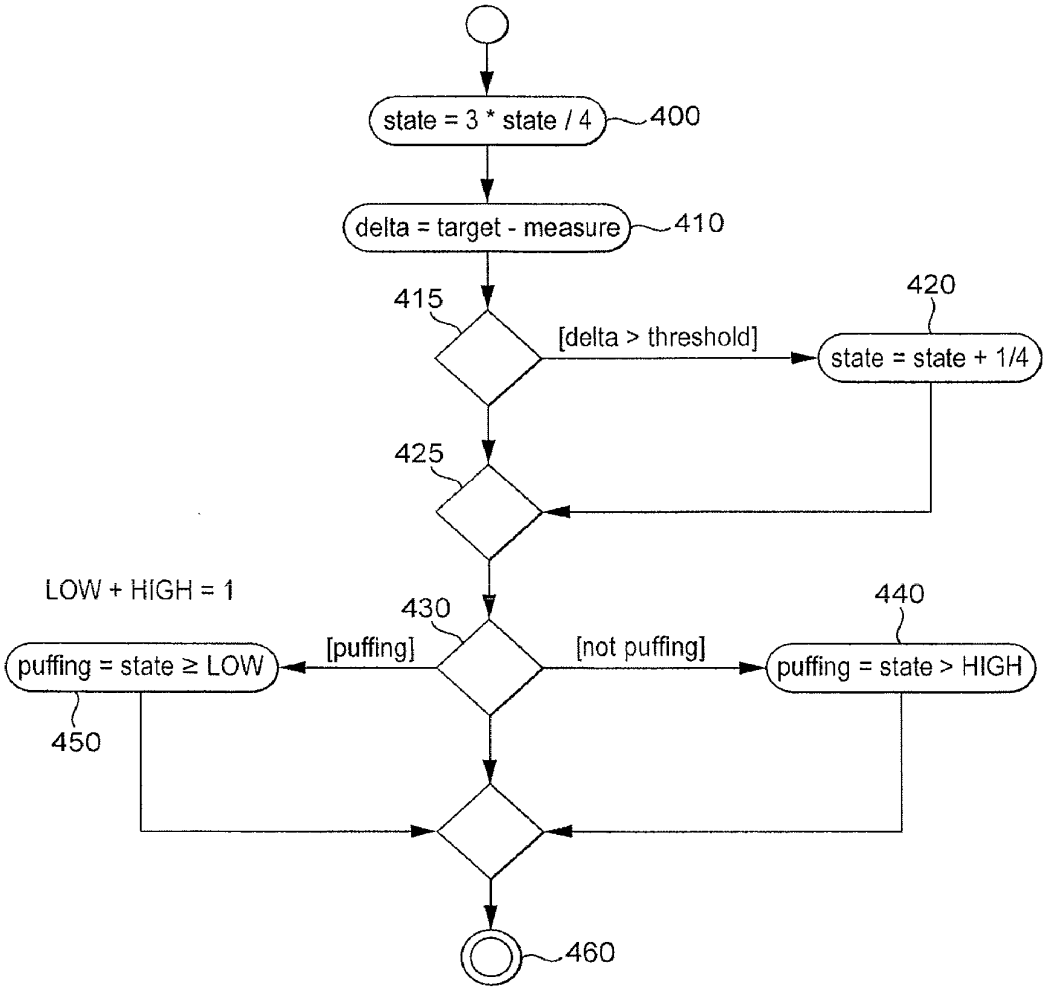

state = 3 * state / 4
400
delta = target - measure
410
415
[delta > threshold]
420
state = state + 1/4
425
LOW + HIGH = 1
430
[puffing]
[not puffing]
440
puffing = state ≥ LOW
puffing = state > HIGH
450
460

FIG. 4

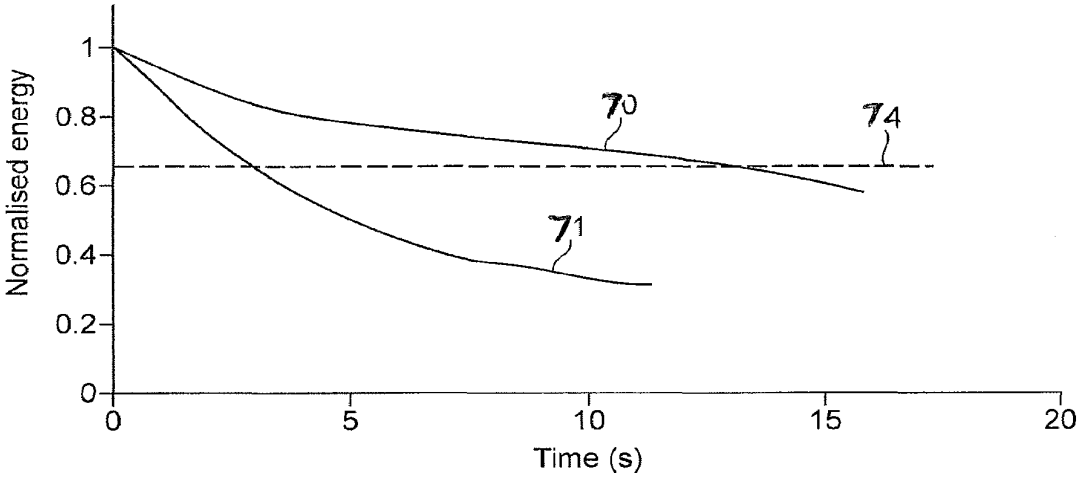

Normalised energy
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
Time (s)
70
71
74

FIG. 5

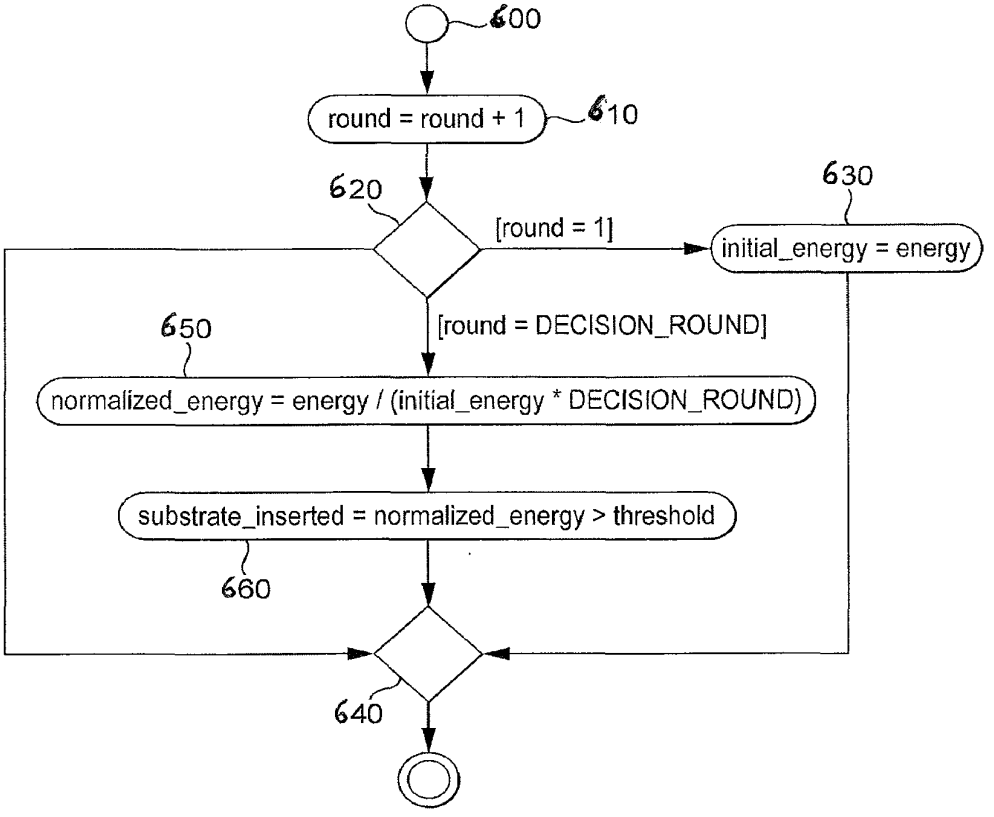

600
round = round + 1
610
620
630
[round = 1]
initial_energy = energy
650
[round = DECISION_ROUND]
normalized_energy = energy / (initial_energy * DECISION_ROUND)
substrate_inserted = normalized_energy > threshold
660
640

FIG. 6

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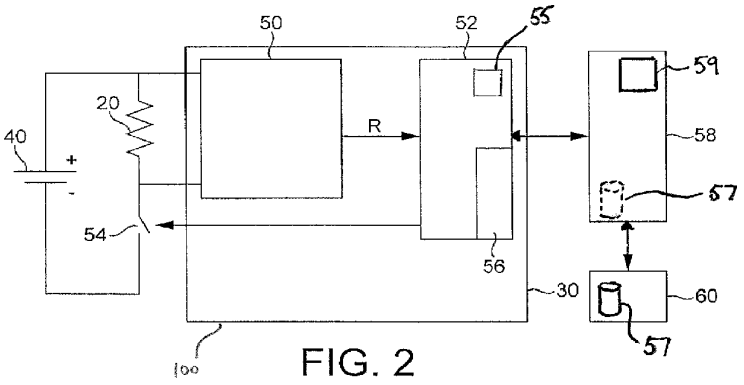



FIG. 2

(57) Abstract: There is provided an aerosol-generating system configured for oral or nasal delivery of a generated aerosol to a user, the system comprising a heater element (20) configured to heat an aerosol-forming substrate to generate an aerosol, a power source (40) connected to the heater element, a controller (30) connected to the heater element and to the power source, wherein the control - ler is configured to control operation of the heater element, the controller including or being connected to a means to detect a change in air flow past the heater element, first data storage means (56) connected to the controller for recording detected changes in airflow past the heater element and data relating to the operation of the heater element, second data storage means comprising a database (57) relating changes in airflow and data relating to the operation of the heater element to the properties of the aerosol delivered to the user and an indication means (59) coupled to the second data storage means for indicating to the user a property of the aerosol delivered to the user. The property or properties of the aerosol delivered to the user may comprise amounts of particular chemical compounds.

WO 2013/098398 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/077066

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/077066

A. CLASSIFICATION OF SUBJECT MATTER
INV. A24F47/00 A61M11/04
ADD.

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)
A24F 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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2011/265806 A1 (ALARCON RAMON [US] ET AL) 3 November 2011 (2011-11-03) | 12-14 |
| A | paragraph [0045] - paragraph [0077] | 1 |
| A | US 2008/257367 A1 (PATERNO GREG [US] ET AL) 23 October 2008 (2008-10-23) paragraph [0010] - paragraph [0018] | 1,12 |
| A | US 5 269 327 A (COUNTS MARY E [US] ET AL) 14 December 1993 (1993-12-14) column 2, line 61 - column 14, line 28 | 1,12 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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 |
|---|---|
| 25 June 2013 | 02/07/2013 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Koob, Michael |

1

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/077066

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 2011265806 A1 | 03-11-2011 | AU 2011245104 A1 | 08-11-2012 |
| | | CA 2797975 A1 | 03-11-2011 |
| | | CN 102970885 A | 13-03-2013 |
| | | EP 2563172 A2 | 06-03-2013 |
| | | US 2011265806 A1 | 03-11-2011 |
| | | WO 2011137453 A2 | 03-11-2011 |
| US 2008257367 A1 | 23-10-2008 | US 2008257367 A1 | 23-10-2008 |
| | | WO 2008130813 A1 | 30-10-2008 |
| US 5269327 A | 14-12-1993 | NONE | |

Form PCT/ISA/210 (patent family annex) (April 2005)

Continuation of Box II.2

Claims Nos.: 15

Claim 15 is unclear and not supported by the description to an extend that a meaningful search is not possible. The claim concerns a computer program but contains merely a reference to method steps. Therefore it is unclear which executable instructions are part of the claimed subject-matter. Furthermore, there is no embodiment disclosed in the whole application.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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WIPO | PCT

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(21) International Application Number:
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21 March 2013 (21.03.2013)

(25) Filing Language: English

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61/614,894 23 March 2012 (23.03.2012) US
13/839,233 15 March 2013 (15.03.2013) US

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(72) Inventor: **SCATTERDAY, Mark**; 4831 North 65th Street, Scottsdale, AZ 85251 (US).

(74) Agent: **CAO, Veronica-Adele, R.**; Weiss & Moy, P.C., 4204 North Brown Ave, Scottsdale, AZ 85251 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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**Published**:

— *with international search report (Art. 21(3))*

WO 2013/142678 A1

(54) Title: SINGLE-USE ELECTRONIC CIGAR

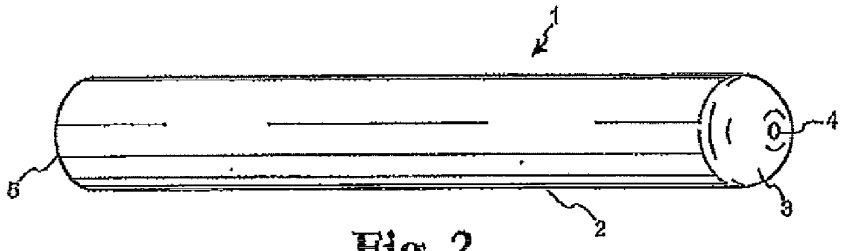



Fig. 2

(57) Abstract: The present disclosure relates to an improved electronic evaporable substance delivery device in the form of a single-use electronic cigar comprises, in combination: a lit tip end, a case, and a mouthpiece end distal from the lit tip end. Both the case and mouth piece end have therein a channel defining a longitudinal vapor path, and are encased in a sheath made from a paper product, preferably cardboard. The mouthpiece end mimics the end of a conventional cigar which a smoker inserts into the mouth. The lit end mimics the end of a conventional cigar that is lit.

# SINGLE-USE ELECTRONIC CIGAR

## CROSS-REFERENCE TO RELATED APPLICATION

[0001] This disclosure claims priority to U.S. Provisional Application Serial No. 61/614,894, tiled SINGLE-USE ELECTRONIC CIGAR to Mark Scatterday that was filed on March 23, 2012.

## TECHNICAL FIELD

[0002] This disclosure generally relates to alternative smoking devices, and more particularly, to a single-use electronic cigar.

## SUMMARY

[0003] This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the DESCRIPTION OF THE DISCLOSURE. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

[0004] In accordance with an embodiment of the present invention, a single-use electronic cigar is disclosed. The electronic cigar comprises: a cylindrical case adapted to contain internal components, wherein the internal components comprise: a cartridge containing liquid having nicotine; a heating member coupled to the cartridge for vaporizing the liquid; a printed circuit board coupled to the heating member; a power source coupled to the printed circuit board ;and a reed switch coupled to the power source; a mouthpiece coupled to one end of the cylindrical case wherein the mouthpiece mimics the end of a conventional cigar that contacts a mouth of a user;

a lit tip end coupled to another end of the cylindrical case, wherein the lit tip end mimics the end of a conventional cigar that is burned; and a sheath coupled to the mouthpiece and to at least a portion of an external portion of the cylindrical case.

[0005] In accordance with another embodiment of the present invention, a single-use electronic cigar is disclosed. The electronic cigar comprises: a cylindrical case adapted to contain internal components, wherein the internal components comprise: a cartridge containing liquid having nicotine; a heating member coupled to the cartridge for vaporizing the liquid; a printed circuit board coupled to the heating member; a power source coupled to the printed circuit board ;and a reed switch coupled to the power source; a mouthpiece coupled to one end of the cylindrical case wherein the mouthpiece mimics the end of a conventional cigar that contacts a mouth of a user; a lit tip end coupled to another end of the cylindrical case, wherein the lit tip end mimics the end of a conventional cigar that is burned; a sheath coupled to the mouthpiece and to at least a portion of an external portion of the cylindrical case; and a display device coupled to the printed circuit board for communicating at least one of nicotine intake and power level to the user.

[0006] In accordance with another embodiment of the present invention, a single-use electronic smoking device is provided. The electronic smoking device comprises: a cylindrical case adapted to contain internal components, wherein the internal components comprise: a cartridge containing liquid having nicotine; a heating member coupled to the cartridge for vaporizing the liquid; a printed circuit board coupled to the heating member; a power source coupled to the printed circuit board ;and a reed switch coupled to the power source; a mouthpiece coupled to one end of the cylindrical case, the mouthpiece having a channel therethrough and a hole; a lit tip end coupled to another end of the cylindrical case; a paper sheath coupled to at least

a portion of an external portion of the cylindrical case; and a display device coupled to the printed circuit board for communicating at least one of nicotine intake and power level to a user.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The novel features believed to be characteristic of the application are set forth in the appended claims. In the descriptions that follow, like parts are marked throughout the specification and drawings with the same numerals, respectively. The drawing figures are not necessarily drawn to scale and certain figures can be shown in exaggerated or generalized form in the interest of clarity and conciseness. The application itself, however, as well as a preferred mode of use, further objectives and advantages thereof, will be best understood by reference to the following detailed description of illustrative embodiments when read in conjunction with the accompanying drawings, wherein:

[0008] **FIGURE 1** is an exterior longitudinal view of the single-use electronic cigar in accordance with one or more aspects of the present disclosure;

[0009] **FIGURE 2** is an exterior longitudinal view of the single-use electronic cigar in accordance with one or more aspects of the present disclosure;

[0010] **FIGURE 3** is a close-up view of the exterior of the single-use electronic cigar in accordance with one or more aspects of the present disclosure;

[0011] **FIGURE 4** is another exterior view of the single-use electronic cigar in accordance with one or more aspects of the present disclosure;

[0012] **FIGURE 5** is a cutaway depiction of the internal structure of the single-use electronic cigar in accordance with one or more aspects of the present disclosure; and

[0013] **FIGURE 6** is a perspective, exploded view of the single-use electronic cigar in

accordance with one or more aspects of the present disclosure.

**[0014]** **FIGURE 7** is a perspective cutaway depiction of the internal structure of a portion of a single-use electronic cigarette in accordance with one or more aspects of the present disclosure.

**[0015]** **FIGURE 8** is a perspective view of the external structure of the single-use electronic cigarette of FIGURE 7.

## DESCRIPTION OF THE DISCLOSURE

[0016] The description set forth below with the appended drawings is intended as a description of presently preferred embodiments of the disclosure and is not intended to represent the only forms in which the present disclosure can be constructed and/or utilized. The description sets forth the functions and the sequence of steps for constructing and operating the disclosure. It is to be understood, however, that the same or equivalent functions and sequences can be accomplished by different embodiments that are also intended to be encompassed within the spirit and scope of this disclosure.

**[0017]** Generally described, the present disclosure relates to an electronic cigar, and, more particularly, to a single-use electronic cigar. **FIGS. 1** and **2** depict the exterior longitudinal view of electronic cigar **1**. Cigar **1** is comprised of substantially cylindrical case **2** which has on one end a substantially spherical mouthpiece end **3**, which mimics the end of a conventional cigar which a smoker inserts into the mouth and has at its endpoint mouthpiece hole **4** as shown in **FIG. 2**, and substantially curvilinear lit tip end **5**, which mimics the end of a conventional cigar which is lit. Cigar **1** can be of various sizes, and preferably is sized to be equivalent to a conventional cigar.

[0018] With reference to **FIG. 4**, cigar 1 is substantially encased with sheath **7**. Sheath **7** completely covers the external surface of mouthpiece end **3** and substantially covers case **2** up to the case-lit tip end juncture (i.e. where the case **2** meets the lit tip end **5**) such that the external portion **6** of lit tip end **5** is not encased in sheath **7** (**FIG. 3**). External portion **6** is made of a hard plastic, rubber, or other desired material.

[0019] To facilitate the single-use functionality of cigar **1**, sheath **7** is made of heavy-duty paper such as a cardboard, binder's board, paperboard, fiberboard, boxboard, solid board, chipboard, so as to give cigar **1** the look, feel, and relative weight of a standard non-electronic cigar. Preferably, sheath **7** is made of cardboard.

[0020] As with most conventional cigars, cigar **1** preferably has label band **18**, as depicted in **FIG. 4**. Label band **18** is comprised of a relatively flat circular paper structure which is placed over a portion of case **2** anywhere along the longitudinal length of case **2**. Label band **18** may have thereon a graphic design which can include any one or more of figures or words, such as the name of the company manufacturing or selling cigar **1** or a congratulatory or other message, such as "It's a Boy!" or "It's Girl!".

[0021] **FIG. 5** is a cutaway depiction of the internal structure of cigar **1**. Cigar **1** is electronically powered, capable of single-use only, does not require "lighting" in the conventional manner that a cigar is commonly lit at lit tip end **5**, and does not produce second-hand smoke of the type associated with cigars. The evaporable substance can include nicotine. Other substances can include medications, herbs, or vitamin compounds that are evaporated for a user to inhale.

[0022] The user may insert mouthpiece end **3** into his or her mouth. Mouthpiece end **3** may comprise a hard plastic, rubber, or other desired material. It should be noted that some users

enjoy chewing on the end of a cigar, and it may be desired to provide mouthpiece end **3** comprised of a deformable material to facilitate such activity. Preferably, mouthpiece end **3** is made of silicone or a silicone-bearing substance.

**[0023]** **FIGS. 5** and **6** provide views of the internal components of cigar **1**. Mouthpiece end **3** contains a channel therethrough which opens into the interior of case **2**. Vapor path hole **9** located on the external surface of the case **2** permits the entry of outside air into case **2**. The user may inhale through mouthpiece end **3** causing a sucking action at mouthpiece end **3** that is communicated via that channel and drawing in ambient air via vapor path hole **9**. In an alternative embodiment, an aperture **26** may be present at the case-lit tip end juncture (**FIG. 3**). When the user inhales the cigar, air will enter into the interior of the case **2** through the aperture **26** at the case-lit tip end juncture.

**[0024]** Preferably, that sucking action may cause reed switch **13** to move, sending a signal to a microprocessor located on printed circuit board **8** that "smoking" has been initiated. The microprocessor may then send a signal, activating heating member **12**. Heating member **12** may be a heating coil, light emitting diode, an infra-red device, a laser, vibration chamber, pressure chamber, butane or other flame, or other device capable of bringing nicotine (or anther substance) to its boiling point.

**[0025]** Heating member **12** is located proximate cartridge **10**, which may contain therein nicotine mixed with a low boiling point substance (e.g., propylene glycol) and, optionally, flavors and/or other additives. For example, flavored nicotine, or other flavored evaporable substances could be provided in cartridge **10**, allowing users the experience of inhaling and tasting different flavors. Preferably, cartridge **10** contains therein a cotton filament impregnated with nicotine or a nicotine-bearing substance. Activation of heating member **12** causes the

contents of cartridge **10** to reach their boiling point, producing a vapor. The vapor is inhaled by the user via the channel located in mouthpiece end **3**. Heat shield **15** may be interposed between heating member **12** and printed circuit board **8**, to protect components thereon.

**[0026]** The microprocessor may maintain heating member **12** at a constant temperature, where desired, using a smart monitoring circuit located on printed circuit board **8**, so as to limit power consumption and/or optimize performance. The microprocessor may utilize an algorithm software program that calculates nicotine consumption by the user and may store the amount of consumption in onboard flash memory integrated into the microprocessor. Printed circuit board **8** may further include at least one display device **17**, in communication with the microprocessor, to relay data to the user regarding, for example, substance intake and/or battery power levels. Display device **17** may be one or more light emitting diode (in one embodiment, substance intake quantity may be communicated by a blinking of the display device, with each blink corresponding to the substance associated with a single cigar), a liquid crystal display, or other display. In one embodiment, display device **17** may be a radio frequency transmitter, adapted to relay data (including data saved in memory) to the user via a remote radio frequency receiver (not shown). In this manner, a user may monitor and/or track substance consumption.

**[0027]** Cigar **1**, including the heating member **12** and microprocessor, is powered by power source **25**. Power source **25** may be a battery, inserted against battery spring **16**.

**[0028]** Although the disclosure describes a single-use electronic cigar, it should be clearly understood that substantial benefit may be derived from the use of another electronic smoking device, such as an electronic cigarette. Referring to **FIGS. 7** and **8**, may also have a mouthpiece end **3** having a channel therethrough and a mouthpiece hole **4**. The electronic cigarette may also have a printed circuit board **8** and at least one display device **17**, in communication with the

microprocessor, to relay data to the user regarding, for example, substance intake and/or battery power levels.

**[0029]** While the disclosure has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the art that the foregoing and other changes in form and details may be made therein without departing from the spirit and scope of the disclosure. The foregoing description is provided to enable any person skilled in the relevant art to practice the various embodiments described herein. Various modifications to these embodiments will be readily apparent to those skilled in the relevant art, and generic principles define herein can be applied to other embodiments. Thus, the claims are not intended to be limited to the embodiments shown and described herein, but are to be accorded the full scope consistent with the language of the claims, wherein reference t o and element in the singular is not intended to mean "one and only one" unless specifically stated, but rather "one or more." All structural and functional equivalents to the elements of the various embodiments described throughout this disclosure that are known or later come to be known to those of ordinary skill in the relevant art are expressly incorporated herein by reference and intended to be encompassed by the claims. Moreover, nothing disclosed herein is intended to be dedicated to the public regardless of whether such disclosure is explicitly recited in the claims.

I CLAIM:

1. An electronic cigar comprising:

a cylindrical case adapted to contain internal components, wherein the internal components comprise:

a cartridge containing liquid having nicotine;

a heating member coupled to the cartridge for vaporizing the liquid;

a printed circuit board coupled to the heating member;

a power source coupled to the printed circuit board ;and

a reed switch coupled to the power source;

a mouthpiece coupled to one end of the cylindrical case wherein the mouthpiece mimics the end of a conventional cigar that contacts a mouth of a user;

a lit tip end coupled to another end of the cylindrical case, wherein the lit tip end mimics the end of a conventional cigar that is burned; and

a sheath coupled to the mouthpiece and to at least a portion of an external portion of the cylindrical case.

2. The electronic cigar of Claim 1 wherein an external surface of the case has an aperture for allowing air to enter into the case when the user inhales through the mouthpiece.

3. The electronic cigar of Claim 1 further comprising an aperture located at a case-lit tip end juncture for allowing air to enter into the case when the user inhales through the mouthpiece.

4. The electronic cigar of Claim 1 wherein the mouthpiece defines:

a channel therethrough; and

a hole for allowing vapor to pass from an interior of the case into the mouth of the user when inhaled.

5. The electronic cigar of Claim 1 wherein the mouthpiece is constructed of a resilient material.

6. The electronic cigar of Claim 5 wherein the resilient material is silicone.

7. The electronic cigar of Claim 1 wherein the sheath is constructed of paper material.

8. The electronic cigar of Claim 7 wherein the paper material is cardboard.

9. The electronic cigar of Claim 1further comprising a microprocessor coupled to the printed circuit board, wherein the microprocessor is programmed to control power consumption.

10. The electronic cigar of Claim 1 further comprising a microprocessor coupled to the printed circuit board, wherein the microprocessor is programmed to control nicotine consumption.

11. The electronic cigar of Claim 1 further comprising a display device coupled to the printed circuit board for communicating at least one of nicotine intake and power level to the user.

12. The electronic cigar of Claim 11 wherein the display comprises at least one light emitting diode.

13. The electronic cigar of Claim 11 wherein the display comprises a liquid crystal display.

14. An electronic cigar comprising:

a cylindrical case adapted to contain internal components, wherein the internal components comprise:

a cartridge containing liquid having nicotine;

a heating member coupled to the cartridge for vaporizing the liquid;

a printed circuit board coupled to the heating member;

a power source coupled to the printed circuit board ;and

a reed switch coupled to the power source;

a mouthpiece coupled to one end of the cylindrical case wherein the mouthpiece mimics the end of a conventional cigar that contacts a mouth of a user;

a lit tip end coupled to another end of the cylindrical case, wherein the lit tip end mimics the end of a conventional cigar that is burned;

a sheath coupled to the mouthpiece and to at least a portion of an external portion of the cylindrical case; and

a display device coupled to the printed circuit board for communicating at least one of nicotine intake and power level to the user.

15. The electronic cigar of Claim 14 further comprising:

an aperture on an external surface of the case;

a channel passing through the mouthpiece; and

a hole in a proximal end of the mouthpiece that is connected to the channel;

wherein air is drawn into the case through the aperture in the case; and

wherein vapor passes from an interior of the case and through the channel of the mouthpiece and out of the hole in the mouthpiece when inhaled.

16. The electronic cigar of Claim 14 further comprising:

an aperture positioned at a case-lit tip end juncture;

a channel passing through the mouthpiece; and

a hole in a proximal end of the mouthpiece that is connected to the channel;

wherein air is drawn into the case through the aperture at the case-lit tip end juncture; and

wherein vapor passes from an interior of the case and through the channel of the mouthpiece and out of the hole in the mouthpiece when inhaled.

17. The electronic cigar of Claim 14 further comprising a microprocessor coupled to the printed circuit board, wherein the microprocessor is programmed to control one of nicotine consumption and power consumption.

18. The electronic cigar of Claim 14 wherein the display comprises one of a liquid crystal display and at least one light emitting diode.

19. The electronic cigar of Claim 14 wherein the sheath is constructed of cardboard.

20. An electronic smoking device comprising:

a cylindrical case adapted to contain internal components, wherein the internal components comprise:

a cartridge containing liquid having nicotine;

a heating member coupled to the cartridge for vaporizing the liquid;

a printed circuit board coupled to the heating member;

a power source coupled to the printed circuit board ;and

a reed switch coupled to the power source;

a mouthpiece coupled to one end of the cylindrical case, the mouthpiece having a channel therethrough and a hole;

a lit tip end coupled to another end of the cylindrical case;

a paper sheath coupled to at least a portion of an external portion of the cylindrical case; and

a display device coupled to the printed circuit board for communicating at least one of nicotine intake and power level to a user.

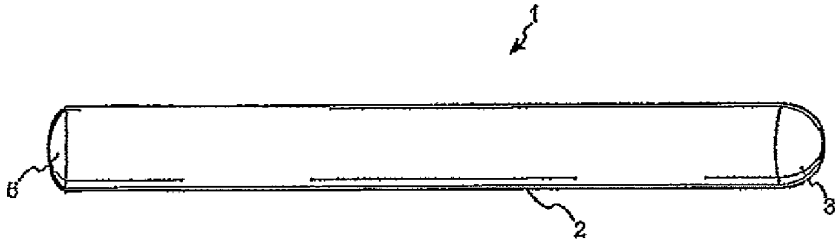



Fig. 1

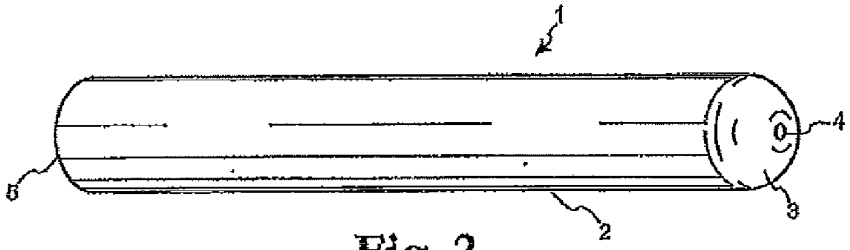



Fig. 2

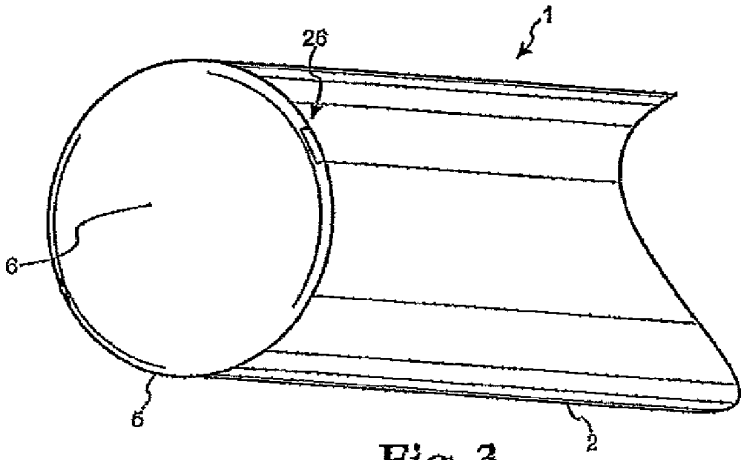



Fig. 3

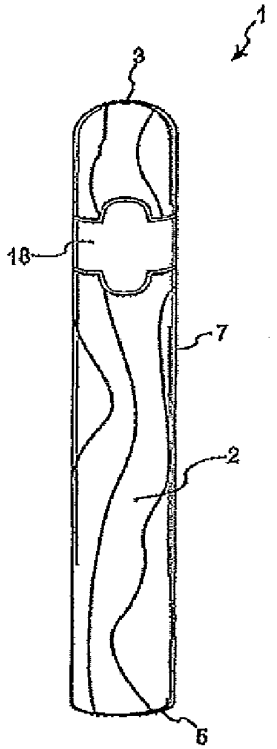



Fig. 4

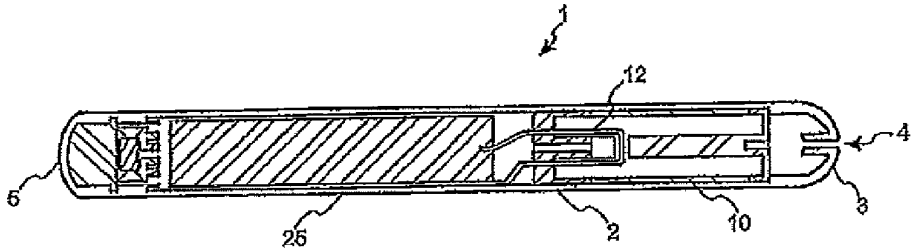



Fig. 5

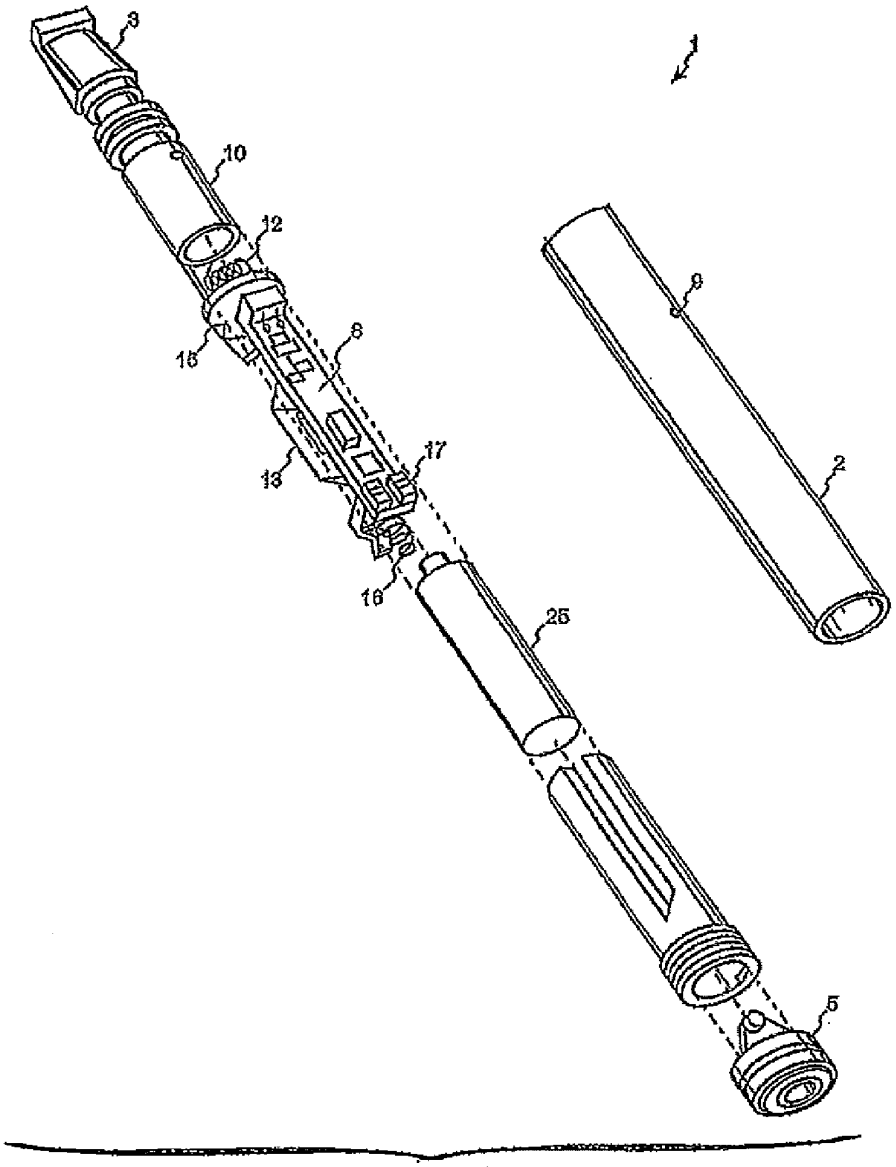



Fig. 6

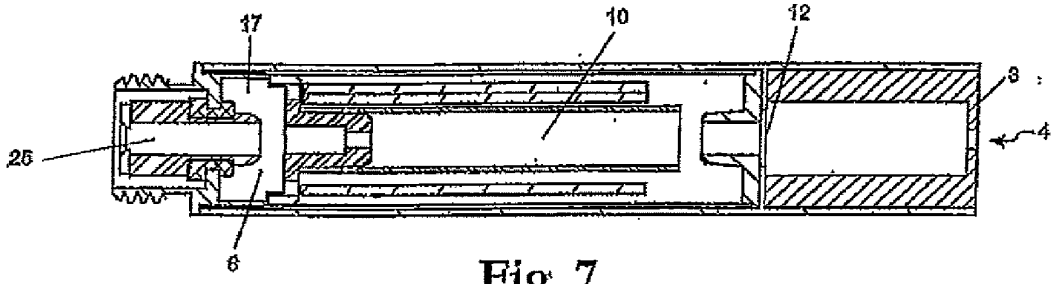



Fig. 7

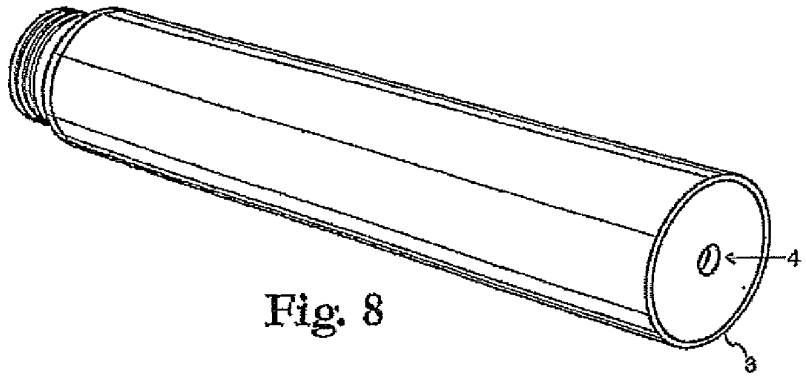



Fig. 8

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/033285

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 15/06 (2013.01)
USPC - 131/273
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)
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USPC - 128/200.14, 202.21; 131/270, 271, 273

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61M 15/06 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2008/0257367 A1 (PATERNO et al) 23 October 2008 (23.10.2008) entire document | 1-20 |
| Y | US 2008/0092912 A1 (ROBINSON et al) 24 April 2008 (24.04.2008) entire document | 1-20 |
| Y | US 3,631,856 A (TAYLOR) 04 January 1972 (04.01.1972) entire document | 1-19 |
| Y | US 2011/0277756 A1 (TERRY et al) 17 November 2011 (17.11.2011) entire document | 6 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 May 2013 | 31 MAY 2013 |
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(54) **Title**: ENHANCED DELIVERY OF NICOTINE, THC, TOBACCO, CANNABIDIOL OR BASE ALKALOID FROM AN ELECTRONIC CIGARETTE OR OTHER VAPOR OR SMOKE PRODUCING DEVICE THROUGH USE OF AN ABSORPTION CONDITIONING UNIT

(57) **Abstract**: A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid includes administering in the oral or nasal cavity an absorption conditioning unit having at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal, and then administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, cannabidiol and a base alkaloid. The absorption conditioning unit may be in a dosage form not containing a drug. The absorption conditioning unit may create a pH in the oral cavity or nasal cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

# ENHANCED DELIVERY OF NICOTINE, THC, TOBACCO, CANNABIDIOL OR BASE ALKALOID FROM AN ELECTRONIC CIGARETTE OR OTHER VAPOR OR SMOKE PRODUCING DEVICE THROUGH USE OF AN ABSORPTION CONDITIONING UNIT

## BACKGROUND

Electronic vapor devices are increasingly popular with consumers. Such devices comprise electronic cigarettes, electronic pipes, electronic hookahs, personal vaporizers and other inhalator embodiments, both electronic and mechanical.

UBS estimates that US e-cigarette sales will reach $500 million by the end of 2012, representing 100% growth from the preceding year (See UBS Tobacco Analyst Nik Modi's May 14, 2012 report entitled "Clearing the Smoke on E-Cigarettes," the entirety of which is incorporated herein by reference). Arguably, the most well-respected tobacco analyst, Bonnie Herzog of Wells Fargo, has gone so far as to suggest in discussing Lorillard: "We remain very encouraged by blu [Lorillard's e-cigarette brand] and see huge upside potential given our belief ecigs could overtake traditional cigarettes in 10 years." See Wells Fargo Lorillard Equity Research dated October 24, 2012, the entirely of which is incorporated herein by reference. British American Tobacco Chief Financial Officer Nicandro Durante stated in an interview with the Financial Times in September 2012 that the size of the market for tobacco alternatives like the e-cigarette could account for as much as 40% of BAT's revenues (which were £15bn in 2011) in 20 years' time. "It will be sizeable in 20 years' time ... it's going to grow," he said.

Despite this rapid sales growth, it is understood that electronic cigarettes fail to deliver a steeply peaked blood plasma delivery of nicotine like the conventional cigarette does.

Still, there are good reasons for using the e-cigarette as compared with cigarettes. The level of toxicants from the electronic cigarette is a small fraction as compared with a conventional cigarette. See, e.g., John H. Lauterbach, Murray Laugesen, James D. Ross, "Suggested protocol for estimation of harmful and potentially harmful constituents in mainstream aerosals generated by electronic delivery systems (ENDS)", SOT, San Francisco, CA, March 10-16, 2012 (http://cigtoxdoc.ehost-

services113.com/sot2012poster1860aspresented.pdf) hereby incorporated by reference).

It is typically considered in the industry that electronic vapor device adoption by consumers would be enhanced by faster, improved nicotine delivery from an electronic vapor device. Thus, there is a need to improve nicotine delivery from an electronic vapor device to its user. There is in addition need for delivery improvement (faster and more efficient) in connection with the use of all vapor devices (mechanical and electronic), of any nicotine, tobacco, or marijuana actives.

## SUMMARY OF THE INVENTION

The present invention relates, *inter alia*, to a method for the administration of nicotine, THC, tobacco, cannabidiol, cocaine or a base alkaloid or combination thereof to a mammal, e.g., a human. The method includes administering an absorption conditioning unit, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capture agent, (c) a penetration agent, and (d) a thermal agent, to the mammal, and then administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, cannabidiol and a base alkaloid.

The present invention also relates to a method for the administration of nicotine, THC, cannabidiol or a base alkaloid to a mammal, including administering an absorption conditioning unit including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration; and then administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

In one aspect of the present invention, an absorption conditioning unit includes a dosage form including at least two agents selected from the group consisting of (a) a buffer agent, (b) a capture agent, (c) a penetration agent, and (d) a thermal agent, wherein said absorption conditioning unit (i) does not have an essentially acidic character, (ii) does not contain a drug, (iii) does not contain THC or other Marijuana derived active ingredient (or any base alkaloid intended as an active ingredient), and (iv) does not contain tobacco except for trace amounts in flavor.

In another aspect of the present invention, an absorption conditioning unit, includes a dosage form including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for the oral or nasal administration of nicotine, THC, cannabidiol, cocaine or any base alkaloid to a mammal, especially to a human, and to a prior administered (and/or contemporaneously administered and/or post administered) absorption conditioning unit useful in such a method.

Nicotine inhalers are known art. For example, Pfizer markets Nicotrol® in the United States. The Nicotrol® inhaler consists of a mouthpiece and a plastic cartridge delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. The cartridge is inserted into the mouthpiece prior to use. Nicotine is released when air is inhaled through the inhaler. No heating element is used – the product relies on the natural propensity of nicotine to sublime at room temperature.

Despite the inhalation-route of administration by the user of Nicotrol®, a buccal route of absorption is described in the Nicotrol® package insert despite the user's inhalation of nicotine from the product (the entire package insert for Nicotrol® is incorporated herein by reference as if fully set forth).

The Nicotrol® package insert describes its method of action: "Most of the nicotine released from the NICOTROL Inhaler is deposited in the mouth. Only a fraction of the dose released, less than 5%, reaches the lower respiratory tract. An intensive inhalation regimen (80 deep inhalations over 20 minutes) releases on the average 4 mg of nicotine content of each cartridge of which about 2 mg is systemically absorbed. Peak plasma concentrations are typically reached within 15 minutes of the end of inhalation.... Absorption of nicotine through the buccal mucosa is relatively slow and the high and rapid rise followed by the decline in nicotine arterial plasma concentrations seen with cigarette smoking are not achieved with the inhaler. After the use of the single inhaler the arterial nicotine concentrations rise slowly to an average of

6 ng/mL in contrast to those of a cigarette, which increase rapidly and reach a mean Cmax of approximately 49 ng/mL within five minutes.... Ad libitum use of the NICOTROL Inhaler typically produces nicotine plasma levels of 6-8 ng/mL, corresponding to about 1/3 of those achieved with cigarette smoking."

The discrepancy between 4 mg of nicotine leaving the cartridge with just 2 mg being absorbed is noted. One source of this discrepancy is that much of the nicotine is not buccally absorbed and is swallowed where nicotine is only poorly absorbed in the GI tract.

Now, the typical cigarette contains less than 2 mg of nicotine (http://www.bigsixsmokes.com/Camel.shtml), yet delivers a far higher peak systemic nicotine plasma concentration (Cmax), far quicker (Tmax), than Nicotrol® (see http://pharmrev.aspetjournals.org/content/ 57/1 / 79/T1.expansion.html which is incorporated by reference). We postulate that the more efficient delivery of nicotine from a cigarette (as compared with the Nicotrol®) is a result of enhanced motility of nicotine occurring in smoke – which results from the burning of a cigarette. This superior motility allows the nicotine to readily reach the intermediate and deep lung where the enormous surface area of the lung promotes rapid absorption (as compared with buccal delivery).

The aerosol composition from a smoked cigarette is described by British American Tobacco at http://www.bat-science.com/groupms/sites/bat_7awfh3.nsf/ vwPagesWebLive/DO7AXGHN?opendocument&SKN=1 (the entirety of which is incorporated by reference, including all links).

Now, the obvious solution to improve nicotine delivery to a human would simply be to smoke a cigarette but for the fact that it is understood that burning tobacco results in carcinogens, and it is not yet known how to effectively filter such carcinogens prior to inhalation. Such filtration is likely not possible although recent BAT sponsored studies suggest that incremental improvements in filtration may be accomplished.

Others, such as Professor Jed Rose have tried to improve nicotine delivery from inhalers by using new nicotine salts (nicotine pyruvate) and thereby obtaining faster nicotine absorption than the Nicotrol® -- though still slower (Tmax) and not as high (Cmax) as a cigarette. See

http://www.eurekalert.org/pub_releases/2010-02/dumc-nsc022210.php, http://tobaccofreeaz.wordpress.com/2011/05/27/new-nicotine-cigarette-gives-rapid-lung-delivery-of-nicotine/ and US Patent Application Publication No. 2012/0006342 A1 ("Tobacco-based aerosol generation system), each of which (together with references therein) is fully incorporated herein by reference as if fully set forth.

While US Patent Application Publication No. 2012/0006342 A1 suggests the use of a gaseous carrier, the poster presentation appears to suggest no additional carrier is used. We believe nicotine pyruvate has enhanced motility that allows the nicotine to more readily reach the lung as compared with the active ingredient of NICOTROL®.

However, Professor Rose's innovation is not directed towards use with existing electronic vapor devices such as an electronic cigarette, and poses its own challenges for commercialization and pharmacokinetic performance.

Now let us discuss the nicotine based electronic cigarette. The effluent vapor of the electronic vapor device like an e-cigarette is heavy and slow moving. Thus, it does not reach the deep lung in substantial part, akin to the NICOTROL® device. The result is pharmacokinetic performance much closer to Nicotrol® than to a cigarette.

Published studies on nicotine update from electronic cigarettes similarly show a substantially lower Cmax and slower Tmax for nicotine delivery than a cigarette does (See e.g. Electronic Cigarettes: Effective Nicotine Delivery After Acute Administration by Andrea Vansickel and Thomas Eissenberg, Nicotine and Tobacco Research Adances Access published February 6, 2012; Clinical Laboratory Assessment of the Abuse Liablity of an Electronic Cigarette" by Andrea Vansickel, Michael Weaver and Thomas Eissenberg submitted 14 October 2011 to the Society for the Study of Addiction, and available online; each of which is specifically incorporated herein by reference).

Now, it has been suggested on electronic cigarette forums (www.e-cigarette-forum.com) to enhance nicotine delivery by chewing a TUMS® antacid by well know e-cigarette blogger "Tropical Bob" but he states that this method does not work ("I concur that e-liquid is NOT alkaline enough. I've

even tried chewing Tums to lower mouth acidity and help absorption. Didn't help and messed up the flavor of the vapor. The only solution is less-acid liquid. This stuff is mostly absorbed by the mouth, according to the Health New Zealand studies, and virtually none is absorbed from the lungs. So get to work, e-liquid makers.") We demonstrate in the examples below why a TUMS® is ineffective. However, Tropical Bob's suggestion to focus on the e-cigarette's liquid composition is misguided.

What is however correct is that nicotine is more readily absorbed across the oral mucosa at a basic pH. The question is how to achieve this, and modifying the pH of the liquid composition in an e-cigarette will not produce substantial results.

It is of course possible to make a less-acidic (or alkaline) liquid for use in a vapor device – however, the delivery of a less-acidic (or alkaline) condensate (i.e. the condensate that forms when the vapor cools in the mouth of the user) is challenging. Simply stated, placing buffer agents in a liquid and then vaporizing them offers little control over the pH of the condensate that forms in the mouth as well as the pH of the saliva in the mouth, which bathes the mucosa and is very important in this process. . If we add NaHCO3 (sodium bicarbonate) to water: HCO3-(aq) + H2O CO32-(aq) + H3O+(aq) Ka = 4.7x10-11; HCO3-(aq) + H2O H2CO3 (aq) + OH-(aq) Kb = 2.3x10-8. The solution will be alkaline. But if we vaporize the water, the vapor would not be 7.0. A complicated reaction is provoked and accelerated by the higher temperatures used to vaporize.

Similarly, it is not practicable to deliver sufficient amounts of capture agents (described below) or penetration enhancers (described below) or thermal agents (described below) via a vapor condensate (or comparable effluent from a non-vapor inhalator).

The present invention seeks to enhance the buccal delivery of nicotine (or Marijuana bioactives of any base alkaloids) from an electronic (or non-electronic) vapor (or other inhalation) device. Because of the nature of vapor effluent, there is a limit to the agents and excipients that may be employed in the composition in the vapor device that will travel with the vapor into the

user's buccal cavity and oral mucosa. Similarly, absorption can be enhanced for the oropharyngial mucosa.

The present invention contemplates a separate "absorption conditioning unit" that is placed in the user's mouth prior to and/or contemporaneously with, the use of the electronic vapor device (or other inhalator). The present invention is not limited to the inhalation of vapor but may also be used with conventionally smoked materials (e.g. a tobacco cigarette or a medical marijuana cigarette) nor is it limited to the oral cavity or the oropharynx and it includes the nasopharnx and the nasal mucosa. The absorption conditioning unit of the present invention will enhance absorption of active ingredients contained in smoke in the oral cavity. Similarly, in the case of base alkaloids that are well absorbed in the GI tract, like marijuana, the swallowing of ph basic compounds (including alkaline saliva produced by the dissolution of the absorption conditioning unit) will create a more basic environment in the GI tract that will favor better GI absorption of the actives in the GI tract (like marijuana).

It may be desirable one or more absorption conditioning units more or less simultaneously, i.e. one in the mouth and one in the nasal cavity, particularly where the user intends to smoke or vaporize. Of course, multiple absorption conditioning units may be used in either cavity at the same time for reasons of dosing and the like, or multiple absorption conditioning units employed in serial fashion.

The absorption conditioning unit is a typically a dosage unit customarily used in the pharmaceutical and/or confection industries. The absorption conditioning unit may comprise any of following non-limitative solid or liquid examples: a tablet, an orally dissolving tablet, a chewable tablet, a multi-layered tablet, a capsule, a liquid-gel, a lozenge, a thin film, a sheet, a slab, a powder, granules, a gummy, a lollipop, a suspension, a toothpaste, a chewing gum or a solution. A solution or suspension may be delivered via a spray or aerosol or like method. However, the absorption conditioning unit will preferably comprise a solid dosage unit. Chewable dosage units are a preferred embodiment for their propensity to spread material around the mouth. Film dosage units are desirable because of small sized and their

ability to be easily co-packaged with the inhalation device. For purposes of this invention, we would like to increase the amount of modified mucosal surface that is exposed to the agents contained in the absorption conditioning unit. Liquids are also good for this purpose but liquids are inevitably costly to distribute. One exception to this, and another preferred embodiment, is a liquid that is constituted by the user whereby dry or concentrated agent-materials are provided to the user who then mixes them with a liquid like for example tap water and used as a an oral gargle and/or oral swishing agent.

The emission from an electronic cigarette is a vapor – formed by heating a liquid (or primarily) liquid composition that is brought into contact with the heating element of the electronic cigarette. Said liquid composition typically comprises a vapor agent that creates a smoke-like vapor when heated (most commonly glycerin or propylene glycol), USP nicotine, water and a flavor system. Said liquid may alternatively comprise a tobacco extract together with a vapor agent (see US 2012/0145170 A1 "METHOD FOR PREPARING TOBACCO EXTRACT FOR ELECTRONIC SMOKING DEVICES" and hereby incorporated by reference). Rate of flow of the liquid composition to the heating element is typically controlled with a wick or sponge like material such that the heating element is not overwhelmed. Drawing on the e-cigarette turns on the heating element (which can be achieved through a variety of ways in including air pressure differentials, a sound-based system and other switches).

The effluent vapor in large part forms a condensate in the mouth – it is too heavy to readily travel to the middle or deep lung. It is understood that nicotine is absorbed across mucosal surfaces (and even the skin) but absorbed very poorly in the GI tract. Thus, to the extent condensate forms in the mouth that is in turn swallowed, the nicotine so swallowed will not reach the blood but rather will be excreted. This explains much of the discrepancy noted above for Nicotrol® whereby 4 mg of nicotine leaves the cartridge and only 2 mg is absorbed. Loss of nicotine to salivary flow is discussed in Fuisz U.S. Patent Application Publication No. 2009/0098192 A1 and Fuisz US Patent No. 8,241,661 discussing salivary flow, the content of each of which is hereby incorporated by reference in its entirety.

The ability of particles to transit to the lung has been considered in the context of pulmonary drug delivery for asthma and related conditions. "Depending on their particle size, inhaled drug particles will deposit in different regions of the lung. Particles <1 μm are likely to reach the peripheral airways and alveoli or be exhaled, particles 1–5 μm will deposit in the large and conducting airways, while particles >5 μm will predominately deposit in the mouth and oropharynx." (Inhaler Technique and Training in People With Chronic Obstructive Pulmonary Disease and Asthma: Effects of Particle Size on Lung Deposition (CME) Toby G.D. Capstick, MRPharmS; Ian J. Clifton, MD). Of course, asthma inhalers typically employ a propellant to further help delivery the particles to the lung. E-cigarettes, personal vaporizers and nicotine inhalers do not have the benefit of propellant but rather rely on the pressure differentials created by the action of the lung itself. While there is some difference of views relative to the particle size of water contained in a water vapor, some argue that droplets in the 2-5 micron range can constitute a vapor. There is not rigid distinction between vapors and gases. Vapors are gases, that is, consist of non-associated molecules. Generally speaking, a gas is considered a vapor when its standard state at that pressure and temperature is a liquid or a solid. So, for example, gaseous water at less than 100° C is usually called a water vapor. The trick, of course, is that the partial pressure of the water vapor is less than one atmosphere. However more importantly, condensation occurs which results in sizes that are too large to operationally do much other than deposit in the mouth, oral pharynx and nasal pharynx.

We teach herein the use of a capture agent, which we define as a material that can (a) temporarily bind condensate and (b) maintain the condensate in contact with mucosal surfaces for a sustained period to enable absorption. This will allow for increased absorption of nicotine (or other actives as discussed herein). By "sustained period," we mean 0.5 to 90 minutes, preferably 3 to 10 minutes.

The capture agent is contained in the absorption conditioning unit where it is released into the mouth (or nasal cavity). Such release is

preferably controlled over a sustained period to ensure availability of the capture agent over a prolonged period.

An additional observation is important here. When a smoker smokes a cigarette, the nicotine uptake in the lung is so rapid and efficient that the loss of nicotine in effluent smoke that is exhaled cannot be seen as a negative aspect of the cigarettes essential pharmacological function. Indeed, the presence of nicotine in such exhaled smoke is has been well studied particularly in research around real or perceived second-hand smoke issues.

There is little doubt that the smoke-like vapor of the e-cigarette (and other vaporizers) is a critical component to consumer acceptance. The inventors are aware of no commercially marketed e-cigarette that does not comprise a vapor agent (glycerin is rapidly becoming the vapor agent of choice). What is interesting here is the dramatic commercial success of the e-cigarette as compared with Nicotrol® -- a product which has a comparable pharmacokinetic performance for the user. The inventors postulate that the cigarette-like experience of the e-cigarette makes the user more relaxed and patient for the slower nicotine delivery of the e-cigarette (as compared with a cigarette). Now, that observation notwithstanding, the e-cigarette would no doubt be even more successful with better nicotine delivery.

In the context of the e-cigarette and its relatively slow nicotine delivery, any nicotine in exhaled vapor is essentially lost nicotine that was actually needed to improve the product (perhaps unlike the cigarette). This is why the capture agent is so important – to capture nicotine and maintain it in buccal or sublingual (or nasal mucosa) contact for effective absorption.

The absorption conditioning unit of the present invention, may, in another embodiment, be used with non-inhalation based products. For example, a user may use an absorption conditioning unit with a conventional smokeless tobacco product, to enhance nicotine absorption for such product (i.e. using an absorption conditioning unit together with a SNUS pouch). Similarly, the absorption conditioning unit may be used with other solid or semi-solid orally consumed products containing base alkaloids, like a marijuana sucker, marijuana brownies, and the like. Marijuana sucker formulations are simple and absorption can be greatly improved upon through

the use of the absorption conditioning unit (for a marijuana sucker recipe, see http://www.medicalmarijuana420depot.com/ cooking%20recipes/ pot%20suckers.htm, which is incorporated by reference).

When the absorption conditioning unit is used with a solid or semi-solid orally consumed product containing a base alkaloid, the capture agent serves to prolong contact of the active ingredient to the mucosa for enhanced absorption prior to swallowing. The use of an absorption conditioning unit with and distinct from a marijuana sucker is a preferred embodiment.

The absorption conditioning unit may further be employed to improve absorption from a liquid compositing containing a base alkaloid. For example, marijuana tinctures are increasingly used through vaporization, and increasingly, through administration to the buccal or oral cavity. The absorption conditioning unit may be used prior to (or simultaneously with, or after) a liquid containing a base alkaloid such as a marijuana tincture to improve absorption therefrom.

While it is possible to use an absorption conditioning unit after the underlying base alkaloid has been delivered, it is a preferred embodiment to use the absorption conditioning unit contemporaneously, or even more preferred, prior to, the administration of the underlying base alkaloid.

Film formers are, without limitation, useful as a capture agent because the condensate (from a vaporizer or smoke) may have solvent activity on condensate, on the one hand, and two, many film agents tend to have muco-adhesive properties that will help maintain the nicotine with mucosal surfaces. Likewise, sugars are useful for this purpose. Other bioadhesive agents may be useful. The film forming polymers described and/or listed in US Patent No. 7,824,588 (the contents of which are incorporated herein by reference) may be useful. The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene

glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

The same capture principle may apply to active that is released from a solid, semi-solid or liquid base alkaloid containing composition, for example, a marijuana sucker that is dissolving in the mouth, or a marijuana tincture delivered to the mouth or administered nasally.

As used herein the phrase "water soluble polymer" and variants thereof refers to a polymer that is at least partially soluble in water, and desirably fully or, predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful as capture agents include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanoes, polyoxalates, poly(.alpha.-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and

sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of .alpha.-amino acids, copolymers of .alpha.-amino acids and caproic acid, copolymers of .alpha.-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338-347 ° F. (170-175° C.); lactide/glycolide 100 L, believed to be 100%, glycolide having a melting point within the range of 437-455°F. (225-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338-347° F. (170-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338-347° F. (170-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

The sugars and preferred combinations of/with sugars described and/or listed at US No. 5,935,600(the contents of which are incorporated herein by reference), may, without limitation, be useful as capture agents. For example, "sugars" are those substances which are based on simple crystalline mono- and di-saccharide structures, i.e., based on $C_5$ and $C_6$ sugar structures. "Sugars" include simple sugars, e.g., glucose, sucrose, maltose, lactose, arabinose, xylose, ribose, fructose, mannose, pentose, galactose sorbose, dextrose, and sugar alcohols, e.g., sorbitol, xylitol, mannitol, pentatol, maltitol, isomalt, sucralose and mixtures of any of these. Maltodextrins may be used Maltodextrins include those mixtures of

carbohydrates resulting from hydrolysis of a saccharide feedstock which are described as solids having a DE of up to and including 65. Maltooligosaccharides produced by selective hydrolysis of cornstarch followed by removal of high and low molecular weight compounds may be used. The general description of maltooligosaccharides as contemplated herein is set forth in U.S. Pat. No. 5,387,431 (the contents of which are incorporated herein by reference). Polydextrose is also contemplated for use as a capture agent. Polydextrose is a non-sucrose, essentially non-nutritive carbohydrate substitute. It can be prepared through polymerization of glucose in the presence of polycarboxylic acid catalyst and polyols. Generally, polydextrose is known to be commercially available in three forms: polydextrose A and polydextrose K, which are powdered solids, and polydextrose N supplied as a 70% solution. Each of these products also contain some low molecular weight components, such as glucose, sorbitol and certain oligomers. Regarding polydextrose, Applicants incorporate herein the contents of U.S. Pat. No. 5,279,849(the contents of which are incorporated herein by reference).

The bioadhesive (and other) agents discussed and/or listed in Pranshu Tangri et al, International Journal of Biopharmaceutics, 2011, 2(1): 36-46 (the contents of which are incorporated herein by reference) may be used as capture agents.

Glycerin and/or propylene glycol solubility is desirable so that the capture agent will better bind the vapor (or smoke) condensate (or some or base alkaloid from a solid, semi solid or liquid composition). Preferably, materials used as capture agents are also water soluble because that they naturally wash out of the mouth without leaving unpleasant residue. The term preferably is pointedly used since non-water soluble polymers will ultimately be washed out of the mouth and swallowed – just less readily.

The absorption conditioning unit may comprise a pH buffer agent (a "buffer agent"). Preferably, the buffer agent is used to raise the pH of the mouth in order to increase nicotine absorption in the buccal cavity in a manner which is based on pka and the Henderson Hasselbach equation. Preferably, the pH of the mouth is increased to 7 to 10, preferably 7.8 to 10, most preferably from 8.5 to 9.5. Preferably, the buffer agent increases the pH of

the oral cavity for a period of ten minutes or more after administration. The same may apply to nasal pH conditioning. As noted above, pH conditioning (or penetration enhancer spillover) of the oral cavity can have a beneficial spillover effect on the GI tract of the user.

Buffering agents may be used to control pH, including without limitation, sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, calcium carbonate, dipotassium phosphate, potassium citrate, sodium phosphate and any other such buffer system. The buffer system may be designed to dynamically control the pH of the product taking into consideration the effect of saliva during use, i.e., a dynamic buffer system. Examples of buffer systems to obtain the preferred pH include dibasic sodium phosphate and monobasic sodium phosphate. Both are FDA accepted buffer materials used and listed in the inactive ingredients list. For example, for a pH of 7, the ratio of monobasic/dibasic can be 4.6/8.6; for a pH of 7.5 the ratio of monobasic/dibasic can be 1.9/11.9; and for a pH of 8.0 the ratio of monobasic/dibasic can be 0.6/13.4. These are mathematically calculated buffer numbers and will need to be adjusted according to the other ingredients added to the formula. They also need to be adjusted for the length of time designed for the dissolution of the dosage unit on the buccal mucosa since saliva can be of a ph of about 6.8 but as it is made in larger amounts in the mouth the ph of saliva can sometimes become more basic. Thus this dynamic buffer range is adjusted in the dosage unit by the amount s of the buffer system since saliva is freshly renewable in the mouth. See Fuisz U.S. Patent Application Publication Nos. 2009/0098192 A1 and US 2011/0318390 A1 discussing dynamic buffering and incorporated herein by reference.

Alkaline buffer agents are easier to work with for sustained release pH control. Acidic agents tend to increase salivary flow which must be addressed in the formulation and practically makes formulation more difficult. The absorption conditioning unit of the present invention will generally not have an acidic character, i.e. lower the pH of water when fully dissolved therein.

The buffer agent may comprise a substantial portion of the absorption conditioning unit, including from1 to 99% by mass of the dosage unit itself.

The absorption conditioning unit may comprise a penetration agent, i.e., a substance that enhances absorption through the mucosa, mucosal coating and epithelium (otherwise known (see U.S. Patent Application Publication No. 2006/0257463 A1, the content of which is incorporated herein by reference) as a "penetration enhancer" or "permeability enhancer"). The penetration agent may comprise but is not limited to polyethylene glycol (PEG), diethylene glycol monoethyl ether (Transcutol), 23-lauryl ether, aprotinin, azone, benzalkomin chloride, cetylperidium chloride, cetylmethylammonium bromide, dextran sulfate, lauric acid, lauric acid/propylene glycol, lysophosphatilcholine, menthol, methoxysalicylate, oleic acid, phosphaidylcholine, polyoxyethylene, polysorbate 80, sodium EDTA, sodium glycholated, sodium glycodeoxycholate, sodium lauryl sulfate, sodium salicylate, sodium taurocholate, sodium taurodeoxycholate, sulfoxides, and various alkyl glycosides or, as described in U.S. Patent Application Publication No. 2006/0257463, bile salts, such as sodium deoxycholate, sodium glycodeoxycholate, sodium taurocholate and sodium glycocholate, surfactants such as sodium lauryl sulfate, polysorbate 80, laureth-9, benzalkonium chloride, cetylpyridinium chloride and polyoxyethylene monoalkyl ethers such as the BRIJ.RTM. and MYRJ.RTM. series, benzoic acids, such as sodium salicylate and methoxy salicylate, fatty acids, such as lauric acid, oleic acid, undecanoic acid and methyl oleate, fatty alcohols, such as octanol and nonanol, laurocapram, the polyols, propylene glycol and glycerin, cyclodextrins, the sulfoxides, such as dimethyl sulfoxide and dodecyl methyl sulfoxide, the terpenes, such as menthol, thymol and limonene, urea, chitosan and other natural and synthetic polymers. Preferably, the penetration agent is a polyol, e.g., polyethylene glycol (PEG), glycerin, maltitol, sorbitol etc. or diethylene glycol monoethyl ether (Transcutol).

Thermal agents may also be employed. Heat increases blood flow which can in turn increase absorption. Physical agents may be employed – for example, in a liquid format the liquid may be pre-heated (like adding agents to water pre-heated for tea). Chemical thermal agents may be employed to provoke an exothermic reaction.

Desirably, the absorption conditioning unit further might, but not necessarily, comprise at least one flavor for more pleasant administration. Some care must go to flavor selection so that the absorption conditioning unit is pleasant yet not disruptive to the flavor delivered by the inhalation device. Tobacco flavor may be desirable as such and not require any other flavor. Appropriate flavors can be sourced from Tobacco Technologies in Eldersburg, Maryland. In many examples, the more neutral the flavor the better so as not to interfere with the flavor of the vapor. Trace amounts of tobacco may present in flavorings, particularly for a tobacco flavored-product.

The absorption conditioning unit may further comprise effervescent agents to effect effervescence to enhance or improve absorption. Care must be taken that the acidic component of most effervescent systems does not interfere with the goal of a basic pH range.

The absorption conditioning unit may be built into the end of an electronic smoking device (or similar non-electronic inhalator, or smoking device) such that the user can remove it either with hands or mouth immediately prior to use. In one embodiment, this can be akin to a cigar smoker "biting off" the end of a cigar, except here the user removes the absorption conditioning unit and retains it in the mouth. It may also be possible to use a flavored liquid that is dispensed, akin to the menthol "crush" systems that are currently sold but adapted for this purpose. It may also be a dissolvable tip which conditions the pH of the saliva.

It is expressly contemplated that the present invention can be used to enhance the delivery of bioactives such nicotine, THC, tobacco, cannabidiol, cocaineor a base alkaloid, or any combination thereof. The present invention can be adapted for use with marijuana/tobacco combinations. Such combinations can involve the vaporization of tobacco and marijuana leaf, or a mixture of extracts from both materials.

The absorption conditioning unit of the present invention may be employed with suitable adaptation (e.g. optimize target buccal pH or target nasal pH) to enhance the absorption of THC (tetrahydrocannabinol), cannabidiols and other active ingredients from cannabis. While the use of marijuana remains controversial, the general trend towards decriminalization

and even legalization is clear. Moreover, the use of medical marijuana is growing rapidly. This takes the form of marijuana leaf, marijuana extract, and marijuana active components that are delivered via approved pharmaceuticals, like GW Pharma's Sativex®, an oral mucosa spray.

The vaporization of marijuana has also become popular but is less visible given the grey market status of marijuana. However, vaporization of marijuana is an increasingly common and accepted form of marijuana use. Indeed, Health Canada's September 2010 document on Marijuana entitled "Information for Health Care Professionals," notes the benefits of vaporization of marijuana as compared with smoking marijuana:

"Vaporization of cannabis has been explored as an alternative to smoking. The advantages of vaporization apparently include the formation of a smaller quantity of toxic by-products such as carbon monoxide, polycyclic aromatic hydrocarbons (PAHs) and tar, as well as a more efficient extraction of THC from the cannabis material (47,48,49,43,50). The subjective effects and plasma concentrations of THC are comparable to those of smoked cannabis with absorption being somewhat faster with the vaporizer (43). The vaporizer is well-tolerated, with no reported adverse effects, and is generally preferred over smoking by most subjects (43). While vaporization is amenable to self-titration (49,43), the proper use of the vaporizer for optimal administration of medicinal cannabis has to be established in more detail (50). The amount and type of cannabis placed in the vaporizer, the vaporizing temperature and duration of vaporization, and the balloon volume are some of the parameters that can affect the delivery of THC (49). Bioequivalence of vaporization compared to smoking has not been established."

The reference to THC absorption being faster with a vaporizer is curious in view of the same document's discussion of buccal and oral routes which show that buccal absorption is relatively slow. This may be explained by the fact that the cited study employed pure THC as opposed to vaporizing marijuana plant material (or an extract therefrom).

"Following a single buccal administration of Sativex® (four sprays of $\Delta^9$-THC 27mg/mL and CBD 25 mg/mL, totaling 10.8mg $\Delta^9$-THC and 10 mg CBD), peak plasma concentrations of both THC and CBD typically occur

within 2-4 h (55). When administered bucally, blood levels of THC and other cannabinoids are lower than those achieved by inhalation of the same dose of smoked cannabis because absorption is slower, redistribution into fatty tissue is rapid and some of the THC undergoes hepatic first-pass metabolism to 11-hydroxy-THC (55)."

"THC can be absorbed orally by ingestion of foods containing cannabis (butters, oils, brownies, cookies), teas prepared from leaves and flowering tops, or through ingestion of capsules containing THC or THC analogues. Absorption from an oral dose of 20 mg THC in a chocolate cookie was described as slow and unreliable (42), with a systemic availability of only 4 to 12% (46). While most subjects displayed peak plasma THC concentrations between 1 to 2 h, some of the 11 subjects in the study only peaked at 6 h and many had more than one peak. Consumption of cannabis-laced brownies containing 2.8% THC was associated with changes in behavior although the effects were slow to appear and variable (51). Peak effects occurred 2.5 to 3.5 h after dosing. Modest changes in pulse and blood pressure were also noted. Tea made from dried cannabis flowering tops (19.1% THCA, 0.6% THC) has been documented, but the bioavailability of THC from such teas is likely to be smaller than that achieved by smoking (52). Only 10-20% of synthetic THC (dronabinol, Marinol®) administered in capsules with sesame oil enters the systemic circulation indicating extensive first-pass metabolism (53). The psychotropic effect or "high" occurs more quickly by the smoking than the oral route, which has been characterized by Iversen (54) as the reason "smoking is the preferred route of cannabis for many people"."

The buccal and/or sublingual use of tinctures is known (See http://patients4medicalmarijuana.wordpress.com/medical-use-of-cannabis-video/marijuana-tincture/, incorporated by reference hereby).

Thus, the dynamic of marijuana vaporization is functionally comparable to tobacco/nicotine. In each case the actives are not effectively delivered to the deep lung but tend to be absorbed buccally. Marijuana is however different in that swallowed condensate is more apt to be absorbed in the GI tract than nicotine.

It is important to note that while the disclosure above discussed electronic vapor devices, it will appreciated that the present invention can equally be employed with non-electronic vapor devices. Electronic – and specifically electrical devices are the most common type of vapor device. However, vapor devices can also be "analog" like for example the butane-fired Ploom® device or the butane fired "click-a-toke." Similarly, vapor can be generated from hookah-like devices powered by hot coals and the like. And, it is possible to have an inhaler – like Nicotrol® -- that does not use any heat source. It should be noted that it is expressly contemplated that the present invention can be used with any inhaler-like device (and not solely with a vapor device). The present invention may also be used with smoking devices (e.g. a marijuana cigarette), or with solid, semi-solid or liquid compositions (e.g. a marijuana sucker or a marijuana tincture).

Because the absorption conditioning unit does not contain tobacco or nicotine, it will generally be exempt from regulation, except where it is part of an approved pharmaceutical product (i.e. a "combination product").

References to nicotine herein include any nicotine salt, nicotine that is naturally or synthetically derived, including from tobacco or any other material.

In addition to nicotine, tobacco and marijuana, derivatives, the present invention (i.e. the absorption conditioning unit) can be readily adapted to assist with the absorption of other bioactive agents generally, and in particular, alkaloids, especially the absorption of inhaled base alkaloids. Preferably, base alkaloids in the form of those with pka of pH 6 or more.

Alkaloids are produced by a large variety of organisms, including bacteria, fungi, plants, and animals, and are part of the group of natural products (also called secondary metabolites). Many alkaloids can be purified from crude extracts by acid-base extraction. Many alkaloids are toxic to other organisms. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals. Examples are the local anesthetic and stimulant cocaine; the psychedelic psilocin; the stimulant caffeine; nicotine; the analgesic morphine; the antibacterial berberine; the anticancer compound vincristine; the antihypertension agent reserpine; the cholinomimeric galatamine; the

spasmolysis agent atropine; the vasodilator vincamine; the anti-arhythmia compound quinidine; the anti-asthma therapeutic ephedrine; and the antimalarial drug quinine. Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly invoke a bitter taste.

Alkaloids are often divided into the following major groups: "True alkaloids", which contain nitrogen in the heterocycle and originate from amino acids. Their characteristic examples are atropine, nicotine, and morphine. This group also includes some alkaloids that besides nitrogen heterocycle contain terpene (e.g., evonine) or peptide fragments (e.g. ergotamine). This group also includes piperidine alkaloids coniine and coniceine although they do not originate from amino acids; "Protoalkaloids", which contain nitrogen and also originate from amino acids. Examples include mescaline, adrenaline and ephedrine; "Polyamine alkaloids" – derivatives of putrescine, spermidine, and spermine; "Peptide and cyclopeptide alkaloids; and "Pseudalkaloids" – alkaloid-like compounds that do not originate from amino acids. This group includes, terpene-like and steroid-like alkaloids, as well as purine-like alkaloids such as caffeine, theobromine and theophylline. Some authors classify as pseudoalkaloids such compounds such as ephedrine and cathinone. Those originate from the amino acid phenylalanine, but acquire their nitrogen atom not from the amino acid but through transamination.

In a preferred aspect of the invention, the absorption conditioning unit does not contain a "drug" as defined hereinafter.

In another preferred aspect of the invention, the absorption conditioning unit does not contain drugs, antigenics, antibodies, tobacco, or cosmaceuticals.

In another preferred aspect of the invention, the absorption conditioning unit does not contain any bioactive agent.

As used herein, the term "bioactive agent" shall mean any pharmaceutical, antigenic, antibody, botanical, tobacco, food, nutraceutical, or cosmaceutical.

While the primary embodiment of the absorption conditioning unit is directed towards, primarily conditioning the oral environment for improved

absorption (and in some cases secondarily conditioning the GI tract), the present invention is expressly contemplated for use to improve absorption via nasal sites. For example, the absorption conditioning unit may comprise a liquid spray or powder that is applied to the nasal cavity prior to the nasal use of a base alkaloid such as but not limited to cocaine.

Some prominent civil libertarians have called for the decriminalization/ legalization of cocaine to follow the current decriminalization/legalization of marijuana. The nasal cavity can be conditioned for enhanced absorption prior to administration of the base alkaloid (e.g. insufflation of cocaine).

For nasal conditioning, the preferred embodiment of the absorption conditioning unit will be a liquid spray, a gel, beads, microcapsules, or a powder that can be deployed in the nasal cavity.

Conditioning the nasal cavity poses some alternative formulation issues than the oral cavity. The relative paucity of salivary secretion as compared with the oral cavity makes things easier in some respects. For example , pH control is more easily effected where there is not a heavy salivary refresh dynamic of new secretion to dilute and lower pH. On the other hand, lack of salivary flow means that dosage units that would dissolve in the oral cavity will not readily dissolve in the nasal cavity. Where a liquid is used, increased viscosity (as compared with water) and increased surface tension (as compared with water) can be used to encourage the liquid absorption conditioning unit to remain at the intended site for sustained effect including without limitation sustained pH buffering. Buffered nasal solutions for nasal irrigation are known (see http://www.sinucleanse.com/images/ parsons-1.pdf, which is fully incorporated by reference), but because the purpose of such liquids is irrigation they are intended to essentially flush out the nasal passages and operate only modestly increased basic pH ranges.

Examples of pharmaceutical bioactive agents include, but are not limited to ace inhibitors, such as Benazepril, Captopril, Enalapril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril and Trandolapril; acne treatments, such as adapalene, azelaic acid, BenzaClin, Benzamycin, Benzoyl Peroxide, clindamycin, Duac, Erythromycin, Glycolic Acid, Isotretinoin, Sulfacetamide with sulfur, Tazarotene and Tretinoin; actinic keratosis, such as declofenac,

fluorouracil; addiction aids, such as buprenorphine, Disulfiram, Naltrexone, Suboxone and varenicline; aldosterone antagonists, such as eplerenone and spironolactone; alpha-1 adrenergic blockers, such as alfuzosin, doxazosin, prazosin, tamsulosin and terazosin; ALS agents, such as riluzole; Alzheimer's Disease medications, such as donepezil, Galantamine, rivastigmine, tacrine and memantine; anesthetics, such as dexmedetomidine, etomidate, ketamine, methohexital, pentobarbital, propofol and thiopental; angiotensin II receptor blockers, such as candesartan, eprosartan mesylate, irbesartan, losartan, olmesartan, telmisartin and valsartan; antacids, such as Aluminum hydroxide, AlOH and magnesium trisilicate; anti-arrhythmics, such as adenosine, amiodarone, Atropine, Bretylium, digoxin-Immune Fab, disopyramide, dofetilide, epinephrine, Esmolol, flecainide, ibutilide, isoproterenol, lidocaine, mexiletine, moricizine, procainamide, propafenone, quinidine, sotalol, tocainide and verapamil; antibiotics, such as Aztreonam, TMP/SMX, Chloramphenicol, Clindamycin, Dapsone, Daptomycin, Ertapenem, Imipenem/cilastatin, Linezolid, Meropenem, Metronidazole, Nitrofurantoin, Quinupristin/Dalfopristin, Rifaximin, Tigecycline, Telithromycin and Tinidazole; anticholinergic acids, such as Dicyclomine, Donnatal, Flavoxate, Glycopyrrolate, Hyoscyamine, Oxybutynin, Propantheline and Tolterodine; anticonvulsants, such as carbamazepine, clonazepam, diazepam, ethosuximide, felbamate, fosphenytoin, gabapentin, levetiracetam, lamotrigine, lorazepam, Oxcarbazepine, Phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate and valproic acid; antidepressants, such as amitriptyline, buproprion, citalopram, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, nefazodone, nortriptyline, nortriptyline, sertraline, trazodone and venlafaxine; anti-diarrheals, such as dephenoxylate+atropine, Imodium and bismuth subsalicylate; anti-emetics, such as Aprepitant, dolasetron, droperidol, granisetron, metoclopramide, ondansetron, prochlorperazine, scopolamine and trimethobenzamide; antifungals, such as Ampho B, Ampho B lipid, anidulafungin , caspofungin, Clotrimazole fluconazole, flucytosine, Griseofulvin, Itraconazole, ketoconazole, Micafungin, nystatin, Posaconazole, terbinafine, voriconazole, butenafine, ciclopirox, clotrimazole, enconazole,

ketoconazole, Miconazole, naftifine, nystatin, oxiconazole terbinafine and Tolnaftate; anti-hepatitis, such as adefovir, entecavir, lamivudine, peginterferon alfa-2a, peginterferon alfa-2b, Rebetron and ribavirin; anti-herpetic agents, such as Acyclovir, famciclovir, valacyclovir, acyclovir, docosanol and penciclovir; antihistamines, such as cetirizine, desloratadine, fexofenadine, loratadine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, hydroxzine and promethazine; anti-hypertension, such as Benazepril & HCTZ, Captopril & HCTZ, Enalapril & HCTZ, Lisinopril & HCTZ, Moexipril & HCTZ, Losartan & HCTZ, Valsartan & HCTZ, Atenolol & chlorthalidone, Bisoprolol & HCTZ, Metoprolol & HCTZ, Nadolol & bendroflumethazide, Propranolol & HCTZ, Timolol & HCTZ, Amlodipine & benazepril, Verapamil & trandolapril, Amiloride & HCTZ, Spironolactone & HCTZ, Triamterene & HCTZ, Clonidine & chlorthalidone, Hydralazine & HCTZ, Methyldopa & HCTZ and Prazosin & polythiazide; anti-hypertensives, such as Aliskiren, Aliskiren, epoprostenol, fenoldopam, hydralazine, minoxidil, nitroprusside, phentolamine and treprostinil; anti-influenza agents, such as amantadine, oseltamivir phosphate, rimantadine and zanamivir; anti-malarials/anti-protozoals/amebicides, such as Atovaquone, Chloroquine, Iodoquinol, Mefloquine, Primaquine, Pyrimethamine, Pyrimethamine -Sulfadoxine and Quinine Sulfate; anti-platelet agents, such as abciximab, dipyridamole/ASA, anagrelide, cilostazol, clopidogrel, dipyridamole, eptifabatide, ticlopidine and tirofiban; antipsychotics, such as aripiprazole, chlorpromazine, Clozapine, fluphenazine, haloperidol, loxapine, molindone, olanzepine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixine, trifluoperazine, ziprasidone and Lithium; antispasmotics, such as Dicyclomine, Donnatal Extentabs, Propantheline, Simethicone, hyoscyamine, Librax, tegaserod and Bellergal-S; anti-tussives/expectorants, such as Benzonatate and guaifenesin; atopic dermatitis medications, such as pimecrolimus and tacrolimus; benzodiazepines and non-benzodiazepine sedatives, such as alprazolam, buspirone, chlordiazepoxide, chlorazepate, clonazepam, diazepam, estazolam, eszcpiclone, flurazepam, lorazepam, midazolam, Oxazepam, ramelteon, temazepam, triazolam, zaleplon and zolpidem; beta blockers, such

as atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, pindolol, propranolol, sotalol and timolol; bile acid sequestrants, such as cholestyramine, colesevelam and colestipol; bisphosphonates, such as alendronate, etidronate, pamidronate, risedronate, tiludronate and Zoledronic acid, Raloxifene and Teriparatide; bladder spasm medications, such as flavoxate,hyoscyamine, darifenacin, oxybutynin, solifenacin, tolterodine and trospium; benign prostatic hypertrophy medications, such as alfuzosin, doxazosin, dutasteride, finasteride, tamsulosin and terazosin; burn preparations, such as mafenide acetate and silver sulfadiazine; calcium channel blockers, such as amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine and nisoldipine; calcium supplements, such as Calcium and Hypocalcemia; cephalosporins, such as Cefadroxil, Cefazolin, Cephradine, Cephalexin, Cefaclor, Cefotetan,Cefoxitin, Cefprozil, Cefuroxime, Cefuroxime, loracarbef, Cefdinir, Cefixime, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime and Cefepime; colony stimulating factors, such as darbepoietin alfa, erythropoietin, filgrastim, oprelvekin, pegfilgrastim and sargramostim; corticosteroids, such as Budesonide, cortisone acetate, dexamethasone, fludrocortisones, hydrocortisone, methylprednisolone and prednisone; corticosteroids Intra-articular, such as Depo-Medrol and Triamcinolone Acetonide; cystitis, such as pentosan polysulfate, Bethanecol and Alum irrigation; decongestants, such as Phenylephrine and Pseudoephedrine; anti-diabetic agents, such as acarbose, Miglitol and metformin, Avandamet.RTM., Glucovance, Metaglip, Metaglip, rosiglitazone, osiglitazone, repaglinide, Chlorpropamide, glimepiride, glyburide, glipizide, Tolazamide, Tolbutamide, Glucagon, extenatide and pramlintide; direct thrombin inhibitors, such as argatroban, Bivalirudin and lepirudin; disease modifying agents, such as adalimumab, anakinra, auranofin, azathioprine, etanercept, hydroxychloroquine, infliximab, leflunomide, methotrexate and sulfasalazine; diuretics, such as Acetazolamide, Amiloride, Amiloride and HCTZ Bendroflumethiazide, Bumetanide, Chlorothiazide, Chlorthalidone, Dichlorphenamide, Eplenerone, Ethacrynic acid, Furosemide, Hydrochlorothiazide, HCTZ/Triampterene, Hydroflumethiazide, Indapamide, Methazolamide, Methyclothiazide,

Methyclothiazide, Metolazone, Polythiazide, Spironolactone, Spironolactone, HCTZ Torsemide, Trichlormethiazide and Triamterene; endocrine agents, such as bromoc cinacalcet cosyntropin, riptine, cabergoline, calcitonin, desmopressin, Leuprolide, octreotide and vasopressin; erectile dysfunction agents, such as Sildenafil, tadalafil, vardenafil; fever medications, such as allopurinol, antihistamines, azathioprine, barbiturates, carbamazepine, cephalosporins, cimetidine, folic acid, hydralazine, hydroxyurea, ibuprofen, isoniazid, methyldopa, nitrofurantoin, penicillins, phenytoin, phenytoin, procainamide, prophylthiouracil, quinidine, streptomycin sulfonamides, sulindac, triamterene and vancomycin; fibrates, such as clofibrate, fenofibrat and gemfibrozil; fluoroquinolones, such as Ciprofloxacin, Gatifloxacin, Levofloxacin, Moxifloxacin, Norfloxacin and Ofloxacin; gastrointestinal agents, such as Alosetron, infliximab, Mesalamine, misoprostol, Neomycin, octreotidev, osalazine, Orlistat, sucralafate, Sulfasalazine and vasopressin; gout treatments, such as allopurinol, colchicine, probenecid, Rasburicase and sulfinpyrazone; H2 receptor blockers, such as cimetidine, famotidine, nizatidine and ranitidine; aAnti-herpetic agents, such as Acyclovir, famciclovir, valacyclovir, acyclovir, docosanol and penciclovir; hypertensive urgency, such as Captopril, Clonidine and Labetalol; hypertensive emergency, such as Enalaprilat, Esmolol, Fenoldopam mesylate, Hydralazine, Labetalol, Nicardipine, Nitroglycerin and Sodium nitroprusside; hemorrhoidal preparations, such as Anusol HC, Anusol Suppository, Dibucaine, pramoxine 1%, Proctofoam-HC and Analpram-HC; inflammatory bowel disease agents, such as balsalazide, budesonide, infliximab, mesalamine, olsalazine and sulfasalazine; Interferon, such as Interferon Alfa-2A, Interferon Alfa-2b, Interferon Alfa-2b and Ribavirin combo Pack, Interferon Alfa-N3, Interferon Beta-1A, Interferon Beta-1B (Betaseron); intermittent claudication, such as cilostazol and pentoxifylline; immunizations, such as Comvax, diphtheria-tetanus toxoid, Hepatitis A vaccine, Hepatitis B vaccine, Influenza vaccine, Fluzone, Lyme disease vaccine, PNEUMOVAX* 23; laxatives, such as Bisacodyl, Cascara, Docusate, Fleet Phospho-Soda, Glycerin, Lacalutose, lubiprostone, Magnesium citrate, Magnesium hydroxide--MOM, Mineral Oil, Pericolace, Psyllium and Senna; low molecular weight heparins, such as

dalteparin, danaparoid, enoxaparin, tinzaparin, fondaparinux; macrolides, such as Azithromycin, Clarithromycin and Erythromycin; magnesium, such as magnesium salt; migraine treatments, such as almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, Cafergot.RTM., Cafergot.RTM., dihydroergotamine and Midrin.RTM.; mouth and lip treatments, such as amlexanox, Benzocaine, carbamide, peroxide, Kenalog in Orabase.RTM., Phenol, chlorhexidine gluconate, clotrimazole, Nystatin, Penciclovir, docosanol, Gelclair, lidocaine viscous, BMX Cocktail, Pilocarpine and Artificial saliva; multiple sclerosis treatments, such as glatiramer, interferon beta-1A and interferon beta-1B; muscle relaxants, such as baclofen, carisprodol, cyclobenzaprine, cyclobenzaprine, Diazepam, Metaxalone, Methocarbamol, Orphenadrine; nasal preparations, such as azelastine, beclomethasone, budesonide, cromolyn, desmopressin acetate, flunisolide, fluticasone, Ipratropium bromide, mometasone, oxymetazoline, phenylephrine, Saline nasal spray, Sumatriptan, triamcinolone and Zolmitriptan; urology treatments, such as Belladonna and opium, flavoxate, hyoscyamine, hyoscyamine, oxybutynin, solifenacin, tolterodine and trospium; neuromuscular blockers, such as Atracurium, Cisatracurium, doxacurium, mivacurium, pancuronium, Rocuronium, Succinylcholine, vecuronium, Mivacurium, Rapacuronium, Rocuronium, Succinylcholine, Atracurium, Cisatracurium, Pancuronium, Vecuronium, Doxacurium, Pipecuronium and Tubocurarine; nitrates, such as Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin ointment, Nitrobid and Nitroglycerin transdermal; NSAID's, such as Arthrotec, diclofenac, Etodolac, indomethacin, Ketorolac, Sulindac, Tolmentin Diflunisal Salsalate Meloxicam, piroxicam, Nabumetone Flurbiprofen, Ibupropen, Ketoprofen, Naproxen, Oxaprozin, celecoxib, Rofecoxib and Valdecoxib; ophthalmic agents, such as, proparacaine, tetracaine, Ciprofloxacin, Erythromycin, Gentamcyin, levofloxacin, levofloxacin, norfloxacin, Ofloxacin, Polysporin.RTM., Polytrim, Sulfacetamide, Tobramycin, Blephamide.RTM., Blephamide.RTM., Maxitrol.RTM., Pred G.RTM. and TobraDex.RTM., Dexamethasone, Fluorometholone, Loteprednol, Prednisone, Rimexolone, azelastine, Cromolyn sodium, emedastine, Epinastine, Ketotifen Fumarate Ophthalmic

Solution 0.025%, Levocabastine, Lodoxamide tromethamine, Naphazoline, Naphcon-A.RTM., nedocromil, Olopatadine, pemirolast, Betaxolol, Betaxolol, Levobunolol, Timolol, Brinzolamide, Dorzolamide, Pilocarpine, bimatoprost, Latanoprost, travoprost, unoprostone, Apraclonidine, Brimonidine, Cosopt.RTM. and Cosopt.RTM., Atropine, Cyclopentolate, Homatropine, Phenylephrine, Phenylephrine, Diclofenac, Flurbiprofen and Ketorolac; ear (otic) preparations, such as Auralgan.RTM., carbamide peroxide, CIPRODEX.RTM., Ciprofloxacin and hydrocortisone, Cortisporin.RTM., Ofloxacin, Triethanolamine and Vosol Otic.RTM.; opiates, such as Codeine Fentanyl Hydrocodone Hydrocodone, Meperidine Methadone, morhphine, xycodone, Propoxyphene, Darvon.RTM., Fioricet, Fiorinal, Soma compound, Tramadol, Anexsia, Darvocet, Darvon Compound, Lorcet, Lortab, Percocet, Percodan, Roxicet, Tylenol with Codeine, Tylox, Vicodin, Wygesic, Buprenorphene, Butorphanol, Dezocine, Nalbuphine, Pentazocine, Nalmefene Naloxone, Suboxone.RTM. and Ziconotide; parkinson's disease treatments, such as amantadine, benztropine, bromocriptine, entacapone, pergolide, pramipexole, ropinirole, selegiline, Sinemet.RTM., tolcapone and trihexyphenidyl; PCA--Patient Controlled Analgesia, such as Fentanyl, Hydromorphone, Meperidine and Morphine; penicillin's, such as Ampicillin, Ampicillin/sulbactam, Amoxicillin, Amoxicillin/Clavulanate, Cloxacillin, Dicloxacillin, Nafcillin, Penicillin G, Penicillin VK, Piperacillin, Piperacillin/Tazobactamm, Ticarcillin, and Ticarcillin/Clavulanate; phosphate supplementation, such as, K-Phos.RTM. Neutral Tablets, K-PHOS.RTM. ORIGINAL, Neutra-Phos.RTM.; potassium supplementation, such as K-LOR, Klor-Con.RTM., Potassium depletion; prostate cancer medications, such as bicalutamide, flutamide, goserelin, leuprolide and nilutamide; proton pump inhibitor's, such as esomeprazole, Lansoprazole, Omeprazole, Pantoprazole and Rabeprazole Sodium; psoriasis medications, such as acitretin, alefacept, Anthralin, Calcipotriene, efalizumab and Tazarotene; renal failure medications, such as Aluminum Hydroxide, Calcium acetate, Calcitriol, Doxercalciferol, Ferric Sodium Gluconate, paricalcitol and sevelamer; pulmonary medications, such as ipratropium, tiotropium, albuterol, bitolterol, levalbuterol, pirbuterol, metaproterenol, formoterol, salmeterol, Advair.RTM.,

Symbicort.RTM., beclomethasone, budesonide, flunisolide, fluticasone, Mometasone furoate, triamcinolone, montelukast Singulair.RTM., zafirlukast, cromolyn sodium, nedocromil, acetylcysteine and aminophylline/theophylline; disease modifying agents, such as adalimumab, anakinra, auranofin, azathioprine, etanercept, hydroxychloroquine, infliximab, leflunomide, methotrexate and sulfasalazine; HMG COA reductase inhibitors, such as Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, Advicor.RTM., Vytorin.RTM. and ezetimibe; stimulants, such as atomoxetine, benzphetamine, Caffeine, dexmethylphenidate, Dextroamphetamine, diethylpropion, Methylphenidate, Modafinil, Pemoline, phendimetrizine, phentermine and sibutramine; tetracyclines such as Doxycycline, Minocycline andTetracycline; thrombolytic agents such as Alteplase; anti-thyroid agents such as methimazole and propylthiouracil; toxicology related medications such as acetylcysteine, Charcoal, deferoxamine, digoxin immune fab, flumazenil, fomepizole, methylene blue, naloxone, sodium polystyrene sulfonate and Sorbitol; anti-mycobacterial agents such as Ethambutol, Isoniazid, Pyrazinamide, rifabutin, Rifamate, Rifampin, Rifapentine and Rifater; topical products such as Alitretinoin, Becaplermin, Calamine, Capsaicin, Doxepin, lidocaine/prilocaine, fluorouracil, Masoprocol, Pimecrolimus, Selenium sulfide and Tacrolimus; topical anti-viral agents such as acyclovir, docosanol, imiquimod, penciclovir, podofilox and podophyllin; topical antibacterials such as bacitracin, metronidazole, mupirocin, bacitracin/neomycin/polymyxin, bacitracin/polymyxin and silver sulfadiazine; topical antifungals such as butenafine, ciclopirox, clotrimazole, econazole, ketoconazole, miconazole, naftifine, nystatin, oxiconazole, terbinafine and tolnaftate; topical anti-parasitic agents such as Crotamiton, Lindane, Permethrin, pyrethrins and piperonyl butoxide; topical burn preparations such as mafenide acetate and silver sulfadiazine; topical corticosteroids such as Aclometasone diproprionate, Desonide, Flucinolone acetonide, Hydrocortisone, Betamethasone dipropionate, betamethasone valerate, clocortolone pivalate, desoximetasone, fluocinolone acetonide, flurandrenolide, fluticasone propionate, Chydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, prednicarbate, triamcinolone,

amcinonide, augmented betamethasone dipropionate, betamethasone dipropionate, desoximetasone, diflorasone diacetate, fluocinolone acetonide, fluocinonide, halcinonide, clobetasol propionate, diflorasone diacetate and halobetasol propionate; urology medications such as pentosan polysulfate, Bethanecol and phenazopyridine; vaginal preparations such as clindamycin, metronidazole, butoconazole, clotrimazole, miconazole, terconazole and tioconazole; vasodilators such as Fenoldopam mesylate, Hydralazine, Nesiritide, Nicardipine, Nitroglycerin, and Sodium Nitroprusside; and vasopressors and inotropes such as Dobutamine, Dopamine, Epinephrine, inamrinone, Milrinone, Norepinephrine, Phenylephrine, and Vasopressin.

Examples of food or nutraceutical bioactive agents include, but are not limited to, constituents in foods or dietary supplements that are responsible for changes in health status, such as components of plants, especially fruits and vegetables, e.g., soy which contains isoflavones and phytoestrogens, tomatoes which contain lycopene that may have anticancer properties, berries such as blueberries and raspberries which contain flavonoids like anthocyanins that may act as antioxidants, green tea which contains epigallocatechin gallate (EGCG) that may have anticancer properties, resveratrol from red grape products as an antioxidant, soluble dietary fiber products, such as psyllium seed husk for reducing hypercholesterolemia, broccoli (sulforaphane) as a cancer preventative, and soy or clover (isoflavonoids) to improve arterial health.

Examples of antigen bioactive agents include, but are not limited to exogenous antigens, endogenous antigens, autoantigens and tumor antigens. Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection. By endocytosis or phagocytosis, these antigens are taken into the antigen-presenting cells (APCs) and processed into fragments. APCs then present the fragments to T helper cells ($CD4^+$) by the use of class II histocompatibility molecules on their surface. Some T cells are specific for the peptide:MHC complex. They become activated and start to secrete cytokines. Cytokines are substances that can activate cytotoxic T lymphocytes (CTL), antibody-secreting B cells, macrophages, and other particles. Endogenous antigens are antigens that

have been generated within the cell, as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. The fragments are then presented on the cell surface in the complex with MHC class I molecules. If activated cytotoxic $CD8^+$T cells recognize them, the T cells begin to secrete various toxins that cause the lysis or apoptosis of the infected cell. In order to keep the cytotoxic cells from killing cells just for presenting self-proteins, self-reactive T cells are deleted from the repertoire as a result of tolerance (also known as negative selection). They include xenogenic (heterologous), autologous and idiotypic or allogenic (homologous) antigens. An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease. These antigens should, under normal conditions, not be the target of the immune system, but, due to mainly genetic and environmental factors, the normal immunological tolerance for such an antigen has been lost in these patients. Tumor antigens or Neoantigens are those antigens that are presented by MHC I or MHC II molecules on the surface of tumor cells. These antigens can sometimes be presented by tumor cells and never by the normal ones. In this case, they are called tumor-specific antigens (TSAs) and, in general, result from a tumor-specific mutation. More common are antigens that are presented by tumor cells and normal cells, and they are called tumor-associated antigens (TAAs). Cytotoxic T lymphocytes that recognize these antigens may be able to destroy the tumor cells before they proliferate or metastasize. Tumor antigens can also be on the surface of the tumor in the form of, for example, a mutated receptor, in which case they will be recognized by B cells.

Examples of botanical bioactive agents include, but are not limited to PMI-004 (advanced botanical formulation for type II diabetes that represents a multi-mechanism bioactive that: 1) in adipocytes increases adiponectin secretion, 2) in the liver lowers PEPCK expression, and 3) in muscle cells increases cellular signaling through the insulin receptor pathway, increasing glucose uptake, glycogen synthase, and glycogen accumulation), PMI-005 (botanical bioactive, derived from a common vegetable, that inhibits gene expression of a variety of pro-inflammatory cytokines (including a-TNF, i-NOS,

IL-1b, and COX-2) that are currently undergoing a human clinical trial in osteoarthritis may also may have utility in the management of severe/life threatening inflammatory conditions, such as in the management of the septic patient), PMI-006 (botanical bioactive, derived from a spice, that inhibits a range of inflammation-related enzymes (including a-TNF and COX-2) and also possesses range of novel bioactivities related to both lipid and glucose metabolism (RXR receptors)), PMI-007 (a powerful, centrally acting, botanical appetite suppressor which acts via a unique central pathway in the nutrient-sensing hypothalamic neurons by increasing ATP content/production, possesses potent anorectic activity without typical CNS appetite suppressor side effects and pre-clinical data for which has shown that the agent suppresses both appetite and reduces weight in animal models, while there is supporting clinical evidence of human efficacy), PMI-008 (botanical bioactive, derived from an agricultural waste processing stream, that blocks fat accumulation/absorption and promotes weight loss via interaction with a variety of lipases including PL, LPL, and HSL), and PMI-016 (a powerful, plant-derived anabolic/ergogenic agent, with no androgenic side effects; could be used in a range of human muscle wasting disorders, including those associated with both cancer and AIDS, as well as general aging (sarcopenia); has been shown to induce protein synthesis in muscle cells (similar to IGF) and promote a reduction in protein degradation, while it has also been shown to increase growth hormone gene transcription and decrease in ubiquitin protein ligase gene transcription; and shows no binding to testosterone receptor in contrast to anabolic steroids). Examples of botanical bioactive agents also include tobacco and all tobacco extracts, as well as nicotine itself.

In the present application, we define "drug" as it is defined in The Food, Drug and Cosmetic Act, which defines a drug as follows. "The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles

intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement." The definitions contained in the Food, Drug and Cosmetic Act as amended and in effect from time to time are hereby incorporated by reference as if fully set forth herein.

Typical confection formulations are not suitable in connection with the present invention. Foremost, confection formulations are typically acidic to provoke additional salivary response. This is good for a juicy candy but is the opposite pH direction to promote nicotine absorption.

The absorption conditioning unit of the present invention can be packaged and sold in a kit together with vapor devices and vapor compositions (or smoking devices). Vapor compositions can be any form of nicotine, tobacco, marijuana or base alkaloid suitable for vaporization. The vapor device can be components useful for doing so -- as simple as a candle or other basic heat source, conventional e-cigarette components, or other personal vaporizer.

The absorption conditioning unit can be adapted for aural and ophthalmic use, i.e. to enhance absorption of base alkaloids to the ear or eye.

The advantageous results of the present invention are evident from the following examples.

Example A (Soft Lozenge)

A soft lozenge was made comprising 300 mg of sodium bicarbonate together with carbowax sentry PEG 1450. The resulting lozenge weighted approximately one gram, had harmless taste and was easily chewable.

The lozenge of this example was provided to a healthy female volunteer, and the pH of her saliva was measured at intervals over a period of ten minutes.

The t0 saliva pH was 6.8; t1 was 8.3; t3 was 8.3; t5 was 8.3 and t10 was 8.1.

For this and the other examples, pH measurements were taken using a Horiba compact portable meter.

Example B (Liquid and Nicotine Delivery)

A healthy male volunteer experienced with nicotine placed approximately 400 mg of sodium bicarbonate in a hot tea cup, and stirred the liquid.

The volunteer took several strong draws on a commercially available Nicotrol® inhaler (10 mg/cartridge, marketed by Pfizer). The volunteer noted a mild throat burn sensation – attributable to nicotine absorption.

The volunteer then took three sips of the hot beverage, and used the same Nicotrol® inhaler again. The volunteer noted a burn sensation throughout the mouth including the roof of the mouth. The user noted the sensation was comparable to the throat sensation. The user felt the nicotine delivery was much stronger.

The same health male volunteer repeated the same experiment this time, except that a tobacco-based e-cigarette from Discreet®. The volunteer noted a similar improvement in nicotine delivery.

This same experiment was repeated with room temperature water (and Nicotrol®) While still being highly effective, it was observed that the heated water seemed to provoke stronger nicotine absorption which may be attributed to thermal effects.

Example C (Liquid)

A liquid was prepared by adding the following ingredients in the following order: Sodium bicarbonate ($NaHCO_3$) 3.35 g; tablet salt 0.315 g; tap water 16.11 g; and glycerin 11.38 g of glycerin.

The liquid of this example was provided to a healthy female volunteer (one ½ teaspoon was swirled in the mouth without swallowing), and the pH of her saliva was measured at intervals over a period of ten minutes.

The T0 pH was 6.5; T1 was 8.5; T3 was 8.7; T4 was 8.2; T8 was 7.5 and T10 was 7.6.

Example D (Liquid)

Example D employed the same ingredients as Example C but they were mixed in a different order. Glycerin was added first, then solids, mixed together and then water added. The solution was mixed and ½ teaspoon swirled in the mouth without swallowing, and the pH of her saliva was measured at intervals over a period of ten minutes.

The T0 pH was 6.5; T1 was 8.4; T2 was 8.5; T3 was 7.9; T5 was 7.9; T7 was 7.5 and T10 was 7.3.

Example E (Non Aqueous Liquid)

This example used the same ingredients as the preceding Examples C and D but eliminated water. A solution was made with three grams of sodium bicarbonate, 6 grams of glycerin and no water. To test the solution, a health female volunteer swished it in the mouth and expectorated.

pH was measured over ten minutes with the following results.

T1 was 8.2; T2 was 8.7; T3 was 8.6; T4 was 8.6; T5 was 8.6; T7 was 8.0 and T10 was 7.2.

Example F (Propylene Glycol)

The following formulation as made: 3 grams glycerin; 1 gram propylene glycol; and 1.5 grams sodium bicarbonate. The solution was mixed and ½ teaspoon was swirled in mouth without swallowing.

T0 pH was 6.5 and T1 as 7.2. Because of disagreeable taste, the test was ended after T1 timepoint.

Example G (Xantham)

Xantham was selected as a capture agent in view of its mucoadhesive properties. As an additional benefit it is relatively insensitive to pH.

Prepared a high viscosity gum by dispersing xantham in glycerin first and then introducing the xantham/glycerin blend to water to hydrate. The composition was 60 ml glyverin, 120 ml water and 1 gram modified xantham. All components were mixed at room temperature yielding a consistent viscosity. One drop 100% pure wintergreen essential oil was added.

To test the xantham composition orally, xantham/glycerin/water gel were blended with baking soda by volume at 2:1 liquid/powder. A ½ teaspoon was taken orally, without swallowing and swirled in mouth for

several seconds. The following pH measurements were taken over a ten minute period.

T0 was 6.5; T1 was 8.4; T2 was 8.4; T3 was 8.6.; T4 was 8.4; T5 was 8.4; T6 was 8.4; T7 was 8.4; T8 was 8.4; T9 was 8.1 and T10 was 8.2.

The experiment was repeated by the same volunteer after thirty minutes and several mouth rinses to demonstrate reproducibility.

T0 was 6.6; T1 was 8.1; T2 was 8.3; T3 was 8.3; T4 was 8.5; T5 was 8.5; T6 was 8.5; T7 was 8.4; T8 was 8.3; T9 was 8.3 and T10 was 8.1.

Xantham seems to have delayed the release of the sodium bicarbonate increasing the timescale for pH>8.0. This suggests a film delivery of sodium bicarbonate.

Example H (Listerine® Film)

Sandwich pouches of Listerine® film as a capture agent with 200 mg of sodium bicarbonate were made and tested.

As a baseline, pH was measured over a ten minute period with a Listerine® film only.

T0 was 6.2; T1 was 6.3; T2 was 6.6; T8 was 6.7 and T10 was 6.5.

Listerine® film pouch with 0.2g sodium bicarbonate was tested by a healthy female volunteer (115 lbs).

T0 was 6.5; T1 was 8.5; T3 was 8.7; T5 was 8.7; T8 was 8.5 and T10 was 8.5.

The product was pleasant to the taste.

The sodium bicarbonate was reduced to 0.1 grams and used by second tester (180 lb male).

The pH results over six minutes were as follows.

T0 was 6.5; T1 was 8.0; T2 was 8.2; T4 was 8.0 and T6 was 7.5.

The experiment was repeated with a the same 115 lb female as tester and 0.2 grams of sodium bicarbonate in a single Listerine® film (the single film was wrapped around the sodium bicarbonate). The pH results over ten minutes were was follows.

T0 was 6.2; T1 was 8.0; T2 was 8.7; T3 was 8.7; T5 was 8.7 and T10 was 8.4.

The process was repeated for the 115lb female with the same formulation (i.e., 0.2 grams baking soda in a single Listerine® film). The pH results over ten minutes were as follows:

T0 was 6.2; T1 was 8.0; T2 was 8.7; T3 was 8.7; T5 was 8.6; and T10 was 8.2.

Thus, results appear to be dependent on subject weight. We then made 0.3 gram sodium bicarbonate/2 Listerine® film pouches for the 180 lb male.

The pH results over ten minutes were as follows.

T0 was at 6.4; T1 was at 8.1; T2 was at 8.6; T3 was at 8.6; T4 was at 8.4; T7 was at 8.4; T9 was at 8.1 and T10 was at 7.7.

Thus the male subjected required 0.3 grams for 180 lbs of body mass as compared with 0.2 grams for 115 lbs.

Example I

In considering acid/base for $CO_2$ generation in the mouth, we considered two commercial products were considered – Alka Seltzer® (anhydrous citric acid) and Briosch® (tartaric acid).

We added Alka Seltzer® Original, two tabs, to a 200 ml bottle of water and measured pH over give minutes.

T0 was 7.35; T1 was 6.23; T2 was 6.35; T4 was 6.14 and T5 was 6.57.

Briosch® was used with 200 ml of water at the recommended dosage and the pH was measured over ten minutes as follows.

TO was 6.81; T(10s) was 4.41; T(30s) was 4.95; T1 was 5.45; T4 was 5.47; T6 was 5.52 and T10 was 5.52.

The Briosch® was more acidic than the Alka Seltzer®.

Next a dry powder blend of 1:2 citric acid/sodium bicarbonate blend was tested orally by our 115 lb female volunteer. pH was measured as follows.

T0 was at 6.4; t(30s) was at 2.9; T1 was at 3.8; T2 was at 5.4; T3 was at 6.5 and T4 was at 6.5. While a very low initial pH was achieved, washout was very rapid and the mix generated a high volume of saliva.

Example J (Other Commercial Products including TUMS®).

Several commercial products were tested using pH papers and a simple procedure as follows. First, rinse mouth with water. Second, wait for 1 minute. Third, take pH of saliva. Fourth, put tablet in mouth for one minute and discard it. Fifth, measure pH as a function of time.

With Tums®, pH was normal at one minute and the test was discontinued. With CVS® Chewable Antacid tablets (childrens) (testing two tabs), pH at one minute was 7.

Example K (Capture of Condensate Using a Polymer)

Two squares were cut of identical surface area (1 by 1 inch) – one from paper and one from an HPC-extruded film sourced from Fuisz LLC of Miami, Florida (containing approximately 2/3's hpc by weight). The two squares were weighted, and then were held above a steaming cup of tap water for approximately forty-five seconds. After thirty seconds the samples were weighed again, demonstrating that HPC film captured approximately 20 mg of water whereas the paper captured just 5 mg.

Example L (Soft Chew)

A soft chew was prepared with the following composition: 6 grams of sodium bicarbonate (29%); 11 grams of Carbowax 1450 (54%); 1 gram of HPMC (5%); 1 gram of powdered sugar (5%); 1 gram of glycerin (5%); 0.5 ml mint extract (2%); and 1 drop of red food coloring.

The resulting soft chew was tested together with Nicotrol® by a healthy volunteer and found to be quite effective for improving nicotine delivery.

Example M (Gummy Preparation))

A gummy was prepared with the following composition: 6 grams of sodium bicarbonate (14%); 20 grams of glycerin (47%); 12 grams of water (28%); 4 grams of unflavored gelatin (9%); 1 g of corn syrup (2%) and 1 drop of red food coloring.

Example N (Gummy with Marijuana Cigarette)

The gummy of example M was used by a healthy male volunteer while smoking a marijuana cigarette. The user reported feeling "high" much faster than normal, and characterized the experience as like using marijuana "at volume 10."

Example O (Gummy with Marijuana Vaporizer)

The gummy of example M was used by a healthy male volunteer while vaporizing marijuana. The user reported more rapid and powerful effects from the marijuana as compared with his typical experience when vaporizing marijuana.

Example P (Gummy with solid tobacco composition/SNUS)

The gummy of example M was used by a health male volunteer while using a pouch of Marlboro® SNUS. The user placed the gummy in the cheek on the same side of the mouth as the SNUS pouch. The user waited several hours and repeated the use of the Marlboro® SNUS pouch. The user perceived better nicotine absorption when the SNUS pouch was used together with gummy of example M.

Example Q (Nasal Absorption Conditioning Unit)

The purpose of this example was to provide an absorption conditioning unit for nasal use, including a buffer agent, a capturing agent and a penetration agent. Additionally, we intended to use increased viscosity to better retain the absorption conditioning unit in the nasal cavity to thereby sustain the conditioning effect.

Our premise was that the nasal cavity is less efficient than the oral cavity in pH maintenance and the best route for a buffer agent would likely be an alkaline pH buffer solution. We considered two compounds of choice: sodium carbonate ($Na_2CO_3$) and sodium bicarbonate ($NaHCO_3$).

The bicarbonate buffer is a well know physiological buffer. The carbonate/bicarbonate volume ratio can be adjusted to produce buffers in the pH range shown in the following table:

Table 1: Sodium Carbonate/Sodium Bicarbonate Buffer Compositions and pH

| pH | | x ml 0.1M-$Na_2CO_3$ | y ml 0.1M-$NaHCO_3$ |
|---|---|---|---|
| 20 °C | 37 °C | | |
| 9.2 | 8.8 | 10 | 90 |
| 9.4 | 9.1 | 20 | 80 |
| **9.5** | **9.4** | **30** | **70** |
| 9.8 | 9.5 | 40 | 60 |
| **9.9** | **9.7** | **50** | **50** |
| 10.1 | 9.9 | 60 | 40 |
| 10.3 | 10.1 | 70 | 30 |
| 10.5 | 10.3 | 80 | 20 |
| 10.8 | 10.6 | 90 | 10 |

$Na_2CO_3 \cdot 10H_2O$, $M_{wt}$ 286.2; 0.1M-solution contains 28.62 g/l. $NaHCO_3$, $M_{wt}$ 84.0; 0.1M-solution contains 8.40 g/l. x ml 0.1M-$Na_2CO_3$ and y ml 0.1M-$NaHCO_3$ mixed.

The pH values are listed at both 20 and 37°C based on .1M solutions of each compound. Based on these results, we selected the 30-70 ratio and 50-50 ratio for initial trials for the nasal spray since they represented the upper range of pH and likely to be the most difficult to thicken effectively.

Our first problem was the actual measurement of nasal pH for pre- and post- alkaline nasal spray administration. We could not generate enough volume for repeatable measurements under any circumstances. Best approach was to adopt the criteria used in US Patent 6,187,332 (EP 1,183,009) (each of which is hereby incorporated by reference in the entirety) for simulating conditions of a runny nose: "In this test a given volume of the preparation is mixed at room temperature with three times that volume of Dulbecco's phosphate buffered saline (pH 7.4)(sold by Fisher Scientific--currently Pittsburgh, Pa.). The pH of the resulting solution is tested and the test is passed if the resulting solution has a pH below 6.0. "

Our pH criterion is different but the approach is considered useful. A Dulbecco phosphate buffer saline solution (DPBS) was purchased and used for all compositions at the 1X, 2X and 3X dilution. A typical composition for DPBS is provided below:

Dulbecco's phosphate-buffered saline (Dulbecco's PBS): 2.7 mM KCl; 1.5 mM $KH_2PO_4$; 136.9 mM NaCl; and 8.9 mM $Na_2HPO_4 \cdot 7H_2O$

The pH of DBPS measured at 22°C to be 7.0. Experimental solutions are summarized below:

Table 2: Experimental buffer solution compositions and pH values at 22-23°C

| $Na_2CO_3$ | $NaHCO_3$ | $Na_2CO_3/NaHCO_3$ | 0X DPBS | 1X DPBS | 2X DPBS | 3X DPBS | 2% MC | 1% HPMC |
|---|---|---|---|---|---|---|---|---|
| .1M | | | 11.5 | 10.9 | 10.8 | 10.6 | | |
| .1M | | | 11.3 | 11.1 | 11.1 | 11.1 | | |
| | .1M* | | 8.1 | 7.9 | 7.5 | 7.5 | | |
| | .1M* | | 8.1 | 7.7 | 7.6 | 7.6 | | |
| | .1M** | | 8.1 | 7.7 | 7.5 | 7.5 | | |
| | | 10/90 | 9.4 | 9.4 | 9.4 | 9.4 | | |
| | | 30/70 | 9.9 | 9.8 | 9.7 | 9.8 | | |
| | | 30/80 | 9.5 | 9.5 | 9.4 | 9.4 | | |
| | | 30/70 | 9.9 | 9.8 | 9.8 | 9.8 | X | |
| | | 30/70 | 9.9 | 9.8 | 9.8 | 9.8 | | X |
| | | 50/50 | 10.0 | 10.0 | 10.0 | 10.0 | | |
| | | 50/50 | 10.0 | 10.0 | 10.0 | 10.0 | | |

Sodium bicarbonate was sourced from Church and Dwight (Arm and Hammer); Sodium Carbonate was sourced from Fisher BioReagents.

For the desired alkalinity, sodium bicarbonate will be insufficient and a proportion of sodium carbonate will be needed to raise the pH of the nasal spray.

We briefly reviewed the technical and patent literature and looked at the compositions of OTC nasal wash/sprays and purchased several products to evaluate.

Composition of Shop-Rite Saline Nasal Spray (1.5 fl oz (44 ml): Active: .65% Sodium Chloride Inactives: Benzalkonium Chloride, Disodium Phosphate, Phenylcarbinol, Monosodium Phosphate, Water

This product had a Poor quality sprayer and spray pattern, and very poor dose control per spray.

pH of the product: 7.2 (22°C) (Lot 3044 Exp 02/16) (1X pH = 7.2) (2X pH = 7.1) (3X pH = 7.1).

Repeated measurements with identical results: 3X pH = 7.1.

Second product evaluated is NeilMed Saline Spray Nasal Wash for sinus and cold relief. Ingredients are listed as UPS Grade Water, USP Sodium Chloride (.9 mg/ml), USP Sodium Bicarbonate (0.5 to 1.0 mg/ml) to neutralize pH. Three spray tips are included for large volume rinse tip, medium stream tip and ultra gentle mist tip. Nasal wash in packaged in a aerosol container.

pH of the product: 7.7 (22°C) (Lot NM452 Exp2016-03) (1X pH = 7.0) (2X pH = 7.0) (3X pH = 7.0). We repeated measurements with identical results: 3X pH = 7.0.

Both products appear to neutralize pH – as cited on their labels. They are neutral pH nasal sprays and washes.

Began preparation of alkaline sodium carbonate and sodium bicarbonate buffers as potential nasal sprays.

50ml $Na_2CO_3$/50ml $Na_2HCO_3$): .1M carbonate/bicarbonate buffer – pH = 10.0 (25°C)

Results of 1X, 2X and 2X DPBS buffer test: (1x pH = 10.0) (2x pH = 10.0) (3x pH = 10.0).

This was a very nice result. Maintains pH with dilution (DPBS) simulating nasal discharge. Repeated with new solutions. 3X dilution pH = 10.0.

Sodium carbonate solution: .1M, pH = 11.5 (25°C) tested in DPBS buffer test: (1X pH = 10.9) (2x pH = 10.8) (3x pH = 10.6).

With a 30/70 volume ratio of carbonate/bicarbonate, pH measured to be 9.9 (1x pH = 9.8) (2x pH = 9.7))(3x pH = 9.8). This works well to maintaining pH.

Took the above buffer and added 10ml more of the .1M sodium bicarbonate solution to reduce buffer pH. Measured pH to be 9.5. Diluted now in buffer power test with DPBS: (1x pH = 9.5) (2x pH = 9.4) (3x pH = 9.4).

We prepared additional buffers with 30/70 carbonate/bicarbonate – with objective of thickening with methyl cellulose, HPMC with and without added PG.

New Solutions: .1M Sodium Carbonate – pH 11.3, .1M Sodium Bicarbonate – pH = 8.1

Buffer at 30/70 volume ratio (Carbonate/Bicarbonate) pH = 9.9.

We prepared 2% Methyl Cellulose (Acros Organics), .5% Propylene Glycol, 97.5% Buffer solution to increase viscosity. Measured viscosity in parallel plates in the shear rate range of 0-25 $s^{-1}$ and solution is Newtonian with viscosity of 140 mPa.s or cps at 24°C.

Sample is aerated from the stirring bar but clears upon standing to a slightly cloudy fluid.

We prepared 1% HPMC (Dow F50), 1% PG and 98% Buffer (pH9.9) with good thickening and clear solution. Measured viscosity in parallel plates in the shear rate range of 0-50 $s^{-1}$ and solution is Newtonian with viscosity of 8-10 mPa.s or cps at 24°C.

Completed buffer power test for the two thickened solutions to be sure that the pH was maintained in dilution with DPBS. Results are provided below.

2% methyl cellulose thickened buffer: (0X pH = 9.9) (1X pH = 9.8) (2X pH = 9.8)(3X pH = 9.8).

1% HPMC thickened buffer: (0X pH = 9.9) (1X pH = 9.8) (2X pH = 9.8) (3X pH = 9.8).

This showed no change In buffer capacity with thickeners or enhancers or capture agents..

Prepared 10/90 volume ratio buffer of sodium carbonate/sodium bicarbonate – pH 9.4. Worked through buffer power test: (1X pH = 9.4) (2X pH = 9.4) (3X pH = 9.4). We had good results at this level.

Made an additional sodium bicarbonate solution, approximately .1M solution, pH = 8.1.

Ran through buffer tests alone without carbonate: (1X pH = 7.9) (2X pH = 7.5) (3X pH = 7.5).

Repeated with one more solution of sodium bicarbonate, , .1M solution, pH = 8.1. (1X pH = 7.7)(2X pH = 7.5) (3X pH = 7.5).

These experiments are summarized in Table 2.

We Claim:

1. A method for the administration of nicotine, THC, cannabidiol or a base alkaloid to a mammal, comprising:

administering an absorption conditioning unit in the oral or nasal cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal; and

administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

2. The method according to claim 1, wherein the absorption conditioning unit does not contain a bioactive.

3. The method according to claim 1, wherein the absorption conditioning unit does not contain a drug.

4. The method according to claim 3, wherein the absorption conditioning unit does not contain an acid.

5. The method according to claim 1, wherein the absorption conditioning unit does not contain an acid.

6. The method according to claim 1, wherein the absorption conditioning unit includes at least the buffer agent.

7. The method according to claim 1, wherein the absorption conditioning unit includes at least the capturing agent, and the capturing agent has mucoadhesive properties.

8. The method according to claim 1, wherein the bioactive agent is a base alkaloid comprising cocaine.

9. A method for the administration of nicotine, THC, cannabidiol, cocaine or abase alkaloid to a mammal, comprising:

administering an absorption conditioning unit including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration; and

administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

10. The method according to claim 9, wherein the absorption conditioning unit does not contain a bioactive.

11. The method according to claim 9, wherein the absorption conditioning unit does not contain an acid.

12. The method according to claim 9, wherein the absorption conditioning unit does not contain a drug.

13. The method according to claim 9, wherein the absorption conditioning unit includes at least a buffer agent.

14. The method according to claim 9, wherein the absorption conditioning unit includes at least a capturing agent having mucoadhesive properties.

15. The method according to claim 9, wherein the bioactive agent is a base alkaloid comprising cocaine.

16. An absorption conditioning unit, comprising a dosage form including at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, wherein said absorption conditioning unit (i) does not have an essentially acidic character, (ii) does not contain a drug, (iii) does not contain THC or other Marijuana derived active ingredient, and (iv) does not contain tobacco except for trace amounts in flavor.

17. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit does not contain an acid.

18. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit includes at least the buffer agent.

19. The absorption conditioning unit according to claim 18, wherein the buffer agent is configured to create a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration

20. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit includes at least the capturing agent, and the capturing agent has mucoadhesive properties.

21. An absorption conditioning unit, comprising a dosage form including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

22. The absorption conditioning unit according to claim 21, wherein the absorption conditioning unit includes at least a capturing agent.

23. The absorption conditioning unit according to claim 22, wherein the capturing agent has mucoadhesive properties.

24. A method for the administration of nicotine, THC, cannabidiol, or base alkaloid to a mammal, comprising:

administering an absorption conditioning unit in the nasal cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal; and

separately administering a bioactive agent in the nasal cavity selected from the group consisting of nicotine, THC, tobacco, cannabidiol, and a base alkaloid.

25. The method according to claim 24, wherein the bioactive agent is a base alkaloid comprising cocaine.

26. A method for the administration of nicotine, THC, cannabidiol or a base alkaloid to a mammal, comprising:

administering an absorption conditioning unit in the oral cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal; and

separately administering a bioactive agent selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid, where such bioactive agent is contained in a solid, semi-solid or liquid based dosage form.

27. The method according to claim 26, wherein the bioactive agent is a base alkaloid comprising cocaine.

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(54) Title: METHOD OF ADMINISTERING NICOTINE, THC, TOBACCO, CANNABIDIOL OR BASE ALKALOID AND ABSORPTION CONDITIONING UNIT

(57) Abstract: A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid includes administering in the oral or nasal cavity an absorption conditioning unit having at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal, and then administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, cannabidiol and a base alkaloid. The absorption conditioning unit may be in a dosage form not containing a drug. The absorption conditioning unit may create a pH in the oral cavity or nasal cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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USPC - 424/443, 439
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>Y | US 2009/0023819 A1 (AXELSSON) 22 January 2009 (22.01.2009) Entire document, especially Abstract, para[0039]- para[0050]. | 1-7, 16-18, 20, 24, 26<br>---<br>10, 19, 25, 27 |
| X<br>--<br>Y | US 2002/0009491 A1 (ROTHBARD et al.) 24 January 2002 (24.01.2002) Entire document, especially Abstract; para[0123], para[0127]- para[0133] and para[0151]. | 1, 8<br>---<br>15, 25, 27 |
| X<br>--<br>Y | US 2006/0198873 A1 (CHAN et al.) 07 September 2006 (07.09.2006) Entire document, especially para[0016]- para[0020], para[0029]- para[0045]. | 9, 11-14, 21-23<br>---<br>10, 15, 19 |
| A | US 2010/0242978 A1 (FUISZ) 30 September 2010 (30.09.2010) Entire document. | 1-27 |
| A | US 2011/0293535 A1 (KOSIK et al.) 01 December 2011 (01.12.2011) Entire document. | 1-27 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
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(54) Title: METHOD OF ADMINISTERING NICOTINE, THC, TOBACCO, CANNABIDIOL OR BASE ALKALOID AND ABSORPTION CONDITIONING UNIT

(57) Abstract: A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid includes administering in the oral or nasal cavity an absorption conditioning unit having at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal, and then administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, cannabidiol and a base alkaloid. The absorption conditioning unit may be in a dosage form not containing a drug. The absorption conditioning unit may create a pH in the oral cavity or nasal cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

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We Claim:

1. A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit in the oral or nasal cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal to create an enhanced absorption condition in the oral or nasal cavity for a period of time; and then

separately administering by inhalation a bioactive agent during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

2. The method according to claim 1, wherein the absorption conditioning unit does not contain a bioactive.

3. The method according to claim 1, wherein the absorption conditioning unit does not contain a drug.

4. The method according to claim 3, wherein the absorption conditioning unit does not contain an acid.

5. The method according to claim 1, wherein the absorption conditioning unit does not contain an acid.

6. The method according to claim 1, wherein the absorption conditioning unit includes at least the buffer agent.

7. The method according to claim 1, wherein the absorption conditioning unit includes at least the capturing agent, and the capturing agent has mucoadhesive properties.

8. The method according to claim 1, wherein the bioactive agent is a base alkaloid comprising cocaine.

9. A method for the administration of nicotine, THC, tobacco, cannabidiol, cocaine or abase alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration to create an enhanced absorption condition in the oral cavity for a period of time; and then

separately administering by inhalation a bioactive agent during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

10. The method according to claim 9, wherein the absorption conditioning unit does not contain a bioactive.

11. The method according to claim 9, wherein the absorption conditioning unit does not contain an acid.

12. The method according to claim 9, wherein the absorption conditioning unit does not contain a drug.

13. The method according to claim 9, wherein the absorption conditioning unit includes at least a buffer agent.

14. The method according to claim 9, wherein the absorption conditioning unit includes at least a capturing agent having mucoadhesive properties.

15. The method according to claim 9, wherein the bioactive agent is a base alkaloid comprising cocaine.

16. An absorption conditioning unit, comprising a dosage form including at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, wherein said absorption conditioning unit (i) does not have an essentially acidic

character, (ii) does not contain a drug, (iii) does not contain THC or other Marijuana derived active ingredient, and (iv) does not contain tobacco except for trace amounts in flavor.

17. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit does not contain an acid.

18. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit includes at least the buffer agent.

19. The absorption conditioning unit according to claim 18, wherein the buffer agent is configured to create a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration

20. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit includes at least the capturing agent, and the capturing agent has mucoadhesive properties.

21. An absorption conditioning unit, comprising a dosage form including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

22. The absorption conditioning unit according to claim 21, wherein the absorption conditioning unit includes at least a capturing agent.

23. The absorption conditioning unit according to claim 22, wherein the capturing agent has mucoadhesive properties.

24. A method for the administration of nicotine, THC, cannabidiol, tobacco or base alkaloid to a mammal, comprising:

*administering a solid or liquid absorption conditioning unit in the nasal* cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a

thermal agent, to the mammal to create an enhanced absorption condition in the nasal cavity for a period of time; and then

separately administering by inhalation a bioactive agent in the nasal cavity during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol, and a base alkaloid.

25. The method according to claim 24, wherein the bioactive agent is a base alkaloid comprising cocaine.

26. A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit in the oral cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal to create an enhanced absorption condition in the oral cavity for a period of time; and then

separately administering by inhalation a bioactive agent during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid, where such bioactive agent is contained in a solid, semi-solid or liquid based dosage form.

27. The method according to claim 26, wherein the bioactive agent is a base alkaloid comprising cocaine.

28. The method according to claim 1, wherein the bioactive agent is contained in a vapor.

29. The method according to claim 9, wherein the bioactive agent is contained in a vapor.

30. The method according to claim 24, wherein the bioactive agent is contained in a vapor.

31. The method according to claim 26, wherein the bioactive agent is contained in a vapor.

## STATEMENT UNDER ARTICLE 19(1)

World Intellectual Property Organization
34, chemin des Colombettes
CH-1211, Geneva
SWITZERLAND

October 10, 2014

Sir:

Responsive to the International Search Report mailed August 11, 2014, the claims have been amended as follows:

Claim 1 is amended;

Claims 2-8 are unchanged;

Claim 9 is amended;

Claims 10-23 are unchanged;

Claim 24 is amended;

Claim 25 is unchanged;

Claim 26 is amended;

Claim 27 is unchanged; and

New claims 28-31 are added.

Respectfully submitted,
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Date of publication of the amended claims and statement: 27 November 2014

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(54) Title: METHOD OF ADMINISTERING NICOTINE, THC, TOBACCO, CANNABIDIOL OR BASE ALKALOID AND ABSORPTION CONDITIONING UNIT

(57) Abstract: A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid includes administering in the oral or nasal cavity an absorption conditioning unit having at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal, and then administering by inhalation a bioactive agent selected from the group consisting of nicotine, THC, cannabidiol and a base alkaloid. The absorption conditioning unit may be in a dosage form not containing a drug. The absorption conditioning unit may create a pH in the oral cavity or nasal cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

AMENDED CLAIMS
received by the International Bureau on 10 October 2014 (10.10.2014)

We Claim:

1. A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit in the oral or nasal cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal to create an enhanced absorption condition in the oral or nasal cavity for a period of time; and then

separately administering by inhalation a bioactive agent during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

2. The method according to claim 1, wherein the absorption conditioning unit does not contain a bioactive.

3. The method according to claim 1, wherein the absorption conditioning unit does not contain a drug.

4. The method according to claim 3, wherein the absorption conditioning unit does not contain an acid.

5. The method according to claim 1, wherein the absorption conditioning unit does not contain an acid.

6. The method according to claim 1, wherein the absorption conditioning unit includes at least the buffer agent.

7. The method according to claim 1, wherein the absorption conditioning unit includes at least the capturing agent, and the capturing agent has mucoadhesive properties.

8. The method according to claim 1, wherein the bioactive agent is a base alkaloid comprising cocaine.

9. A method for the administration of nicotine, THC, tobacco, cannabidiol, cocaine or abase alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration to create an enhanced absorption condition in the oral cavity for a period of time; and then

separately administering by inhalation a bioactive agent during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol and a base alkaloid.

10. The method according to claim 9, wherein the absorption conditioning unit does not contain a bioactive.

11. The method according to claim 9, wherein the absorption conditioning unit does not contain an acid.

12. The method according to claim 9, wherein the absorption conditioning unit does not contain a drug.

13. The method according to claim 9, wherein the absorption conditioning unit includes at least a buffer agent.

14. The method according to claim 9, wherein the absorption conditioning unit includes at least a capturing agent having mucoadhesive properties.

15. The method according to claim 9, wherein the bioactive agent is a base alkaloid comprising cocaine.

16. An absorption conditioning unit, comprising a dosage form including at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, wherein said absorption conditioning unit (i) does not have an essentially acidic

character, (ii) does not contain a drug, (iii) does not contain THC or other Marijuana derived active ingredient, and (iv) does not contain tobacco except for trace amounts in flavor.

17. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit does not contain an acid.

18. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit includes at least the buffer agent.

19. The absorption conditioning unit according to claim 18, wherein the buffer agent is configured to create a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration

20. The absorption conditioning unit according to claim 16, wherein the absorption conditioning unit includes at least the capturing agent, and the capturing agent has mucoadhesive properties.

21. An absorption conditioning unit, comprising a dosage form including at least at least one material that creates a pH in the oral cavity of 7.8-10 for a period of ten minutes or more after administration, the dosage form not containing an acid and not containing a drug.

22. The absorption conditioning unit according to claim 21, wherein the absorption conditioning unit includes at least a capturing agent.

23. The absorption conditioning unit according to claim 22, wherein the capturing agent has mucoadhesive properties.

24. A method for the administration of nicotine, THC, cannabidiol, tobacco or base alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit in the nasal cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a

thermal agent, to the mammal to create an enhanced absorption condition in the nasal cavity for a period of time; and then

separately administering by inhalation a bioactive agent in the nasal cavity during the period in which the enhanced absorption condition is created, the bioactive agent being selected from the group consisting of nicotine, THC, tobacco, cannabidiol, and a base alkaloid.

25. The method according to claim 24, wherein the bioactive agent is a base alkaloid comprising cocaine.

26. A method for the administration of nicotine, THC, tobacco, cannabidiol or a base alkaloid to a mammal, comprising:

administering a solid or liquid absorption conditioning unit in the oral cavity, comprising at least two agents selected from the group consisting of (a) a buffer agent, (b) a capturing agent, (c) a penetration agent, and (d) a thermal agent, to the mammal to create an enhanced absorption condition in the oral cavity for a period of time; and then

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27. The method according to claim 26, wherein the bioactive agent is a base alkaloid comprising cocaine.

28. The method according to claim 1, wherein the bioactive agent is contained in a vapor.

29. The method according to claim 9, wherein the bioactive agent is contained in a vapor.

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Claim 25 is unchanged;

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Claim 27 is unchanged; and

New claims 28-31 are added.

Respectfully submitted,
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(54) **Title**: IMPROVED AEROSOL FROM TOBACCO

(57) **Abstract**: In one aspect, there is provided a method of administering nicotine to a user via inhalation of the nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the level of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine in the aerosol is lower than the level in combusted tobacco.

# IMPROVED AEROSOL FROM TOBACCO

## FIELD OF THE INVENTION

The present disclosure relates, in general, to the use of an aerosol generating device that heats tobacco and generates an aerosol which comprises fewer harmful and potentially harmful constituents (HPHC) therein as compared to tobacco combusted in conventional cigarettes whilst retaining levels of nicotine. Inhalation of the aerosol also exposes the user to lower levels and/or fewer harmful and potentially harmful constituents (HPHC).

## BACKGROUND OF THE INVENTION

Smoking articles in which tobacco is heated rather than combusted have been proposed in the art. One aim of such heated smoking articles is to try and reduce known harmful aerosol constituents of the type produced by the combustion and pyrolytic degradation of tobacco in conventional cigarettes. There have been numerous estimates of the number of chemicals in conventional cigarette aerosol. Some estimates suggest that there around 5,300 chemicals. Many of these chemicals are generated by the thermal decomposition, pyrolysis and/or incomplete combustion of tobacco at temperatures in excess of 300 °C. For example, carbon monoxide (CO) is produced from the pyrolysis of tobacco plant components and from the incomplete combustion of tobacco at temperatures above 300 °C; nitrogen oxide (NO) forms over two main temperature regions, 300 °C and 450 °C, respectively; hydrocarbons and aldehydes (such as formaldehyde and acrolein) are produced by the thermal decomposition of tobacco constituents and have main peak temperatures of formation above 300 °C; phenols are products of the pyrolysis of structural carbohydrate, lignin and aliphatic and aromatic acid components of tobacco with temperatures of formation ranging from 250 °C to 550 °C; polycyclic aromatic hydrocarbons (PAHs) have been associated with the decomposition of tobacco structural components at temperatures above 400 °C; 1,3-butadiene, benzene, and styrene form at temperatures above 400 °C; and tobacco-specific nitrosamines (TSNAs) are present in tobacco and can be either transferred by distillation or pyro-synthesised at temperatures between 200 and 400 °C.

Typically in heated smoking articles, an aerosol is generated by the transfer of heat from a heat source to a physically separate aerosol-forming substrate or material, which may be located within, around or downstream of the heat source. During smoking, volatile compounds are released from the aerosol-forming substrate by heat transfer from the heat source and entrained in air drawn through the smoking article. As the released compounds cool, they condense to form an aerosol that is inhaled by the user.

Aerosol-generating articles and devices for consuming or smoking heated smoking articles are known in the art. They can include, for example, electrically heated aerosol-generating devices

in which an aerosol is generated by the transfer of heat from one or more electrical heating elements of the aerosol-generating device to the aerosol-forming substrate of a heated smoking article.

It would be highly desirable to be able to generate an aerosol from tobacco in which the level of one or more known HPHCs normally produced by combustion of tobacco are decreased to low or negligible or non-detectable levels and whilst retaining levels of nicotine in the aerosol that are acceptable to the user. The present disclosure seeks to address this need.

## SUMMARY OF THE INVENTION

The present inventors have found that when tobacco is heated to a controlled temperature (for example, in a manner which ensures that pyrolysis is reduced and combustion does not occur) rather than combusted, a significant reduction in the levels of one or more HPHCs (other than nicotine) can occur in the aerosol produced by the heated tobacco versus the combusted tobacco. Suitably, the tobacco is electrically heated. In particular, in the aerosol of the heated tobacco it has been found that the levels of many HPHCs (other than nicotine) that would otherwise be present in aerosol from combusted tobacco are detectable at negligible levels or even not detectable at all. Thus, lower amounts of HPHCs (other than nicotine) are released in the aerosol of the heated tobacco making the aerosol less complex. When the aerosol is inhaled by a (human) user it has also been found that lower amounts of the one or more HPHCs (other than nicotine) are consumed.

Another surprising aspect is that the aerosol that is generated by heating still contains levels of nicotine that are acceptable to the user. Thus, whilst the aerosol produced by the heating of tobacco becomes less complex in that lower amounts or fewer HPHCs are contained therein, the levels of nicotine are maintained at acceptable levels. Thus, acceptable levels of nicotine are delivered to the user (for example, absorbed into the bloodstream) upon inhalation of the aerosol.

Even more surprising is that the nicotine profile delivery to the bloodstream of the user is very similar to the profile observed from combusted tobacco. The nicotine profile delivery observed in combusted tobacco is generally the profile which is most acceptable to the user since it delivers high levels of nicotine in a short period of time (for example, more than 10ng/ml in about 9 minutes).

The heating of tobacco in accordance with the present disclosure has therefore been found to provide a number of advantages. It provides an aerosol that may bring potential health benefits to the user since lower levels of one or more HPHCs are observed therein as compared to combusted tobacco. Moreover, an acceptable level of nicotine is delivered via an acceptable nicotine delivery profile.

In one aspect, there is provided a method of inhaling of an aerosol comprising nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing a user to inhale the aerosol derived from the electrically heated tobacco; optionally measuring the levels of at least nicotine and one or more HPHCs therein; and wherein the aerosol contains levels of nicotine that are about the same (for example, substantially identical or the same) as the levels in combusted tobacco; and wherein the aerosol contains levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

In certain embodiments, the levels of chemical constituents in tobacco are determined using standard ISO methods as described herein – including ISO standard 3402 or ISO standard 3308 or a combination thereof. In certain embodiments, the aerosol from combusted tobacco is from a conventional/reference cigarette – such as the reference cigarette 3R4F or 2R4F. The levels of the chemical constituents in the reference cigarettes 3R4F or 2R4F are published in Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 25, No. 1, February 2012.

In a further aspect there is provided a method of smoking via inhalation of an aerosol comprising nicotine comprising the steps of: (a) providing to a user an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the aerosol contains levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

In one embodiment, the HPHC other than nicotine in the aerosol generated by the electrically heated tobacco is selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

In one embodiment, the one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs

being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

In one embodiment, the levels of one or more HPHCs other than nicotine are reduced to levels in the user that are comparable with smoking abstinence.

In one embodiment, the levels of carbon monoxide, benzene, acrolein and 1,3-butadiene in the user are lower than the levels generated from combusted tobacco.

In one embodiment, the carboxyhemoglobin (carbon monoxide marker) level in the user is about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or the S-PMA (benzene marker) level in the user is to about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the 3-HPMA (acrolein marker) level in the user is about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the MHBMA (1,3-butadiene marker) level in the user is about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

In one embodiment, the carboxyhemoglobin (carbon monoxide marker) level in the user is about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and the S-PMA (benzene marker) level in the user is to about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and the 3-HPMA (acrolein marker) level in the user is about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and the MHBMA (1,3-butadiene marker) level in the user is about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

Suitably, the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

In one embodiment, the level of one or more metabolic enzymes is reduced in the user following inhalation of the aerosol generated from electrically heated tobacco as compared to the level in

a user following inhalation of an aerosol generated from combusted tobacco, suitably, wherein the level is reduced to levels that are comparable with smoking abstinence.

In one embodiment, the profile of nicotine delivery via inhalation of the aerosol generated by electrically heated tobacco is substantially the same as that obtained via inhalation of an aerosol generated from combusted tobacco.

In one embodiment, the concentration of nicotine in the blood plasma increases to a maximum concentration within about 9 minutes of inhaling the aerosol from electrically heated tobacco.

In one embodiment, the maximum concentration of nicotine that is delivered to the blood plasma of the user from inhaling the aerosol from electrically heated tobacco is between about 6 and 8 ng/ml of nicotine in plasma.

In one embodiment, the $t_{max}$ is between about 6 and 10 minutes or between about 7 and 9 minutes – such as about 8 minutes.

In one embodiment, mean $AUC_{0-\infty}$ is between about 17 and 21 ng.h/mL, suitably between about 18 and 20 ng.h/mL, suitably, about 19 ng.h/mL, suitably, about 19.083 ng.h/mL.

In one embodiment, mean and $AUC_{0-t'}$ is between about 0.4 and 0.7 ng.h/mL, suitably between about 0.5 ng.h/mL and about 0.6 ng.h/mL, suitably about 0.5262 ng.h/mL.

In one embodiment, the heating element that electrically heats the tobacco is inserted into the tobacco and wherein a continuous supply of energy is supplied to the heating element, said continuous supply of energy being monitored during use of the device.

In one embodiment, the concentration of nicotine that is delivered to the bloodstream of user is greater than about 60% of the concentration of nicotine delivered to the bloodstream of user via combustion of tobacco.

In one embodiment, the electrical heating of the tobacco is controlled electronically over a period of time.

In one embodiment, the aerosol generating device includes a temperature control sensor to avoid overheating the tobacco.

In one embodiment, the tobacco is homogenised tobacco material.

In one embodiment, the aerosol-forming substrate comprises a gathered sheet of homogenised tobacco material.

In one embodiment, the sheet is crimped.

In another aspect, there is provided a method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma after about 9 minutes after inhalation; (ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between

about 1%-2% in blood after about 2 days of consuming aerosol generated from the electrically heated tobacco; and/or (iii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (v) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco.

In another aspect, there is provided a method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma after about 9 minutes after inhalation; (ii) carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1%-2% in blood after about 2 days of consuming aerosol generated from the electrically heated tobacco; and (iii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and (v) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco.

In another aspect, there is provided a method of reducing the absorption of one or more HPHCs other than nicotine in a user inhaling aerosol generated from tobacco comprising the steps of: (a) providing a tobacco product to a user; (b) electrically heating said tobacco product to a temperature of less than about 400 degrees Celsius; (c) allowing the aerosol derived from the electrically heated tobacco to be inhaled by the user and absorbed into the bloodstream of the user; and (d) optionally measuring the levels of nicotine and/or one or more other HPHCs in said user; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

In another aspect, there is provided a method of smoking via inhalation of an aerosol comprising nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated

tobacco; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma after about 9 minutes after inhalation; (ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (iii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (v) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

In another aspect, there is provided a method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma after about 9 minutes after inhalation; (ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (iii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (v) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

In another aspect, there is provided the use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

In another aspect, there is provided the use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein (i) the nicotine concentration

in the user is between about 6 and 8 ng/ml in plasma about 9 minutes after inhalation; and (ii) carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1%-2% in blood after about 2 days of consuming aerosol generated from the electrically heated tobacco; and/or (iii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (v) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco.

In another aspect, there is provided the use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma about 9 minutes after inhalation; and (ii) carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1%-2% in blood after about 2 days of consuming aerosol generated from the electrically heated tobacco; and (iii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and (v) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco.

In another aspect, there is provided a method of delivering nicotine to a user, wherein the nicotine delivery profile is substantially the same as combusted tobacco and wherein the levels of one or more HPHCs other than nicotine in the bloodstream of the user are lower than the levels from combusted tobacco comprising the use of an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius by a heating element of the aerosol-generating device.

In another aspect, there is provided an aerosol generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein said aerosol comprises: (i) levels of nicotine are about the same as the levels in combusted tobacco; and (ii) levels of one or more HPHCs other than nicotine that are lower than the level in combusted tobacco.

In one embodiment, the HPHC other than nicotine is selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-

butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N'-nitrosoanatabine (NAT), N'-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

In one embodiment, one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

In another aspect, there is provided a method of producing an aerosol as described herein, comprising the steps of: (i) electrically heating tobacco to a temperature of less than about 400 degrees Celsius; (ii) allowing the electrically heated tobacco to produce an aerosol; and (iii) optionally, isolating or collecting the aerosol.

In another aspect, there is provided an aerosol generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein said aerosol comprises: (i) levels of nicotine are about the same as the levels in combusted tobacco; and (ii) wherein 4 aminobiphenyl, 2-aminonaphthalene and 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1ng/mg nicotine; wherein carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine; wherein isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine; wherein N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine; wherein acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine; wherein ammonia is present in the aerosol at between about 9 and 11 ng/mg nicotine; and wherein acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine.

In another aspect, there is provided an aerosol generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein 4 aminobiphenyl, 2-aminonaphthalene and 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1ng/mg nicotine; wherein carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine; wherein isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine; wherein N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine; wherein acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine; wherein ammonia is present in the aerosol at

between about 9 and 11 ng/mg nicotine; and wherein acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine.

In another aspect, there is provided an aerosol-generating device comprising: (i) a heating element that heats tobacco to create an aerosol; and (ii) tobacco that is heated by the heating element the improvement comprising that the heating element electrically heats the tobacco to a temperature of less than about 400 degrees Celsius and the aerosol generated by the aerosol-generating device contains levels of nicotine that are about the same as the levels in combusted tobacco and the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

In another aspect, there is provided an aerosol-generating device comprising a heating element that heats, for example, electrically heats, tobacco to a temperature of between about 300 and 374 degrees Celsius.

In one embodiment, the aerosol-generating device is for use with an electric heating element, the aerosol-generating device comprising: (i) tobacco; (ii) a support element located immediately downstream of the aerosol-forming substrate; (iii) an aerosol-cooling element located downstream of the support element; and (iv) an outer wrapper circumscribing the aerosol-forming substrate, the support element and the aerosol-cooling element, wherein the support element abuts the aerosol-forming substrate.

In another aspect, there is provided a method of determining if a user uses an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing a sample from the user; and (b) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein, either directly or via biomarker(s); wherein (i) if the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2% in blood after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine in urine after about 2 days of consuming aerosol generated from electrically heated tobacco is indicative that said user uses the aerosol-generating device.

In another aspect, there is provided a sample isolated from a user 2 days after using an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2%;

and/or (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine ; and/or (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine ; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

In another aspect, there is provided a sample isolated from a user 2 days after using an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2%; and (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine ; and (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine ; and (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

In one embodiment, the levels of carbon monoxide, benzene, acrolein and 1,3-butadiene are determined.

In another aspect, there is provided a method of monitoring a user consuming nicotine via inhalation of an aerosol comprising nicotine through an aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius, comprising the steps of: (a) providing the user with the aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine through the aerosol generating device; (c) providing or obtaining one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during consumption by the user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used: (i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and/or (iii)a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine ; and/or (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine after; wherein correlation between the samples and the levels in step (e) is indicative that the user is exposed to levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

In another aspect, there is provided a method of monitoring a user consuming nicotine via inhalation of an aerosol comprising nicotine through an aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius, comprising the steps of: (a) providing the user with the aerosol generating device that electrically heats

tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine through the aerosol generating device; (c) providing or obtaining one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during consumption by the user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used: (i) carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and (iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine after; wherein correlation between the samples and the levels in step (c) is indicative that the user is responding favourably to the consumption of nicotine through the device.

In another aspect, there is provided a method of measuring a user's response to the inhalation of nicotine comprising the steps of: (a) providing the user with an aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine created by the aerosol generating device; (c) providing or obtaining one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during inhalation by the user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used: (i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and/or (iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and/or (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

In another aspect, there is provided a method of measuring a user's response to the inhalation of nicotine comprising the steps of: (a) providing the user with an aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine created by the aerosol generating device; (c) providing or obtaining one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during inhalation by the user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if

different types of samples are used: (i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and (iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

In one embodiment, the levels of at least carbon monoxide, benzene, acrolein and 1,3-butadiene are measured.

In another aspect, there is provided a method, a use, an aerosol, or an aerosol-generating device substantially as described herein with reference to the accompanying drawings.

The following embodiments may be embodiments of any of the aspects of mentioned above, either alone or in combination.

In another embodiment, the level of one or more HPHCs (other than nicotine) is reduced to levels that are comparable with smoking abstinence.

In another embodiment, the HPHC other than nicotine in the aerosol generated by the electrically heated tobacco is selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

In another embodiment, one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

In another embodiment, the levels of one or more HPHCs other than nicotine are reduced to levels in the user that are comparable with smoking abstinence.

In another embodiment , the levels of carbon monoxide, benzene, acrolein and 1,3-butadiene in the user are lower than the levels generated from combusted tobacco.

In another embodiment, the carboxyhemoglobin (carbon monoxide marker) level in the user is about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or the S-PMA (benzene marker) level in the user is to about 0.5 micro.g/g

creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the 3-HPMA (acrolein marker) level in the user is about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the MHBMA (1,3-butadiene marker) level in the user is about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

In another embodiment, the carboxyhemoglobin (carbon monoxide marker) level in the user is about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and the S-PMA (benzene marker) level in the user is to about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and the 3-HPMA (acrolein marker) level in the user is about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and the MHBMA (1,3-butadiene marker) level in the user is about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

In another embodiment, the level of one or more metabolic enzymes is reduced in the user following inhalation of the aerosol generated from electrically heated tobacco as compared to the level in a user following inhalation of an aerosol generated from combusted tobacco, suitably, wherein the level is reduced to levels that are comparable with smoking abstinence.

In another embodiment, the profile of nicotine delivery via inhalation of the aerosol generated by electrically heated tobacco is substantially the same as that obtained via inhalation of an aerosol generated from combusted tobacco.

In another embodiment, the concentration of nicotine in the blood plasma increases to a maximum concentration within about 9 minutes of inhaling the aerosol from electrically heated tobacco.

In another embodiment, the maximum concentration of nicotine that is delivered to the blood plasma of the user from inhaling the aerosol from electrically heated tobacco is between about 6 and 8 ng/ml of nicotine in plasma.

In another embodiment, the concentration of nicotine that is delivered to the bloodstream of user is greater than about 60% of the concentration of nicotine delivered to the bloodstream of user via combustion of tobacco.

In another embodiment, the electrical heating of the tobacco is controlled electronically over a period of time.

In another embodiment, the aerosol generating device includes a temperature control sensor to avoid overheating the tobacco.

In another embodiment, the tobacco is homogenised tobacco material.

In another embodiment, the aerosol-forming substrate comprises a gathered sheet of homogenised tobacco material.

In another embodiment, the sheet is crimped.

In another embodiment, the HPHC other than nicotine is selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N'-nitrosoanatabine (NAT), N'-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

In another embodiment, one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

In another embodiment, the aerosol-generating device is for use with an electric heating element, the aerosol-generating device comprising: (i) tobacco; (ii) a support element located immediately downstream of the aerosol-forming substrate; (iii) an aerosol-cooling element located downstream of the support element; and (iv) an outer wrapper circumscribing the aerosol-forming substrate, the support element and the aerosol-cooling element, wherein the support element abuts the aerosol-forming substrate.

In another embodiment, the levels of carbon monoxide, benzene, acrolein and 1,3-butadiene are determined.

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a delivery profile of nicotine in the bloodstream of a human test user using a conventional cigarette in which tobacco is combusted (square symbols) versus heated tobacco (triangular symbols) according to the present disclosure. The time course for nicotine absorption is similar in both systems. Maximum blood concentration of nicotine delivered using the heated system of the present disclosure is 70.25% of the maximum blood concentration of nicotine achieved when using a conventional cigarette in which tobacco is combusted. Total nicotine absorption is 77.41% of the total nicotine absorption in the conventional cigarette in which tobacco is combusted.

**Figure 2** illustrates changes of biomarkers of exposure adjusted for creatinine and shows the levels of carbon monoxide in exhaled breath (Figure 2A), and the levels of 1,3-butadiene, acrolein, and benzene in urine (see Figures 2B, 2C, and 2D, respectively) from test users using

the heated system (triangular symbol) versus the conventional cigarette in which tobacco is combusted (square symbol). Significant reductions in carbon monoxide, benzene, acrolein and 1,3-butadiene levels are seen in users using the heated system as compared to the conventional cigarette.

**Figure 3** illustrates the levels of the metabolic enzyme CYP1A2 in test users using the heated system (right hand bar) versus the conventional cigarette in which tobacco is combusted (left hand bar). Levels of CYP1A2 are significantly lower in users using the heated system and are reduced to levels that are comparable with smoking abstinence (30%).

**Figure 4A** illustrates the chemical analysis of aerosol produced via combustion of tobacco (MM-2008 median) versus heating of tobacco using menthol flavoured tobacco (platform 1 menthol) and regular tobacco (platform 1 regular). The metals shown with an asterisk were below LOQ/LOD.

**Figure 4B** illustrates the aerosol composition of aerosols produced via combustion of tobacco (reference cigarette) versus heating of tobacco (platform 1). As can be seen, the composition of the two aerosols is very different.

**Figure 5** is a schematic cross-sectional diagram of an aerosol-generating article for use with an aerosol generating-device comprising a heating element.

**Figure 6** is a schematic cross-sectional diagram of an aerosol-generating system comprising an electrically heated aerosol-generating device comprising a heating element and an aerosol-generating article according to the embodiment illustrated in Figure 5.

**Figure 7** is a schematic cross-sectional diagram of the electrically heated aerosol generating device illustrated in Figure 6.

**Figure 8** shows the relative deliveries of 18 HPHCs for THS compared to the 3R4F reference cigarette (see Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 25, No. 1, February 2012) (on a per mg nicotine basis). Abbreviations: NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosonornicotine. This clearly demonstrates that for both the regular and menthol versions of the tobacco there are reductions of more than 80% in HPHCs, with the exception of $NH_3$ which is reduced by about 40%. The actual figures for these graphs are shown in Table 4. Table 4 compares HPHC deliveries according to the present disclosure with 3R4F on a per mg nicotine basis. HPHC values are corrected on a mass per mg nicotine basis. All mean and standard deviation (SD) values are based on the number of replicates (n). *Data in shaded squares (with n+0) are indicative of values below the limit of quantitation (LOQ). In this case the LOQ value has been used as the worst case. The two columns on the right of the table provide the deliveries as a percentage of the 3R4F delivery. Abbreviations: HPHC, harmful and potentially harmful constituents; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

**Figure 9** shows the relative deliveries of 58 HPHCs obtained according to the present disclosure compared with the 3R4F cigarette (on a per mg nicotine basis). Abbreviations: NAB, N-nitrosoanabasine; NAT, N-nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitroso-nornicotine.

**DEFINITIONS**

As used herein, reference to 'conventional cigarettes' means cigarettes in which tobacco is burnt or combusted. Typically temperatures of greater than 750 degrees Celsius will be reached during the burn in which the processes involved include combustion and/or pyrolysis. Tobacco is combusted in conventional cigarette smoking. In one embodiment, the conventional cigarette can be reference cigarette – such as reference cigarette 3R4F and 2R4F (see, for example, Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 25, No. 1, February 2012).

As used herein, 'a smoker' can be a female or a male, otherwise healthy human who has a smoking history, for example of at least three years of consecutive smoking and a minimum of 10 non-mentholated conventional cigarettes per day with a maximum yield of 1 mg nicotine. Smoking status can be verified with a urinary cotinine test (cotinine ≥200 ng/ml). Randomisation quotas can be used to ensure that each gender and smoking stratum represent at least 40% of the study population.

The term 'aerosol-forming substrate' is used to describe a substrate capable of releasing upon heating volatile compounds, which can form an aerosol. The aerosol generated from aerosol-forming substrates of aerosol-generating articles described herein may be visible or invisible and may include vapours (for example, fine particles of substances, which are in a gaseous state, that are ordinarily liquid or solid at room temperature) as well as gases and liquid droplets of condensed vapours.

The terms 'upstream' and 'downstream' are used to describe the relative positions of elements, or portions of elements, of the aerosol-generating article in relation to the direction in which a user draws on the aerosol-generating article during use thereof.

The term 'aerosol-cooling element' is used to describe an element having a large surface area and a low resistance to draw. In use, an aerosol formed by volatile compounds released from the aerosol-forming substrate passes over and is cooled by the aerosol-cooling element before being inhaled by a user. In contrast to high resistance to draw filters and other mouthpieces, aerosol-cooling elements have a low resistance to draw. Chambers and cavities within an aerosol-generating article are also not considered to be aerosol cooling elements.

The term 'aerosol-generating device' is used to describe a device that interacts with an aerosol-forming substrate of an aerosol-generating article to generate an aerosol. Suitably, the aerosol generated by an aerosol-generating article to generate an aerosol that is directly inhalable into a

user's lungs thorough the user's nose or mouth. The aerosol-generating device may be a holder for a smoking article.

As used herein to describe an aerosol-generating article, the term 'longitudinal' refers to describe the direction between the downstream end and the upstream end of the aerosol-generating article and the term 'transverse' is used to describe the direction perpendicular to the longitudinal direction.

As used herein to describe an aerosol-generating article, the term 'diameter' refers to describe the maximum dimension in the transverse direction of the aerosol-generating article. As used herein, the term 'length' is used to describe the maximum dimension in the longitudinal direction of the aerosol-generating article.

The term 'homogenised tobacco material' denotes a material formed by agglomerating particulate tobacco.

The term 'sheet' denotes a laminar element having a width and length substantially greater than the thickness thereof.

The term 'gathered' is used to describe a sheet that is convoluted, folded, or otherwise compressed or constricted substantially transversely to the longitudinal axis of the aerosol-generating article.

The term 'textured sheet' denotes a sheet that has been crimped, embossed, debossed, perforated or otherwise deformed. The aerosol-forming substrate may comprise a gathered textured sheet of homogenised tobacco material comprising a plurality of spaced-apart indentations, protrusions, perforations or a combination thereof.

The term 'crimped sheet' denotes a sheet having a plurality of substantially parallel ridges or corrugations. Suitably, when the aerosol-generating article has been assembled, the substantially parallel ridges or corrugations extend along or parallel to the longitudinal axis of the aerosol-generating article. This advantageously facilitates gathering of the crimped sheet of homogenised tobacco material to form the aerosol-forming substrate. However, it will be appreciated that crimped sheets of homogenised tobacco material for inclusion in the aerosol-generating article may alternatively or in addition have a plurality of substantially parallel ridges or corrugations that are disposed at an acute or obtuse angle to the longitudinal axis of the aerosol-generating article when the aerosol-generating article has been assembled.

The term "substantially cylindrical" is to be understood to include the shape of a cylinder or a tapered cylinder of circular or substantially circular cross-section, or which have the shape of a cylinder or a tapered cylinder of elliptical or substantially elliptical cross-section. In a preferred embodiment, a substantially cylindrical object has the shape of a cylinder having a circular cross-section.

The term 'aerosol former' is used to describe any suitable known compound or mixture of compounds that, in use, facilitates formation of an aerosol and that is substantially resistant to

thermal degradation at the operating temperature of the aerosol-generating article.

The term 'penetration force' is used to describe the maximum insertion force during insertion of the heating element into the aerosol-forming substrate of the aerosol-generating article and prior to the aerosol-generating article reaching a position of maximum insertion.

The term 'crush force' is used to describe the maximum insertion force after the aerosol-generating article reaches a point of maximum insertion.

The term 'volatile flavour component' is used to describe any volatile component that is added to an aerosol-generating article in order to provide a flavour.

The term 'menthol' is used to describe the compound 2-isopropyl-5-methylcyclohexanol in any of its isomeric forms.

As used herein, resistance to draw is expressed with the units of pressure 'mm WG' or 'mm of water gauge' and is measured in accordance with ISO 6565:2002.

**DETAILED DESCRIPTION**

The present inventors have found that smokers who switch from conventional cigarette smoking in which tobacco is combusted to aerosol-generating devices in which tobacco is heated (for example, electrically heated) to a temperature of less than about 400 degrees Celsius can (significantly) reduce their exposure to one or more HPHCs. Whilst reducing their exposure to one or more HPHCs, acceptable levels, amounts or concentrations of nicotine are delivered to the user (for example, absorbed into the bloodstream) via an acceptable nicotine delivery profile. One or more HPHCs may even be reduced to levels that are comparable with smoking abstinence.

An example of an aerosol-generating article which can be used to heat tobacco in accordance with the present disclosure is shown in Figures 5 to 7.

Figure 5 illustrates an aerosol-generating article 10. The aerosol-generating article 10 comprises four elements arranged in coaxial alignment: an aerosol-forming substrate 20, a support element 30, an aerosol-cooling element 40, and a mouthpiece 50. These four elements are arranged sequentially and are circumscribed by an outer wrapper 60 to form the aerosol-generating article 10. The aerosol-generating 10 has a proximal or mouth end 70, which a user inserts into his or her mouth during use, and a distal end 80 located at the opposite end of the aerosol-generating article 10 to the mouth end 70.

In use air is drawn through the aerosol-generating article by a user from the distal end 80 to the mouth end 70. The distal end 80 of the aerosol-generating article may also be described as the upstream end of the aerosol-generating article 10 and the mouth end 70 of the aerosol-generating article 10 may also be described as the downstream end of the aerosol-generating article 10. Elements of the aerosol-generating article 10 located between the mouth end 70 and the distal end 80 can be described as being upstream of the mouth end 70 or, alternatively,

downstream of the distal end 80.

The aerosol-forming substrate 20 is located at the extreme distal or upstream end of the aerosol-generating article 10. In the embodiment illustrated in Figure 5, aerosol-forming substrate 20 comprises a gathered sheet of crimped homogenised tobacco material circumscribed by a wrapper. The crimped sheet of homogenised tobacco material may comprise an aerosol-former – such as glycerine.

The support element 30 is located immediately downstream of the aerosol-forming substrate 20 and abuts the aerosol-forming substrate 20. In the embodiment shown in Figure 5, the support element is a hollow cellulose acetate tube. The support element 30 locates the aerosol-forming substrate 20 at the extreme distal end 80 of the aerosol-generating article 10 so that it can be penetrated by a heating element of an aerosol-generating device. As described further below, the support element 30 acts to prevent the aerosol-forming substrate 20 from being forced downstream within the aerosol-generating article 10 towards the aerosol-cooling element 40 when a heating element of an aerosol-generating device is inserted into the aerosol-forming substrate 20. The support element 30 also acts as a spacer to space the aerosol-cooling element 40 of the aerosol-generating article 10 from the aerosol-forming substrate 20.

The aerosol-cooling element 40 is located immediately downstream of the support element 30 and abuts the support element 30. In use, volatile substances released from the aerosol-forming substrate 20 pass along the aerosol-cooling element 40 towards the mouth end 70 of the aerosol-generating article 10. The volatile substances may cool within the aerosol-cooling element 40 to form an aerosol that is inhaled by the user. In the embodiment illustrated in Figure 5, the aerosol-cooling element comprises a crimped and gathered sheet of polylactic acid circumscribed by a wrapper 90. The crimped and gathered sheet of polylactic acid defines a plurality of longitudinal channels that extend along the length of the aerosol-cooling element 40.

The mouthpiece 50 is located immediately downstream of the aerosol-cooling element 40 and abuts the aerosol-cooling element 40. As shown in Figure 5, the mouthpiece 50 comprises a conventional cellulose acetate tow filter of low filtration efficiency.

To assemble the aerosol-generating article 10, the four elements described above are aligned and tightly wrapped within the outer wrapper 60. In the embodiment illustrated in Figure 5, the outer wrapper is a conventional cigarette paper. As shown in Figure 5, an optional row of perforations is provided in a region of the outer wrapper 60 circumscribing the support element 30 of the aerosol-generating article 10.

As shown in Figure 5, a distal end portion of the outer wrapper 60 of the aerosol-generating article 10 is circumscribed by a band of tipping paper (not shown).

The aerosol-generating article 10 illustrated in Figure 5 is designed to engage with an aerosol-generating device comprising a heating element in order to be consumed by a user. In use, the

heating element of the aerosol-generating device heats the aerosol-forming substrate 20 of the aerosol-generating article 10 to a sufficient temperature to volatilize compounds that are capable of forming an aerosol, which is drawn downstream through the aerosol-generating article 10 and inhaled by the user.

Figure 6 illustrates a portion of an aerosol-generating system 100 comprising an aerosol-generating device 110 and an aerosol-generating article 10 according to the embodiment described above and illustrated in Figure 5.

The aerosol-generating device comprises a heating element 120. As shown in Figure 6, the heating element 120 is mounted within an aerosol-generating article receiving chamber of the aerosol-generating device 110. In use, the user inserts the aerosol-generating article 10 into the aerosol-generating article receiving chamber of the aerosol-generating device 110 such that the heating element 120 is directly inserted into the aerosol-forming substrate 20 of the aerosol-generating article 10 as shown in Figure 6. In the embodiment shown in Figure 6, the heating element 120 of the aerosol-generating device 110 is a heater blade.

The aerosol-generating device 110 comprises a power supply and electronics (shown in Figure 7) that allow the heating element 120 to be actuated. Such actuation may be manually operated or may occur automatically in response to a user drawing on an aerosol-generating article 10 inserted into the aerosol-generating article receiving chamber of the aerosol-generating device 110. A plurality of openings is provided in the aerosol-generating device to allow air to flow to the aerosol-generating article 10; the direction of air flow is illustrated by arrows in Figure 6.

The support element 40 of the aerosol-generating article 10 resists the penetration force experienced by the aerosol-generating article 10 during insertion of the heating element 120 of the aerosol-generating device 110 into the aerosol-forming substrate 20. The support element 40 of the aerosol-generating article 10 thereby resists downstream movement of the aerosol-forming substrate within the aerosol-generating article 10 during insertion of the heating element of the aerosol-generating device into the aerosol-forming substrate.

Once the internal heating element 120 is inserted into the aerosol-forming substrate 10 of the aerosol-generating article 10 and actuated, the aerosol-forming substrate 20 of the aerosol-generating article 10 is heated to a temperature of less than about 400 degrees Celsius (or other temperature as discussed herein) by the heating element 120 of the aerosol-generating device 110. At this temperature, volatile compounds are evolved from the aerosol-forming substrate 20 of the aerosol-generating article 10. As a user draws on the mouth end 70 of the aerosol-generating article 10, the volatile compounds evolved from the aerosol-forming substrate 20 are drawn downstream through the aerosol-generating article 10 and condense to form an aerosol that is drawn through the mouthpiece 50 of the aerosol-generating article 10 into the user's mouth.

As the aerosol passes downstream thorough the aerosol-cooling element 40, the temperature of the aerosol can be reduced due to transfer of thermal energy from the aerosol to the aerosol-cooling element 40. When the aerosol enters the aerosol-cooling element 40, its temperature is approximately 60 degrees Celsius. Due to cooling within the aerosol-cooling element 40, the temperature of the aerosol as it exits the aerosol-cooling element is approximately 40 degrees Celsius.

In Figure 7, the components of the aerosol-generating device 110 are shown in a simplified manner. Particularly, the components of the aerosol-generating device 110 are not drawn to scale in Figure 5. Components that are not relevant for the understanding of the embodiment have been omitted to simplify Figure 7.

As shown in Figure 7, the aerosol-generating device 110 comprises a housing 130. The heating element 120 is mounted within an aerosol-generating article receiving chamber within the housing 130. The aerosol-generating article 10 (shown by dashed lines in Figure 7) is inserted into the aerosol-generating article receiving chamber within the housing 130 of the aerosol-generating device 110 such that the heating element 120 is directly inserted into the aerosol-forming substrate 20 of the aerosol-generating article 10.

Within the housing 130 there is an electrical energy supply 140, for example a rechargeable lithium ion battery. A controller 150 is connected to the heating element 120, the electrical energy supply 140, and a user interface 160, for example a button or display. The controller 150 controls the power supplied to the heating element 120 in order to regulate its temperature. Additional components (for example, one or more sensors or controllers) may be included that are able to monitor and/or regulate the temperature of the heating element 120 and/or the temperature of the tobacco such that the temperature thereof is controlled within a defined temperature range. Suitably, the additional components (for example, the one or more sensors or controllers) may be included that are able to monitor and/or regulate the temperature of the heating element 120 and/or the temperature of the tobacco. Although the support element of the aerosol-generating article according to the embodiment described above and illustrated in Figure 5 is formed from cellulose acetate, it will be appreciated that this is not essential and that aerosol-generating articles according to other embodiments may comprise support elements formed from other suitable materials or combination of materials.

Similarly, although the aerosol-generating article illustrated in Figure 5 comprises an aerosol-cooling element comprising a crimped and gathered sheet of polylactic acid, it will be appreciated that this is not essential and that aerosol-generating articles may comprise other aerosol-cooling elements.

Furthermore, although the aerosol-generating article illustrated in Figure 5 has four elements circumscribed by an outer wrapper, it will be appreciated than this is not essential and that aerosol-generating articles may comprise additional elements or fewer elements.

It will also be appreciated that while the four elements of the aerosol-generating article illustrated in Figure 5 are circumscribed by an outer wrapper of conventional cigarette paper, this is not essential and that the elements of aerosol-generating articles may be circumscribed by other outer wrappers.

It will further be appreciated that dimensions provided for elements of the aerosol-generating article illustrated in Figure 5 and parts of the aerosol-generating device illustrated in Figure 6 are merely exemplary, and that suitable alternative dimensions may be chosen.

The aerosol-generating article for use with an aerosol-generating device can comprise a heating element, the aerosol-generating article comprising: an aerosol-forming substrate; a support element located immediately downstream of the aerosol-forming substrate; an aerosol-cooling element located downstream of the support element; and an outer wrapper circumscribing the aerosol-forming substrate, the support element and the aerosol-cooling element, wherein the support element abuts the aerosol-forming substrate. Suitably, the heating element is an electrical heat element. The heating element can be adapted to heat tobacco a temperature described herein.

The aerosol-forming substrate can be located at an extreme upstream end of the aerosol-generating article. The aerosol-generating article can further comprise: a front plug upstream of the aerosol-forming substrate, wherein the outer wrapper circumscribes the front plug and the front plug is penetrable by a heating element of an aerosol-generating device. The aerosol-forming substrate can comprise a gathered sheet of homogenised tobacco material. The sheet of homogenised tobacco material can be crimped. The support element can comprise a hollow tubular element. The support element can comprise a hollow cellulose acetate tube. The aerosol-cooling element can be located immediately downstream of the support element and abuts the support element. The aerosol-cooling element can comprise a gathered sheet of biodegradable polymeric material. The aerosol-cooling element can comprise a gathered sheet of polylactic acid. The aerosol-generating article can further comprise: a mouthpiece located at an extreme downstream end of the aerosol-generating article, wherein the outer wrapper circumscribes the mouthpiece. The mouthpiece can comprise a plug of cellulose acetate tow.

A method of using an aerosol-generating article as described herein with an aerosol-generating device is provided comprising a heating element, suitably an electrical heating element that heats to the temperature described herein, the method comprising the steps of: inserting the heating element of the aerosol-generating device into the aerosol-forming substrate of the aerosol-generating article; raising the temperature of the heating element of the aerosol-generating device to heat the aerosol-forming substrate of the aerosol-generating article to a temperature as described herein to generate an aerosol; and withdrawing the heating element of the aerosol-generating device from the aerosol-forming substrate of the aerosol-generating article. An aerosol-generating system is also described comprising: an aerosol-generating

device comprising a heating element; and an aerosol-generating article for use with the aerosol-generating device, the aerosol-generating article comprising: an aerosol-forming substrate; a support element located immediately downstream of the aerosol-forming substrate; an aerosol-cooling element located downstream of the support element; and an outer wrapper circumscribing the aerosol-forming substrate, the support element and the aerosol-cooling element, wherein the support element abuts the aerosol-forming substrate and the aerosol-forming substrate is penetrable by the heating element of the aerosol-generating device. The method can comprise the steps of: inserting the heating element of the aerosol-generating device into the aerosol-forming substrate of the aerosol-generating article; raising the temperature of the heating element of the aerosol-generating device to heat the aerosol-forming substrate of the aerosol-generating article to generate an aerosol; and withdrawing the heating element of the aerosol-generating device from the aerosol-forming substrate of the aerosol-generating article. Suitably, the heating element is an electrical heating element. Suitably, the heating element heats and suitably maintains the tobacco to a temperature of between about 374 and 325 degrees Celsius, between about 374 and 330 degrees Celsius, between about 374 and 335 degrees Celsius, between about 374 and 340 degrees Celsius, between about 374 and 345 degrees Celsius, between about 374 and 350 degrees Celsius, between about 374 and 355 degrees Celsius, between about 374 and 360 degrees Celsius, between about 374 and 365 degrees Celsius, or between about 374 and 370 degrees Celsius. In certain embodiments, the tobacco may be heated to and suitably maintained at a temperature of between about 373 and 325 degrees Celsius, between about 373 and 330 degrees Celsius, between about 373 and 335 degrees Celsius, between about 373 and 340 degrees Celsius, between about 373 and 345 degrees Celsius, between about 373 and 350 degrees Celsius, between about 373 and 355 degrees Celsius, between about 373 and 360 degrees Celsius, between about 373 and 365 degrees Celsius, or between about 373 and 370 degrees Celsius. In certain embodiments, the tobacco may be heated to and suitably maintained at a temperature of between about 372 and 325 degrees Celsius, between about 372 and 330 degrees Celsius, between about 372 and 335 degrees Celsius, between about 372 and 340 degrees Celsius, between about 372 and 345 degrees Celsius, between about 372 and 350 degrees Celsius, between about 372 and 355 degrees Celsius, between about 372 and 360 degrees Celsius, between about 372 and 365 degrees Celsius, or between about 372 and 370 degrees Celsius. In certain embodiments, the tobacco may be heated to and suitably maintained at a temperature of between about 371 and 325 degrees Celsius, between about 371 and 330 degrees Celsius, between about 371 and 335 degrees Celsius, between about 371 and 340 degrees Celsius, between about 371 and 345 degrees Celsius, between about 371 and 350 degrees Celsius, between about 371 and 355 degrees Celsius, between about 371 and 360 degrees Celsius, between about 371 and 365 degrees Celsius, or between about 371 and 370 degrees Celsius.

In one embodiment, the actual operation temperature is retrieved from a lookup table which stores resistivity and temperature relationships for the at least one heating element. In another embodiment, the resistivity is determined by evaluating a polynomial of the form $\rho(T) = \rho_o*(1 + \alpha1\ T + \alpha2\ T^2)$ where $\rho(T)$ is the measured resistivity of the at least one heating element or the plurality of heating elements, $\rho_o$ is a reference resistivity and $\alpha1 + \alpha2$ are polynomial coefficients. The evaluation may be performed by a controller. Accordingly, the derivation of the measure of the heating element temperature can comprise evaluating the polynomial. Alternatively, polynomial functions of higher degrees or other mathematical functions may be used to describe the variation of the resistivity of the at least one heating element as a function of temperature. Alternatively, a piece-wise linear approximation may be used. This alternative simplifies and speeds up the calculation. In use, a controller can measure the resistivity $\rho$ of the heating element. The controller then converts the resistivity of the heating element into a value for the actual operation temperature of the heating element, by comparing the measured resistivity $\rho$ with the look-up table. In the next step, the controller compares the derived actual operation temperature with the predetermined maximum operation temperature. If the actual operation temperature is below the lower range of the predetermined maximum operation temperature, the controller supplies the heating element with additional electrical energy in order to raise the actual operation temperature of the heating element. If the actual operation temperature is above the upper range of the predetermined maximum operation temperature, the controller reduces the electrical energy supplied to the heating element in order to lower the actual operation temperature back into the acceptable range of the predetermined maximum operation temperature. A continuous supply of energy can be provided to the heating element and this supply of energy can be increased or decreased but not switched off. The supply of energy can be continuously monitored and feedback to the controller. The resistance of the heating element can be expressed as $R = V/I$; where V is the voltage across the heating element and I is the current passing through the heating element. The resistance R depends on the configuration of the heating element as well as the temperature and is expressed by the following relationship:

$$R = \rho(T) * L/S \qquad \text{equation 1}$$

where $\rho(T)$ is the temperature dependent resistivity, L is length and S the cross sectional area of the heating element. L and S are fixed for a given heating element configuration and can be measured. Thus, for a given heating element design R is proportional to $\rho(T)$. The resistivity $\rho(T)$ of the heating element can be expressed in the polynomial described above. Thus, knowing the length and cross-section of the heating element, it is possible to determine the resistance R, and therefore the resistivity $\rho$ at a given temperature by measuring the heating

element voltage V and current I. Suitably, the calculation may be simplified by representing the resistivity ρ versus temperature curve in one or more, suitably two, linear approximations in the temperature range applicable to tobacco. This simplifies evaluation of temperature which is desirable in a controller having limited computational resources.

In a preparation of the controlling of the maximum operation temperature, a value for the maximum operation temperature of the device can be selected. The controller heats the heating element by continuously supplying electrical energy to the heating element via feedback and monitoring of the electrical energy that is delivered. In use, the controller measures the resistivity ρ of the heating element. The controller then converts the resistivity of the heating element into a value for the actual operation temperature of the heating element, by comparing the measured resistivity ρ with the look-up table. In the next step, the controller compares the derived actual operation temperature with the predetermined maximum operation temperature. If the actual operation temperature is below the lower range of the predetermined maximum operation temperature, the controller can supply the heating element with additional electrical energy in order to raise the actual operation temperature of the heating element. If the actual operation temperature is above the upper range of the predetermined maximum operation temperature, the controller reduces the electrical energy supplied to the heating element in order to lower the actual operation temperature back into the acceptable range of the predetermined maximum operation temperature.

The heating element is generally not puff actuated. Instead the energy delivered to the heating element is continuously supplied, monitored and managed so that the amount of energy delivered to the heating element is increased to decreased but not switched off. Thus, in one embodiment, a continuous supply of energy is supplied to the heating element of the aerosol-generating device, said continuous supply of energy being (electronically) monitored during use of the device.

Considering now the impact of heating tobacco on the level, amount or concentration of HPHC(s), the skilled person will be aware that numerous different types of HPHCs are known to exist in aerosol generated from combusted tobacco. These HPHCs will normally be delivered to the user (for example, absorbed into the bloodstream) upon inhalation of the aerosol. Non-limiting examples of HPHCs include, but are not limited to, nicotine, nicotine-free dry particulate matter (NFDPM *eg.* tar), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N'-nitrosoanatabine (NAT), N'-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia,

arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof. Analytical methods for measuring HPHCs are known in the art and include liquid chromatography-tandem mass spectrometry (LC-MS/MS) and spectrophotometry. Various sample sources will be used for measuring the one or more HPHCs in a user – including blood (or a component thereof – such as plasma), urine, exhaled breath and the like. Thus, by way of example, nictotine is typically measured in plasma by LC-MS/MS. Sometimes, the HPHC(s) will not be measured directly, especially in a sample derived or derivable from a user (for example, a smoker) to be tested. Instead, one or more biomarkers for the HPHC(s) may be tested instead. An exemplary list of HPHCs, biomarkers for HPHCs, methods of measuring HPHCs/biomarkers and the source *of* sample are described in Tables 1 and 3. In certain embodiments, the HPHCs are selected from the constituents in either Table 1 or Table 3.

As described herein, one or more HPHCs (other than nicotine) are reduced in the aerosol produced by the heated tobacco as compared to combusted tobacco. One or more HPHCs can even be reduced to levels that are equivalent or comparable to smoking abstinence. The reduction in the levels of the one or more HPHC(s) (other than nicotine) may be greater than about 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% or more as compared to combusted tobacco. In reducing the levels of one or more of these HPHCs in aerosol produced upon heating of tobacco, it has been observed that the levels of the one or more of HPHCs that are inhaled by and delivered to the user (for example, absorbed into the bloodstream) can also be reduced. Thus it is possible to reduce the exposure of a user to one or more HPHCs (other than nicotine). The reduction in the levels of the one or more HPHC(s) (other than nicotine) in the user (for example, in the urine and/or the plasma and/or bloodstream and/or the exhaled breath of the user) may be greater than about 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% or more as compared to combusted tobacco. The level of reduction is significant and the levels of the one or more HPHCs (other than nicotine) may be reduced to levels that are observed in abstaining users.

In certain embodiments of the disclosure the levels of one or more metabolic enzymes are also reduced in the user as compared to a user using combusted tobacco. One such example is a reduction in CYP1A2 enzyme activity. Smoking is a potent inducer of CYP1A2, which significantly lowers clozapine serum concentrations in users compared with non-users.

A chemical analysis of the aerosol generated by heating tobacco has revealed significant differences in the aerosol obtained in heated tobacco versus combusted tobacco as generated in conventional cigarettes. An example of the aerosol chemistry observed from heated tobacco as compared to combusted tobacco is shown in Figures 4A, 8 and 9. The actual figures for the graph of Figure 8 are shown in Table 4. Table 4 compares HPHC deliveries obtained according to the present disclosure with 3R4F on a per mg nicotine basis. HPHC values are corrected on a mass per mg nicotine basis.

The level of nicotine is substantially the same in both systems. In one embodiment, the level of nicotine is at least about 70% of the maximum concentration of a conventional/reference cigarette – such as 3R4F. The levels of a number of HPHCs (other than nicotine) are significantly lower in the heated tobacco with levels of HPHCs being about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% or more lower than those levels observed in combusted tobacco. Thus, in one exemplary chemistry profile of aerosol the nicotine levels are substantially the same at those generated by combusted tobacco in conventional/reference cigarette whereas the level of one or more HPHCs (other than nicotine) is (significantly) reduced. The mainstream smoke chemistry of the reference cigarettes 3R4F and 2R4F is known in the art and has been published in Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 25, No. 1, February 2012. In one embodiment, the nicotine levels in aerosol obtained or obtainable according to the present disclosure are substantially the same at those generated by combusted tobacco whereas the levels of one or more HPHCs (other than nicotine) is reduced as compared to combusted tobacco. Suitably, these comparisons with combusted tobacco are made by reference to the values from a reference cigarette such as 3R4F (see Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 25, No. 1, February 2012). Methods for measuring nicotine and other HPHCs are described therein.

Standard methods for measuring the chemical constituents of aerosol are also described in this *Contributions to Tobacco Research* article. Standard ISO methods can be used. Cigarettes can optionally be conditioned using ISO standard 3402 (ISO 3402: Tobacco and tobacco products – Atmosphere for conditioning and testing. International Organization for Standardization, Geneva, Switzerland, 1999) *ie*. at least 48 hours at target conditions of 22 °C ± 1 °C and a relative humidity of 60 % ± 3 %. Smoke can be generated using ISO machine smoking conditions following ISO Standard 3308 (ISO 3308: Routine analytical cigarette smoking machine - Definitions and standard conditions. International Organization for Standardization, Geneva, Switzerland, 2000).

Cigarettes can be artificially smoked using methods that are known in the art. For example, cigarettes can be smoked on a 20-port Borgwaldt smoking machine (for example, RM20H, Hamburg, Germany) or on 30-port rotary smoking machine with an active sidestream smoke exhaust (for example, type Philip Morris Research Laboratories (PMRL), SM2000, equipped with a programmable dual-syringe pump (see EP1832745). Puff volume, puff duration, and puff frequency for ISO smoking conditions can be 35 mL, 2 s, and 1/min.

Analytes in smoke can be quantified and optionally compared according to established methodology, for example using ISO 4387 (ISO 4387: Determination of total and nicotine-free dry particulate matter using routine analytical smoking machine. International Organization for Standardization, Geneva, Switzerland, 1991)as previously described (*Toxicology* 195 (2004)

31–52). Total particulate matter (TPM) can be determined gravimetrically from the smoke trapped on Cambridge glass fiber filters according to ISO 4387 (ISO 4387: Determination of total and nicotine-free dry particulate matter using routine analytical smoking machine. International Organization for Standardization, Geneva, Switzerland, 1991). Nicotine can be determined by gas chromatography (GC) with flame ionization detection from a 2-propanol extract of the TPM filter. Water can be determined from the same 2-propanol extract by Karl Fischer titration (ISO 10315: Cigarettes - Determination of nicotine in smoke condensate - Gas chromatographic method (2nd ed.). International Organization for Standardization, Geneva, Switzerland, 2000). Carbon monoxide can be determined by non-dispersive infra-red photometry (ISO 8454: Cigarettes - Determination of carbon monoxide in the vapour phase of cigarette smoke - NDIR method (3rd ed.). International Organization for Standardization, Geneva, Switzerland, 2007.). 'Tar' yield can be calculated as the TPM yield minus the nicotine and water yields (ISO 4387: Determination of total and nicotine-free dry particulate matter using routine analytical smoking machine. International Organization for Standardization, Geneva, Switzerland, 1991). Aldehydes, derivatised with 2,4-dinitrophenylhydrazine and stabilized with pyridine, can be determined by high-performance liquid chromatography with ultraviolet (HPLC/UV) detection using water/acetonitrile (9:1) and methanol as solvents (CORESTA: Recommended Method No. 74 - Determination of selected carbonyls in mainstream cigarette smoke by high performance liquid chromatography (HPLC). Cooperation Centre for Scientific Research Relative to Tobacco, 2011). Vinyl chloride, 1,3-butadiene, isoprene, benzene, toluene, acrylonitrile, and styrene in the gas phase can be trapped in three impingers containing methanol at approximately –78 °C cooled with 2-propanole and dry ice and analysed after addition of internal standards by GC using a CP PoraBond Q column (25 m x 0.25 mm, 3 µm) coupled to a mass spectrometer (GC-MS) with electron impact ionization in single ion monitoring mode (CORESTA: Recommended Method No. 70 - Determination of selected volatile organic compounds in the mainstream smoke of cigarettes - gas chromatography- mass spectrometry method. Co-operation Centre for Scientific Research Relative to Tobacco, 2010). Styrene and acetamide in TPM can be extracted from a glass fiber filter using acetone and analyzed after addition of internal standards by GC using a DB-WAX column (30 m x 0.25 mm, 0.25 µm) coupled to a mass spectrometer (GC/MS) with electron impact ionization in single ion monitoring mode. The analysis of acrylamide after extraction from a glass fiber filter can be performed as described in *J. Chromatogr. Sci.* 46 (2008) 659–663. Ethylene oxide in the gas phase can be trapped in an impinger containing toluene at approximately –78 °C (cooled with 2-propanole and dry ice) which is connected in series with a glass fiber filter as first trap. After addition of the internal standard propylene oxide-d6, the toluene solution can be analysed by GC using a CP PoraPlot U column (25 m x 0.25 mm, 8 µm) and hydrogen as carrier gas coupled to a mass spectrometer (GC-MS) with electron impact ionization in single ion

monitoring mode (*J. Chromatogr. Sci.* 44 (2006) 32–34). 2-nitro-propane can be determined from mainstream smoke trapped on a silica cartridge by adding 2-methyl-2-nitropropane as internal standard, washing the cartridge with pentane and eluting the target analyte using 15% diethyl ether in n-pentane. 2-nitropropane can be analysed by GC-MS/MS in chemical ionization mode using iso-butane as ionization gas, helium as carrier gas and argon as collision gas. Aromatic amines can be determined by extracting TPM-filters with dilute hydrochloric acid, followed by back extraction, derivatisation, clean-up by solid phase extraction, and analysis by GC with a triple quadrupole mass spectrometer (*Rapid Commun. Mass. Spectrom.* 17 (2003) 2125–2132.). Nitrogen oxides can be determined by online gas phase chemiluminescence according to the CORESTA recommended method (CORESTA: Recommended Method (3rd Draft): The determination of nitric oxide in mainstream smoke of cigarettes by chemiluminescent analysis; Available at http://legacy.library.ucsf.edu/tid/vsm05c00). Hydrogen cyanide can be trapped in two impingers with sodium hydroxide solution connected in series. An aliquot can be analysed by headspace GC with nitrogen sensitive detection after acidification of the samples with phosphoric acid. Ammonia can be trapped on a glass fiber filter and a wash bottle connected in series. The glass fiber filter is extracted with the content of the wash bottle, derivatised with dansyl chloride, and analysed by HPLC with a tandem mass spectrometer (HPLC/MS-MS) (*J. Agric. Food Chem.* 59 (2011) 92–97). Volatile *N*-nitrosamines can be collected on a glass fiber filter and in two wash bottles containing a citrate/phosphate buffer solution with ascorbic acid to inhibit artificial generation of *N*-nitrosamines. The glass fiber filter is extracted with citrate/phosphate buffer solution with ascorbic acid and combined with the buffer solution of the wash bottles. The combined buffer solution is three times extracted with dichloromethane and the concentrated chloromethane phase is eluted through an alumina column. After elution with dichloromethane and another concentration step, the extract is analysed by GC with a thermal energy analyzer. Tobacco-specific *N*-nitrosamines (TSNAs) can be analysed as published in *Anal. Chem.* 77 (2005) 1001–1006. TSNAs can be extracted with ammonium acetate solution from TPM trapped on a glass fiber filter pad, and analysed by HPLC/MS-MS. Phenols can be extracted from a TPM filter with trichloromethane/acetone after addition of the internal standards phenol-d6, catechol-d6 and hydroquinone-d6. An aliquot of the extract can be derivatised with *N,O*-bis- (trimethylsilyl)-trifluoracetamide/1% trimethyl-chlorosilane and the trimethylsilyl ethers of the phenols are analysed by GC-MS using electron impact ionization in single ion monitoring mode. Polycyclic aromatic hydrocarbons can be extracted from TPM filters with pentane/isooctane (9:1) after addition of the labeled internal standards. The sample clean-up is performed by a 2-step solid phase extraction using aminopropyl cartridges eluted with n-hexane, and octadecyl cartridges eluted with methanol. After concentration of the eluate by solvent evaporation and dissolving in isooctane, the 13 target analytes can be determined by GC-MS using electron impact ionization in single ion

monitoring mode. Arsenic, cadmium, chromium, nickel, lead, and selenium can be trapped in quartz glass tubes using electrostatic precipitation. The condensate can be dissolved with dichloromethane/methanol mixture, and after addition of nitric acid, hydrogen peroxide, and water, the samples can be subjected to microwave digestion and analysed with atomic absorption spectroscopy. In the case of matrix interferences, selenium can be re-analysed with the flow injection analysis system furnace technique. Mercury, after electrostatic precipitation of the particle phase, can be trapped in 2 impingers containing potassium permanganate in sulphuric acid. For microwave digestion hydrogen peroxide can be added. The digest can be made up with water and an aliquot was analyzed with a mercury analyser.

The smoke constituent yields for the 3R4F and 2R4F reference cigarettes as determined using the ISO standard are shown in Table A of Beiträge zur Tabakforschung International/*Contributions to Tobacco Research* Volume 25, No. 1, February 2012. Briefly, 3R4F has (per cigarette) 0.707 mg nicotine, 38.5 µg 1, 3-butadiene, 395 µg isoprene, 26.4 µg acetonitrile, 1.01 ng 4-aminobiphenyl, 45.7 µg benzene and 38.3 ng cadmium. Briefly, 2R4F has (per cigarette) 0.678 mg nicotine, 38.9 µg 1,3-butadiene, 411 µg isoprene, 26.5 µg acetonitrile, 1.04 ng 4-aminobiphenyl, 46.6 µg benzene and 38.5 ng cadmium.Said HPHCs are selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels in aerosol obtained or obtainable according to the present disclosure are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are reduced to negligible or undetectable levels, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels in aerosol obtained or obtainable according to the present disclosure are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are present at levels of less than 1% of the composition of the aerosol generated from heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile,

benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 0 to about 10% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: carbon monoxide, acrolein, 1,3 butadiene and benzene or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 0 to about 20% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: carbon monoxide, acrolein, 1,3 butadiene and benzene or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 0 to about 20% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3 butadiene, isoprene, acrylonitrile, benzene, toluene, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia cadmium and mercury or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 0 to about 20% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: carbon monoxide, formaldehyde, acetone, acrolein, crotonaldehyde, methyl-ethly ketone, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3 butadiene, isoprene, acrylonitrile, benzene, toluene, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia cadmium and mercury or a combination of one or more thereof or a combination thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are

decreased to levels of between about 20 to about 40% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: pyridine, mercury and lead or a combination of one or more thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 40 to about 60% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), butyraldehyde and ammonia or a combination of one or more thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas: (i) the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 0 to about 20% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3 butadiene, isoprene, acrylonitrile, benzene, toluene, quinoline, styrene, N'-nitrosonornicotine (NNN), N'-nitrosoanatabine (NAT), N'-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia cadmium and mercury or a combination of one or more thereof; (ii) the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 20 to about 40% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: pyridine, mercury and lead or a combination of one or more thereof; and (iii) the levels of one or more of HPHCs (other than nicotine) are decreased to levels of between about 40 to about 60% of the levels generated by combusted tobacco, said HPHCs being selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), butyraldehyde and ammonia or a combination of one or more thereof.

In another embodiment, the nicotine levels are substantially the same at those generated by combusted tobacco whereas: (i) the levels of carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3 butadiene, isoprene, acrylonitrile, benzene, toluene, quinoline, styrene, N'-nitrosonornicotine (NNN), N'-nitrosoanatabine (NAT), N'-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia cadmium and mercury are decreased to levels of between about 0 to about 20% of the levels generated by combusted tobacco; (ii) the levels of pyridine, mercury and lead are decreased to levels of between about 20 to about 40% of the levels generated by combusted tobacco; and

(iii) the levels nicotine-free dry particulate matter (NFDPM), butyraldehyde and ammonia are decreased to levels of between about 40 to about 60% of the levels generated by combusted tobacco.

Referring to Table 4, in certain embodiments, 4-aminobiphenyl, 2-aminonaphthalene, 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1ng/mg nicotine. In certain embodiments, carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine. In certain embodiments, isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine. In certain embodiments, N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine. In certain embodiments, acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine. In certain embodiments, ammonia is present in the aerosol at between about 9 and 11 ng/mg nicotine. In certain embodiments, acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine. Referring to Table 4, in certain embodiments, 4-aminobiphenyl, 2-aminonaphthalene, 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1ng/mg nicotine; carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine; isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine; N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine; acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine; ammonia is present in the aerosol at between about 9 and 11 ng/mg nicotine; and acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine.

Although the present disclosure can result in a reduction in the levels of one or more HPHCs (other than nicotine) it is highly advantageous that the aerosol that is inhaled still creates acceptable levels of nicotine in the user. This will make the consumption experience much more acceptable to the user. As can be seen in Figure 1, heated tobacco can be used to deliver between about 7-8 ng/ml to the blood plasma of a user whereas combusted tobacco delivers between about 10-11 ng/ml to the blood plasma of a user. Accordingly, the amount of nicotine that is delivered to the user (for example, absorbed into the bloodstream) via the heating of tobacco is greater than about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the level of nicotine delivered via the combustion of tobacco. The extent of exposure to nicotine in the bloodstream of the user via the heated tobacco route can be about 10%, 15%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29% or 30% lower than via the combusted cigarette route.

In another embodiment, the overall pharmocokinetic profile of nicotine delivery is similar in the heated and combusted tobacco systems but with a lower exposure to nicotine following single use of the heated tobacco system (see Figure 1). The pharmacokinetic profile of nicotine

delivery using combusted tobacco is compared with heated tobacco in Figure 1. As can be seen, the overall pharmacokinetic profiles of nicotine delivery from heated tobacco systems are similar to combusted tobacco systems in that the levels of nicotine attained in the bloodstream by both systems rapidly increase within the first 6 minutes of smoking and reach their maximum levels at between 6 and 9 minutes. The levels of nicotine then tail off after about 9 minutes decreasing steadily thereafter.

Heating the tobacco in a manner which reduces pyrolysis and avoids combustion decreases the formation of HPHCs in the aerosol produced by the tobacco. It can result in a simplification in the composition of the aerosol and/or a reduction in the levels of many HPHCs.

Suitably, the tobacco is heated up to or below 400 °C. Thus, tobacco is heated and not burnt. More suitably, the tobacco is electrically heated up to or below 400 °C. In certain embodiments, the tobacco may be heated to a desired temperature of less than about 390 degrees Celsius, less than about 380 degrees Celsius, less than about 370 degrees Celsius, less than about 360 degrees Celsius, less than about 350 degrees Celsius, less than about 340 degrees Celsius, less than about 330 degrees Celsius, less than about 325 degrees Celsius.

In certain embodiments, the tobacco may be heated to a temperature of between about 390 and 325 degrees Celsius, between about 390 and 330 degrees Celsius, between about 390 and 335 degrees Celsius, between about 390 and 340 degrees Celsius, between about 390 and 345 degrees Celsius, between about 390 and 350 degrees Celsius, between about 390 and 355 degrees Celsius, between about 390 and 360 degrees Celsius, between about 390 and 365 degrees Celsius, between about 390 and 370 degrees Celsius, between about 390 and 375 degrees Celsius, between about 390 and 380 degrees Celsius, or between about 390 and 385 degrees Celsius.

In certain embodiments, the tobacco may be heated to a temperature of between about 380 and 325 degrees Celsius, between about 380 and 330 degrees Celsius, between about 380 and 335 degrees Celsius, between about 380 and 340 degrees Celsius, between about 380 and 345 degrees Celsius, between about 380 and 350 degrees Celsius, between about 380 and 355 degrees Celsius, between about 380 and 360 degrees Celsius, between about 380 and 365 degrees Celsius, between about 380 and 370 degrees Celsius or between about 380 and 375 degrees Celsius

In certain embodiments, the tobacco may be heated to a temperature of between about 375 and 325 degrees Celsius, between about 375 and 330 degrees Celsius, between about 375 and 335 degrees Celsius, between about 375 and 340 degrees Celsius, between about 375 and 345 degrees Celsius, between about 375 and 350 degrees Celsius, between about 375 and 355 degrees Celsius, between about 375 and 360 degrees Celsius, between about 375 and 365 degrees Celsius, or between about 375 and 370 degrees Celsius.

In certain embodiments, the tobacco may be heated to a temperature of between about 374 and

325 degrees Celsius, between about 374 and 330 degrees Celsius, between about 374 and 335 degrees Celsius, between about 374 and 340 degrees Celsius, between about 374 and 345 degrees Celsius, between about 374 and 350 degrees Celsius, between about 374 and 355 degrees Celsius, between about 374 and 360 degrees Celsius, between about 374 and 365 degrees Celsius, or between about 374 and 370 degrees Celsius.

In certain embodiments, the tobacco may be heated to a temperature of between about 373 and 325 degrees Celsius, between about 373 and 330 degrees Celsius, between about 373 and 335 degrees Celsius, between about 373 and 340 degrees Celsius, between about 373 and 345 degrees Celsius, between about 373 and 350 degrees Celsius, between about 373 and 355 degrees Celsius, between about 373 and 360 degrees Celsius, between about 373 and 365 degrees Celsius, or between about 373 and 370 degrees Celsius.

In certain embodiments, the tobacco may be heated a temperature of between about 372 and 325 degrees Celsius, between about 372 and 330 degrees Celsius, between about 372 and 335 degrees Celsius, between about 372 and 340 degrees Celsius, between about 372 and 345 degrees Celsius, between about 372 and 350 degrees Celsius, between about 372 and 355 degrees Celsius, between about 372 and 360 degrees Celsius, between about 372 and 365 degrees Celsius, or between about 372 and 370 degrees Celsius.

In certain embodiments, the tobacco may be heated to a temperature of between about 371 and 325 degrees Celsius, between about 371 and 330 degrees Celsius, between about 371 and 335 degrees Celsius, between about 371 and 340 degrees Celsius, between about 371 and 345 degrees Celsius, between about 371 and 350 degrees Celsius, between about 371 and 355 degrees Celsius, between about 371 and 360 degrees Celsius, between about 371 and 365 degrees Celsius, or between about 371 and 370 degrees Celsius.

The heating (for example, the electrical heating) of the tobacco will typically be achieved by electronically controlled means. The electronically controlled means may not only control the temperature used to heat the tobacco but it may also control the rate of heating of the tobacco.

Thus, in certain embodiments of this disclosure, the desired temperature is reached over a period of about 10 seconds, about 20 seconds, about 30 seconds, about 40 seconds, about 50 seconds, about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 6 minutes, about 7 minutes, about 8 minutes, about 9 minutes or about 10 minutes or more. Typically, the desired temperature will be reached before the user consumes the tobacco in the aerosol-generating device. The aerosol-generating device may include an electronic indicator – such as an LED – to indicate that the desired temperature has been reached.

As can be seen in at least Figure 2, users who use an aerosol-generating device in which tobacco contained in the aerosol-generating device is heated to a temperature of less than about 400 degrees Celsius to create an aerosol can have a characteristic biomarker profile. Whilst the level of nicotine in the smoker remains elevated (for example, as shown in Figure 1 a

smoker can have a nicotine concentration of about 7ng/ml) the levels of one or more biomarkers are reduced after a period of using the aerosol-generating device due to the lower levels of the one or more HPHCs that are present in aerosol inhaled by the smoker. By way of example, after 2 days of using the aerosol-generating device the smoker can have a biomarker profile in which: (i) the carbon monoxide level in the sample is between about 1%-2% (for example, about 1.5%); and/or (ii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine (for example, about 0.8, about 0.7 about 0.6 or about 0.5 micro.g/g creatinine ); and/or (iii) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine (for example, about 300 micro.g/g creatinine ); and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine (for example, about 0.5 micro.g/g creatinine). By way of further example, after 2 days of using the aerosol-generating device the smoker can have a biomarker profile in which: (i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2% (for example, about 1.5%); (ii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine (for example, about 0.8 micro.g/g creatinine ); (iii) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine (for example, about 300 micro.g/g creatinine ); and (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine (for example, about 0.5 micro.g/g creatinine ). This biomarker profile can be useful to identify smokers who use the device and also to assess the potential health benefits to the smoker that is using the device. Thus, in a further aspect there is provided a method of determining if a smoker uses an aerosol-generating device in which tobacco contained therein is heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing a sample from the smoker; and (b) determining the levels of one or more of carbon monoxide, benzene, acrolein and 1,3-butadiene therein; wherein (i) if the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2% after about 2 days of consuming aerosol generated from heated tobacco; and/or (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine after about 2 days of consuming aerosol generated from heated tobacco; and/or (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine after about 2 days of consuming aerosol generated from heated tobacco; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine after about 2 days of consuming aerosol generated from heated tobacco is indicative that said user uses the aerosol-generating device.

In a further aspect, there is also provided a method of identifying a user using an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing a sample from the user; and (b) determining the

levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein; wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (ii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iii) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco is indicative that said user uses the aerosol-generating device.

The user can be identified from a pool of two or more users. The method may be used to evaluate a batch of test results (for example, a batch of blind test results in which it is not known which form of combusted or electrically heated tobacco the user has been using) in order to identify one or more users that have been using electrically heated tobacco.

In a further aspect, there is provided a sample isolated, obtained or collected from a smoker at least 2 days (for example, 2 days, 3 days, 4, days, 5 days, 6 days or 7 days) after using an aerosol-generating device in which tobacco contained therein is heated to a temperature of less than about 400 degrees Celsius to create an aerosol, wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2%; and/or (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine ; and/or (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine ; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine .

Suitably, the levels of carbon monoxide, benzene, acrolein and 1,3-butadiene are determined. If a conventional cigarette is heated at up to or less than 400 °C this can result in an aerosol which is unacceptable to the user. In addition to controlling the temperature at which the tobacco is heated, modification of the tobacco blend may be desirable in order to create tobacco – such as tobacco stick - which produces an acceptable taste and flavour for the user, while also reducing the level of one or more HPHCs inhaled as described herein.

The user can be a smoker as defined herein. The user can be a current smoker, a smoker who has elected to stop smoking, a smoker who is trying to stop smoking or a smoker who is receiving therapy – such as nictotine replacement therapy - to stop smoking or to try to stop smoking. The user can be a single user or a pool of two or more users. For a pool of users, the smoking status of the pool of users can be the same but generally it will be different. When comparisons are being made between users using combustible tobacco (for example,

conventional cigarettes) and electrically heated tobacco then it is generally preferred that the average lung capacity or lung volume of the users will be about the same.

In one embodiment, an aerosol-forming agent can be included in the tobacco blend to facilitate producing an aerosol that is more acceptable to the user. Suitable aerosol-formers are known in the art and include, but are not limited to: polyhydric alcohols, such as propylene glycol, triethylene glycol, 1,3-butanediol and glycerine; esters of polyhydric alcohols, such as glycerol mono-, di- or triacetate; and aliphatic esters of mono-, di- or polycarboxylic acids, such as dimethyl dodecanedioate and dimethyl tetradecanedioate. Particularly suitable aerosol formers are polyhydric alcohols or mixtures thereof, such as propylene glycol, triethylene glycol, 1,3-butanediol and, most suitably, glycerine. The aerosol-forming substrate may comprise a single aerosol former. Alternatively, the aerosol-forming substrate may comprise a combination of two or more aerosol formers. Suitably, the aerosol-forming substrate has an aerosol former content of greater than about 5% on a dry weight basis. The aerosol aerosol-forming substrate may have an aerosol former content of between approximately 5% and approximately 30% on a dry weight basis. In one embodiment, the aerosol-forming substrate has an aerosol former content of approximately 20% on a dry weight basis.

In other embodiments, the aerosol-forming substrate comprises a gathered textured sheet of homogenised tobacco material. In other embodiments, the aerosol-forming substrate comprises a gathered crimpled sheet of homogenised tobacco material. In one embodiment, a combination of an aerosol-forming substrate comprising gathered sheets of homogenised tobacco are used. They may be made by methods known in the art, for example the methods disclosed in WO 2012/164009 A2.

Use of a textured sheet of homogenised tobacco material may advantageously facilitate gathering of the sheet of homogenised tobacco material to form the aerosol-forming substrate. In certain embodiments, the aerosol-forming substrate may comprise a gathered sheet of homogenised tobacco material that is substantially evenly textured over substantially its entire surface. For example, the aerosol-forming substrate may comprise a gathered crimped sheet of homogenised tobacco material comprising a plurality of substantially parallel ridges or corrugations that are substantially evenly spaced-apart across the width of the sheet.

The aerosol-forming substrate may be in the form of a plug comprising an aerosol-forming material circumscribed by a paper or other wrapper. Where an aerosol-forming substrate is in the form of a plug, the entire plug including any wrapper is considered to be the aerosol-forming substrate.

In one embodiment, the aerosol-generating substrate comprises a plug comprising a gathered textured sheet of homogenised tobacco material circumscribed by a wrapper. In a particularly preferred embodiment, the aerosol-generating substrate comprises a plug comprising a gathered crimped sheet of homogenised tobacco material circumscribed by a wrapper.

In certain embodiments, sheets of homogenised tobacco material for use in the aerosol-generating substrate may have a tobacco content of approximately 70% or more by weight on a dry weight basis.

Sheets of homogenised tobacco material for use in the aerosol-generating substrate may comprise one or more intrinsic binders, that is tobacco endogenous binders, one or more extrinsic binders, that is tobacco exogenous binders, or a combination thereof to help agglomerate the particulate tobacco. Alternatively, or in addition, sheets of homogenised tobacco material for use in the aerosol-generating substrate may comprise other additives including, but not limited to, tobacco and non-tobacco fibres, aerosol-formers, humectants, plasticisers, flavourants, fillers, aqueous and non-aqueous solvents and combinations thereof.

Suitable extrinsic binders for inclusion in sheets of homogenised tobacco material for use in the aerosol-generating substrate are known in the art and include, but are not limited to: gums such as, for example, guar gum, xanthan gum, arabic gum and locust bean gum; cellulosic binders such as, for example, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, methyl cellulose and ethyl cellulose; polysaccharides such as, for example, starches, organic acids, such as alginic acid, conjugate base salts of organic acids, such as sodium-alginate, agar and pectins; and combinations thereof.

Suitable non-tobacco fibres for inclusion in sheets of homogenised tobacco material for use in the aerosol-generating substrate are known in the art and include, but are not limited to: cellulose fibers; soft-wood fibres; hard-wood fibres; jute fibres and combinations thereof. Prior to inclusion in sheets of homogenised tobacco material for use in the aerosol-generating substrate, non-tobacco fibres may be treated by suitable processes known in the art including, but not limited to: mechanical pulping; refining; chemical pulping; bleaching; sulfate pulping; and combinations thereof.

Sheets of homogenised tobacco material for use in the aerosol-generating substrate should have sufficiently high tensile strength to survive being gathered to form the aerosol-generating substrate. In certain embodiments non-tobacco fibres may be included in sheets of homogenised tobacco material for use in the aerosol-generating substrate in order to achieve an appropriate tensile strength.

For example, homogenised sheets of tobacco material for use in the aerosol-generating substrate may comprise between approximately 1% and approximately 5% non-tobacco fibres by weight on a dry weight basis.

Returning now to the aerosol-generating device that can be used in accordance with the present disclosure, the aerosol-generating device generally comprises two ends: a proximal end through which aerosol exits the aerosol-generating device and is delivered to a user and a distal end. In use, a user may draw on the proximal end in order to inhale aerosol generated by the aerosol-generating device. The proximal end may also be referred to as the mouth end or the

downstream end and is downstream of the distal end. The distal end may also be referred to as the upstream end and is upstream of the proximal end.

Generally, the aerosol-generating device is a smoking device that generates an aerosol that is directly inhalable into a user's lungs through the user's mouth. The aerosol-generating device is a smoking article that is capable, upon heating, of generating a nicotine-containing aerosol that is directly inhalable into a user's lungs through the user's mouth.

For the avoidance of doubt, in the following description the term 'heating element' is used to mean one or more heating elements.

The aerosol-forming substrate can be located at the upstream end of the aerosol-generating article.

In alternative embodiments, the aerosol-generating article may comprise a front-plug upstream of the aerosol-forming substrate, wherein the front plug is penetrable by a heating element of an aerosol-generating device. In such alternative embodiments, the front-plug may be located at the upstream end of the aerosol-generating article.

In such embodiments, the front-plug may prevent egress of the aerosol-forming substrate from the upstream end of the aerosol-forming substrate during handling and shipping. The front-plug may also assist in positioning the aerosol-forming substrate at a predetermined distance from the upstream end of the aerosol-forming substrate for optimum engagement with a heating element of an aerosol-generating device.

The front-plug may be configured to prevent egress of the aerosol-forming substrate from the aerosol-generating article during use, for example as a heating element of the aerosol-generating device is withdrawn from the aerosol-generating article. The aerosol-forming substrate of the aerosol-generating article may shrink into contact with a heating element of the aerosol-generating device during heating of the aerosol-forming substrate to generate an aerosol. The aerosol-forming substrate may also shrink such that its contact with the outer wrapper circumscribing the components of the aerosol-generating article is reduced. This may loosen the aerosol-forming substrate within the aerosol-generating article. Inclusion of a front-plug may facilitate removal of a heating element from the aerosol-generating article by resisting upstream movement of the aerosol-forming substrate during withdrawal of a heating element of an aerosol-generating device from the aerosol-forming substrate of aerosol-generating article.

Alternatively or in addition, the front-plug may be configured to wipe a surface of the heating element of the aerosol-generating device as the heating element of the aerosol-generating device is withdrawn from the aerosol-generating article.

The front-plug may define a hole or slit through which a heating element of an aerosol-generating device can pass. The hole or slit defined in the front-plug may be dimensioned to engage with a heating element of an aerosol-generating device passed therethrough. For example, the dimensions of the hole or slit defined in the front-plug may almost exactly match

the dimensions of a cross-section of the heating element of the aerosol-generating device. Alternatively, the hole or slit may have smaller dimensions than a cross-section of the heating element of the aerosol-generating device. In such embodiments, the heating element may need to deform the front-plug in order to pass through the hole or slit.

One or more holes or slits may be defined in the front-pug. For example, an aerosol-generating article intended to be used with an aerosol-generating device having three heating elements may comprise a front-plug with three holes or slits defined therein, each arranged to accept one of the three heating elements of the aerosol-generating device.

Alternatively, the front-plug may be formed of a pierceable material.

The front-plug may be made from an air permeable material that allows air to be drawn through the front plug. In such embodiments, a user may draw air downstream through the aerosol-generating article through the front-plug.

The front-plug may be formed from an air permeable filter material. The front-plug may conveniently be formed from an air permeable material used to form mouthpiece filters for a conventional lit-end cigarette. For example, the front-plug may be formed from cellulose acetate tow. The permeability of the front-plug may be varied to help control resistance to draw of the aerosol-generating article.

Alternatively, the front-plug may be formed from an air impermeable material. In such embodiments, the aerosol-generating article may further comprise one or more air inlets downstream of the front plug through which air may be drawn into the aerosol-generating article.

The front-plug may be formed from a low strength material in order to reduce the force required to penetrate the front plug with a heating element of an aerosol-generating device.

The front plug may be formed from a fibrous material or a foam material. Where the front-plug is formed from a fibrous material, the fibres of the fibrous material may be substantially aligned along the longitudinal direction of the aerosol-generating article in order to reduce the force required to penetrate the front plug with a heating element of an aerosol-generating device.

In some embodiments, the front-plug may be at least partially formed from an aerosol-forming substrate. For example, the front-plug may be at least partially formed from an aerosol-forming substrate comprising tobacco.

The front-plug may be formed from a pierceable material that may be deformed by a heating element of an aerosol-generating device upon insertion of the heating element into the aerosol-generating article and that regains its shape when the heating element is withdrawn from the aerosol-generating article.

For example, the front-plug may be formed from a pierceable resilient material that deforms to allow a heating element of an aerosol-generating device to pass the front plug when the front plug is pierced by the heating element. When the heating element is withdrawn from the

aerosol-generating article, the hole or slit pierced through the front-plug by the heating element may fully or partially close. In such embodiments, the front-plug may advantageously provide a cleaning function by wiping the heating element of the aerosol-generating device as the heating element is withdrawn from the aerosol-generating article.

However, it will be appreciated that the front-plug does not need to be formed from a resilient material in order to provide a cleaning function. For example, a cleaning function may also be provided on withdrawal of a heating element of an aerosol-generating device from the aerosol-generating article where the front plug defines a hole or slit having dimensions that almost exactly match or are smaller than the dimensions of a cross-section of the heating element.

The front-plug may have an external diameter that is approximately equal to the external diameter of the aerosol-generating article.

The front-plug may have an external diameter of at least 5 millimetres. The front-plug substrate may have an external diameter of between approximately 5 millimetres and approximately 12 millimetres, for example of between approximately 5 millimetres and approximately 10 millimetres or of between approximately 6 millimetres and approximately 8 millimetres. In one embodiment, the front-plug has an external diameter of 7.2 millimetres +/- 10%.

The front plug may have a length of at least 2 millimetres, at least 3 millimetres or at least 4 millimetres. The front-plug may have a length of between approximately 2 millimetres and approximately 10 mm, for example of between approximately 4 millimetres and approximately 8 mm.

The front-plug may be substantially cylindrical.

The aerosol-forming substrate may be a solid aerosol-forming substrate. The aerosol-forming substrate may comprise both solid and liquid components.

The aerosol-forming substrate comprises tobacco. In addition, the aerosol-forming substrate may comprise a non-tobacco containing aerosol-forming material.

Optionally, the solid aerosol-forming substrate may contain tobacco or non-tobacco volatile flavour compounds, which are released upon heating of the solid aerosol-forming substrate. The solid aerosol-forming substrate may also contain one or more capsules that, for example, include additional tobacco volatile flavour compounds or non-tobacco volatile flavour compounds and such capsules may melt during heating of the solid aerosol-forming substrate.

Optionally, the solid aerosol-forming substrate may be provided on or embedded in a thermally stable carrier. The carrier may take the form of powder, granules, pellets, shreds, strands, strips or sheets. The solid aerosol-forming substrate may be deposited on the surface of the carrier in the form of, for example, a sheet, foam, gel or slurry. The solid aerosol-forming substrate may be deposited on the entire surface of the carrier, or alternatively, may be deposited in a pattern in order to provide a non-uniform flavour delivery during use.

In one embodiment, the aerosol-forming substrate comprises an aerosol former.

In one embodiment sheets of homogenised tobacco material for use in the aerosol-generating article are formed from a slurry comprising particulate tobacco, guar gum, cellulose fibres and glycerine by a casting process.

The aerosol-forming element may have an external diameter that is approximately equal to the external diameter of the aerosol-generating article.

The aerosol-forming substrate may have an external diameter of at least 5 millimetres. The aerosol-forming substrate may have an external diameter of between approximately 5 millimetres and approximately 12 millimetres, for example of between approximately 5 millimetres and approximately 10 millimetres or of between approximately 6 millimetres and approximately 8 millimetres. In a preferred embodiment, the aerosol-forming substrate has an external diameter of 7.2 millimetres +/- 10%.

The aerosol-forming substrate may have a length of between approximately 7 millimetres and approximately 15 mm. In one embodiment, the aerosol-forming substrate may have a length of approximately 10 millimetres. In a preferred embodiment, the aerosol-forming substrate has a length of approximately 12 millimetres.

The aerosol-forming substrate may be substantially cylindrical.

The support element is located immediately downstream of the aerosol-forming substrate and abuts the aerosol-forming substrate.

The support element may be formed from any suitable material or combination of materials. For example, the support element may be formed from one or more materials selected from the group consisting of: cellulose acetate; cardboard; crimped paper, such as crimped heat resistant paper or crimped parchment paper; and polymeric materials, such as low density polyethylene (LDPE). In a preferred embodiment, the support element is formed from cellulose acetate.

The support element may comprise a hollow tubular element. In a preferred embodiment, the support element comprises a hollow cellulose acetate tube.

The support element may have an external diameter that is approximately equal to the external diameter of the aerosol-generating article.

The support element may have an external diameter of between approximately 5 millimetres and approximately 12 millimetres, for example of between approximately 5 millimetres and approximately 10 millimetres or of between approximately 6 millimetres and approximately 8 millimetres. In a preferred embodiment, the support element has an external diameter of 7.2 millimetres +/- 10%.

The support element may have a length of between approximately 5 millimetres and approximately 15 mm. In a preferred embodiment, the support element has a length of approximately 8 millimetres.

During insertion of a heating element of an aerosol-generating device into an aerosol-forming substrate of an aerosol-generating article, a user may be required to apply some force in order to overcome the resistance of the aerosol-forming substrate of the aerosol-generating article to insertion of the heating element of the aerosol-generating device. This may damage one or both of the aerosol-generating article and the heating element of the aerosol-generating device. In addition, the application of force during insertion of the heating element of the aerosol-generating device into the aerosol-forming substrate of the aerosol-generating article may displace the aerosol-forming substrate within the aerosol-generating article. This may result in the heating element of the aerosol-generating device not being fully inserted into the aerosol-forming substrate, which may lead to uneven and inefficient heating of the aerosol-forming substrate of the aerosol-generating article.

In preferred embodiments, the support element is configured to resist downstream movement of the aerosol-forming substrate during insertion of the heating element of the aerosol-generating device into the aerosol-forming substrate of aerosol-generating article.

The insertion force experienced by the aerosol-generating article as it is inserted into the aerosol-generating device by a user may be divided into three parts: friction force, penetration force and crush force.

As the aerosol-generating article is initially inserted into the aerosol-generating device and prior to the heating element of the aerosol-generating device being inserted into the aerosol-forming substrate of the aerosol-generating article, the insertion force is dominated by the force required to overcome friction due to interference between the exterior surface of the aerosol-generating article and the interior surface of the aerosol-generating device. As used herein, the term 'friction force' is used to describe the maximum insertion force prior to insertion of the heating element of the aerosol-generating device into the aerosol-forming substrate of the aerosol-generating article.

As the aerosol-generating article is inserted further into the aerosol-generating device and prior to the aerosol-generating article reaching a position of maximum insertion, the insertion force is dominated by the force required to overcome resistance of the aerosol-forming substrate of the aerosol-generating article to insertion of the heating element of the aerosol-generating device.

Once the aerosol-generating article reaches a point of maximum insertion, the insertion force is dominated by the force required to deform the aerosol-generating article. At the position of maximum insertion, the extreme upstream end of the aerosol-generating article may come into contact with a surface, for example a bottom or rear surface, of the aerosol-generating device, which prevents the aerosol-generating article from being inserted further into the aerosol-generating device.

The support element of the aerosol-generating article resists the penetration force experienced by the aerosol-generating article during insertion of a heating element of an aerosol-generating

device into the aerosol-forming substrate.

In one embodiment, the support element is configured to resist a penetration force of at least 2.5 N during insertion of a heating element of an aerosol-generating device into the aerosol-forming substrate.

In another embodiment, the support element is configured to resist a penetration force of at least 4 N during insertion of a heating element of an aerosol-generating device into the aerosol-forming substrate.

The support element of the aerosol-generating article resists downstream movement of the aerosol-forming substrate within the aerosol-generating article during insertion of a heating element of an aerosol-generating device into the aerosol-forming substrate.

This may help to ensure that the heating element of the aerosol-generating device is fully inserted into the aerosol-forming substrate and so avoid uneven and inefficient heating of the aerosol-forming substrate of the aerosol-generating article.

The support element may have a fracture force of at least 40 N, for example at least 45 N or at least 50 N as measured using a standard compression test.

The aerosol-cooling element may be located immediately downstream of the support element and abut the support element.

The aerosol-cooling element may be located between the support element and a mouthpiece located at the extreme downstream end of the aerosol-generating article.

The aerosol-cooling element may have a total surface area of between approximately 300 square millimetres per millimetre length and approximately 1000 square millimetres per millimetre length. In a preferred embodiment, the aerosol-cooling element has a total surface area of approximately 500 square millimetres per millimetre length.

The aerosol-cooling element may be alternatively termed a heat exchanger.

The aerosol-cooling element may have a low resistance to draw. That is, the aerosol-cooling element offers a low resistance to the passage of air through the aerosol-generating article. The aerosol-cooling element does not substantially affect the resistance to draw of the aerosol-generating article.

The aerosol-cooling element may have a porosity of between 50% and 90% in the longitudinal direction. The porosity of the aerosol-cooling element in the longitudinal direction is defined by the ratio of the cross-sectional area of material forming the aerosol-cooling element and the internal cross-sectional area of the aerosol-generating article at the position of the aerosol-cooling element.

The aerosol-cooling element may alternatively be referred to as a heat exchanger.

The aerosol-cooling element may comprise a plurality of longitudinally extending channels. The plurality of longitudinally extending channels may be defined by a sheet material that has been one or more of crimped, pleated, gathered and folded to form the channels. The plurality of

longitudinally extending channels may be defined by a single sheet that has been one or more of crimped, pleated, gathered and folded to form multiple channels. Alternatively, the plurality of longitudinally extending channels may be defined by multiple sheets that have been one or more of crimped, pleated, gathered and folded to form multiple channels.

It is preferred that airflow through the aerosol-cooling element does not deviate to a substantive extent between adjacent channels. In other words, it is preferred that the airflow through the aerosol-cooling element is in a longitudinal direction along a longitudinal channel, without substantive radial deviation. In some embodiments, the aerosol-cooling element is formed from a material that has a low porosity, or substantially no-porosity other than the longitudinally extending channels. For example, the aerosol-cooling element may be formed from a sheet material having low porosity or substantially no porosity that has been one or more of crimped, pleated, gathered and folded to form the channels.

In some embodiments, the aerosol-cooling element may comprise a gathered sheet of material selected from the group consisting of metallic foil, polymeric material, and substantially non-porous paper or cardboard. In some embodiments, the aerosol-cooling element may comprise a gathered sheet of material selected from the group consisting of polyethylene (PE), polypropylene (PP), polyvinylchloride (PVC), polyethylene terephthalate (PET), polylactic acid (PLA), cellulose acetate (CA), and aluminium foil.

In a preferred embodiment, the aerosol-cooling element comprises a gathered sheet of biodegradable material. For example, a gathered sheet of non-porous paper or a gathered sheet of biodegradable polymeric material, such as polylactic acid or a grade of Mater-Bi® (a commercially available family of starch based copolyesters).

In a particularly preferred embodiment, the aerosol-cooling element comprises a gathered sheet of polylactic acid.

The aerosol-cooling element may be formed from a gathered sheet of material having a specific surface area of between approximately 10 square millimetres per milligram and approximately 100 square millimetres per milligram weight. In some embodiments, the aerosol-cooling element may be formed from a gathered sheet of material having a specific surface area of approximately 35 $mm^2/mg$.

When an aerosol that contains a proportion of water vapour is drawn through the aerosol-cooling element, some of the water vapour may condense on a surface of the aerosol-cooling element. In such cases, it is preferred that the condensed water remains in droplet form on the surface of the aerosol-cooling element rather than being absorbed into the aerosol-cooling element. Thus, it is preferred that the aerosol-cooling element is formed from material that is substantially non-porous or substantially non-absorbent to water.

The aerosol-cooling element may act to cool the temperature of a stream of aerosol drawn through the aerosol-cooling element by means of thermal transfer. Components of the aerosol

will interact with the aerosol-cooling element and loose thermal energy.

The aerosol-cooling element may act to cool the temperature of a stream of aerosol drawn through the aerosol-cooling element by undergoing a phase transformation that consumes heat energy from the aerosol stream. For example, the aerosol-cooling element may be formed from a material that undergoes an endothermic phase transformation such as melting or a glass transition.

The aerosol-cooling element may act to lower the temperature of a stream of aerosol drawn through the aerosol-cooling element by causing condensation of components such as water vapour from the aerosol stream. Due to condensation, the aerosol stream may be drier after passing through the aerosol-cooling element. In some embodiments, the water vapour content of an aerosol stream drawn through the aerosol-cooling element may be lowered by between approximately 20% and approximately 90%. The user may perceive the temperature of a drier aerosol to be lower than the temperature of a moister aerosol of the same actual temperature.

In some embodiments, the temperature of an aerosol stream may be lowered by more than 10 degrees Celsius as it is drawn through the aerosol-cooling element. In some embodiments, the temperature of an aerosol stream may be lowered by more than 15 degrees Celsius or more than 20 degrees Celsius as it is drawn through the aerosol-cooling element.

In some embodiments, the aerosol-cooling element removes a proportion of the water vapour content of an aerosol drawn through the aerosol-cooling element. In some embodiments, a proportion of other volatile substances may be removed from the aerosol stream as the aerosol is drawn through the aerosol-cooling element. For example, in some embodiments a proportion of phenolic compounds may be removed from the aerosol stream as the aerosol is drawn through the aerosol-cooling element.

Phenolic compounds may be removed by interaction with the material forming the aerosol-cooling element. For example, the aerosol-cooling element may be formed from a material that adsorbs the phenolic compounds (for example phenols and cresols).

Phenolic compounds may be removed by interaction with water droplets condensed on the surface of the aerosol-cooling element.

As noted above, the aerosol-cooling element may be formed from a sheet of suitable material that has been one or more of crimped, pleated, gathered or folded to define a plurality of longitudinally extending channels. A cross-sectional profile of such an aerosol-cooling element may show the channels as being randomly oriented. The aerosol-cooling element may be formed by other means. For example, the aerosol-cooling element may be formed from a bundle of longitudinally extending tubes. The aerosol-cooling element may be formed by extrusion, molding, lamination, injection, or shredding of a suitable material.

The aerosol-cooling element may comprise an outer tube or wrapper that contains or locates the longitudinally extending channels. For example, a pleated, gathered, or folded sheet

material may be wrapped in a wrapper material, for example a plug wrapper, to form the aerosol-cooling element. In some embodiments, the aerosol-cooling element comprises a sheet of crimped material that is gathered into a rod-shape and bound by a wrapper, for example a wrapper of filter paper.

The aerosol-cooling element may have an external diameter that is approximately equal to the external diameter of the aerosol-generating article.

The aerosol-cooling element may have an external diameter of a diameter of between approximately 5 millimetres and approximately 10 millimetres, for example of between approximately 6 millimetres and approximately 8 millimetres. In a preferred embodiment, the aerosol-cooling element has an external diameter of 7.2 millimetres +/- 10%.

The aerosol-cooling element may have a length of between approximately 5 millimetres and approximately 25 mm. In a preferred embodiment, the aerosol-cooling element has a length of approximately 18 millimetres.

In some embodiments, the aerosol-cooling element may comprise a gathered sheet of material selected from the group consisting of metallic foil, polymeric material, and substantially non-porous paper or cardboard. In some embodiments, the aerosol-cooling element may comprise a gathered sheet of material selected from the group consisting of polyethylene (PE), polypropylene (PP), polyvinylchloride (PVC), polyethylene terephthalate (PET), polylactic acid (PLA), cellulose acetate (CA), and aluminium foil.

In a preferred embodiment, the aerosol-cooling element comprises a gathered sheet of biodegradable polymeric material, such as polylactic acid or a grade of Mater-Bi® (a commercially available family of starch based copolyesters).

In a particularly preferred embodiment, the aerosol-cooling element comprises a gathered sheet of polylactic acid.

The aerosol-generating article may comprise a volatile flavour-generating component located in the aerosol-cooling element. For example, the aerosol-generating article may comprise a volatile flavour-generating component located in a longitudinally extending channel of the aerosol-cooling element.

The volatile flavour-generating component may be in the form of a liquid or a solid. The volatile flavour-generating compound may be coupled to, or otherwise associated with, a support element. The volatile flavour-generating component may comprise menthol.

Menthol may be used in solid or liquid form. In solid form, menthol may be provided as particles or granules. The term 'solid menthol particles' may be used to describe any granular or particulate solid material comprising at least approximately 80% menthol by weight.

Suitably, 1.5 mg or more of the volatile flavour generating component is included in the aerosol-generating article.

The volatile flavour-generating component may be coupled to a fibrous support element. The

fibrous support element may be any suitable substrate or support for locating, holding, or retaining the flavour-generating component. The fibrous support element may be, for example, a paper support. Such a paper support may be saturated with a liquid component such as liquid menthol. The fibrous support may be, for example, a thread or twine. Such a thread or twine may be saturated in a liquid component such as liquid menthol. Alternatively, such a thread or twine may be threaded to or otherwise coupled to a solid flavour generating component. For example, solid particles of menthol may be coupled to a thread.

Suitably, the volatile flavour-generating component is supported by an elongate fibrous support element, such as a thread or twine. Suitably, the volatile flavour-generating component is disposed radially inward from an inner surface of the outer wrapper within the aerosol-generating article with the longitudinal axis of the elongate fibrous support element disposed substantially parallel to the longitudinal axis of the aerosol-generating article.

The aerosol-generating article may comprise a mouthpiece located at the downstream end of the aerosol-generating article.

The mouthpiece may be located immediately downstream of the aerosol-cooling element and abut the aerosol-cooling element.

The mouthpiece may comprise a filter. The filter may be formed from one or more suitable filtration materials. Many such filtration materials are known in the art. In one embodiment, the mouthpiece may comprise a filter formed from cellulose acetate tow.

The mouthpiece suitably has an external diameter that is approximately equal to the external diameter of the aerosol-generating article.

The mouthpiece may have an external diameter of a diameter of between approximately 5 millimetres and approximately 10 millimetres, for example of between approximately 6 millimetres and approximately 8 millimetres. In a preferred embodiment, the mouthpiece has an external diameter of 7.2 millimetres +/- 10%.

The mouthpiece may have a length of between approximately 5 millimetres and approximately 20 millimetres. In a preferred embodiment, the mouthpiece has a length of approximately 14 millimetres.

The mouthpiece may have a length of between approximately 5 millimetres and approximately 14 millimetres. In a preferred embodiment, the mouthpiece has a length of approximately 7 millimetres.

The aerosol-forming substrate, the support element and the aerosol-cooling element and any other elements of the aerosol-generating article, such as the front-plug and mouthpiece where present, are circumscribed by an outer wrapper. The outer wrapper may be formed from any suitable material or combination of materials.

The outer wrapper can be a cigarette paper.

A downstream end portion of the outer wrapper may be circumscribed by a band of tipping

paper.

The appearance of the aerosol-generating article may simulate the appearance of a conventional lit-end cigarette.

The aerosol-generating article may have an external diameter of between approximately 5 millimetres and approximately 12 millimetres, for example of between approximately 6 millimetres and approximately 8 millimetres. In a preferred embodiment, the aerosol-generating article has an external diameter of 7.2 millimetres +/- 10%.

The aerosol-generating article may have a total length of between approximately 30 millimetres and approximately 100 millimetres. In a preferred embodiment, the aerosol-generating article has a total length of approximately 45 millimetres.

The aerosol-generating device may comprise: a housing; a heating element; an electrical power supply connected to the heating element; and a control element configured to control the supply of power from the power supply to the heating element.

The housing may define a cavity surrounding the heating element, the cavity configured to receive the aerosol-generating article.

The aerosol-generating device may be a portable or handheld aerosol-generating device that is comfortable for a user to hold between the fingers of a single hand.

The aerosol-generating device may be substantially cylindrical in shape.

The aerosol-generating device may have a length of between approximately 70 millimetres and approximately 120 millimetres.

The device may include other heaters in addition to the internal heating element that is inserted into the aerosol-forming substrate of the aerosol-generating article.

The power supply may be any suitable power supply, for example a DC voltage source such as a battery. In one embodiment, the power supply is a Lithium-ion battery. Alternatively, the power supply may be a Nickel-metal hydride battery, a Nickel cadmium battery, or a Lithium based battery, for example a Lithium-Cobalt, a Lithium-Iron-Phosphate, Lithium Titanate or a Lithium-Polymer battery.

The control element may be a simple switch. Alternatively the control element may be electric circuitry and may comprise one or more microprocessors or microcontrollers.

The aerosol-generating system may comprise an aerosol-generating device and one or more aerosol-generating articles configured to be received in the cavity of the aerosol-generating device.

The heating element of the aerosol-generating device may be any suitable heating element capable of being inserted into the aerosol-forming substrate of the aerosol-generating article. For example, the heating element may be in the form of a pin or blade.

The heating element may have a tapered, pointed or sharpened end to facilitate insertion of the heating element into the aerosol-forming substrate of the aerosol-generating article.

The resistance to draw (RTD) of the aerosol-generating article after insertion of the heating element may be between approximately 80 mm WG and approximately 140 mm WG.

Features described in relation to one aspect or embodiment may also be applicable to other aspects and embodiments. For example, features described in relation to aerosol-generating articles and aerosol-generating systems described above may also be used in conjunction with methods of using aerosol-generating articles and aerosol-generating systems described above.

Mechanical and/or electrical parts or elements of the aerosol-generating articles and/or aerosol-generating systems can be modified or adapted by routine experimentation in order to optimise the HPHC levels and/or the nicotine delivery profile. Thus, a method of testing, adapting or improving a device is also described in which the aerosol-generating article and/or the aerosol-generating system is modified and the modification is then tested to determine if the modification is beneficial. This process may be repeated two or more times. Thus, in one aspect, there is provided a method of modifying or adapting an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing the aerosol-generating article; (b) making one or more modifications to one or more component parts or elements thereof; and (c) testing the aerosol-generating article to determine if the modification(s) has a beneficial effect on the aerosol-generating article, said testing comprising the steps of: (i) determining the levels one or more HPHCs other than nicotine in the aerosol, wherein a reduction in the levels of one or more HPHCs in the aerosol is indicative that the one or more modifications has a beneficial effect on the aerosol-generating article; and/or (ii) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein in the user after inhaling the aerosol; wherein a reduction in one or more, suitably, all of these levels, is indicative that the one or more modifications have a beneficial effect on the aerosol-generating article. For example, different heating elements or the operation of the heating element can be adjusted and the impact thereof can be determined. In certain embodiments, the modified aerosol-generating article can be tested within the parameters of determining if the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the aerosol contains levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco. In certain embodiments, the modified aerosol-generating article can be tested within the parameters of at least a reduction in carbon monoxide and/or benzene and/or acrolein and/or 1,3-butadiene. In certain embodiments, the modified aerosol-generating article can be tested within the parameters of a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine ; and/or a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine ; and/or a MHBMA (1,3-butadiene

marker) level in the user is between about 0.1 to 1 micro.g/g creatinine .

Tobacco for use here may be derived or derivable from naturally occurring plants, mutant plants, non-naturally occurring plants or transgenic plants. Suitably, the tobacco is derived or is derivable from any species of the genus *Nicotiana*, including *N. rustica* and *N. tabacum* (for example, LA B21, LN KY171, TI 1406, Basma, Galpao, Perique, Beinhart 1000-1, K326, Hicks Broadleaf and Petico). Other species include *N. acaulis, N. acuminata, N. acuminata var. multiflora, N. africana, N. alata, N. amplexicaulis, N. arentsii, N. attenuata, N. benavidesii, N. benthamiana, N. bigelovii, N. bonariensis, N. cavicola, N. clevelandii, N. cordifolia, N. corymbosa, N. debneyi, N. excelsior, N. forgetiana, N. fragrans, N. glauca, N. glutinosa, N. goodspeedii, N. gossei, N. hybrid, N. ingulba, N. kawakamii, N. knightiana, N. langsdorffii, N. linearis, N. longiflora, N. maritima, N. megalosiphon, N. miersii, N. noctiflora, N. nudicaulis, N. obtusifolia, N. occidentalis, N. occidentalis subsp. hesperis, N. otophora, N. paniculata, N. pauciflora, N. petunioides, N. plumbaginifolia, N. quadrivalvis, N. raimondii, N. repanda, N. rosulata, N. rosulata subsp. ingulba, N. rotundifolia, N. setchellii, N. simulans, N. solanifolia, N. spegazzinii, N. stocktonii, N. suaveolens, N. sylvestris, N. thyrsiflora, N. tomentosa, N. tomentosiformis, N. trigonophylla, N. umbratica, N. undulata, N. velutina, N. wigandioides, and N. x sanderae.* In a highly preferred embodiment, the tobacco is derived or derivable from a plant of the genus Nicotiana or the species *Nicotiana tabacum.* The use of tobacco cultivars and elite tobacco cultivars is also contemplated. Particularly useful *Nicotiana tabacum* varieties include Burley type, dark type, flue-cured type, and Oriental type tobaccos. Non-limiting examples of varieties or cultivars are: BD 64, CC 101, CC 200, CC 27, CC 301, CC 400, CC 500, CC 600, CC 700, CC 800, CC 900, Coker 176, Coker 319, Coker 371 Gold, Coker 48, CD 263, DF911, DT 538 LC Galpao tobacco, GL 26H, GL 350, GL 600, GL 737, GL 939, GL 973, HB 04P, HB 04P LC, HB3307PLC, Hybrid 403LC, Hybrid 404LC, Hybrid 501 LC, K 149, K 326, K 346, K 358, K394, K 399, K 730, KDH 959, KT 200, KT204LC, KY10, KY14, KY 160, KY 17, KY 171, KY 907, KY907LC, KTY14xL8 LC, Little Crittenden, McNair 373, McNair 944, msKY 14xL8, Narrow Leaf Madole, Narrow Leaf Madole LC, NBH 98, N-126, N-777LC, N-7371LC, NC 100, NC 102, NC 2000, NC 291, NC 297, NC 299, NC 3, NC 4, NC 5, NC 6, NC7, NC 606, NC 71, NC 72, NC 810, NC BH 129, NC 2002, Neal Smith Madole, OXFORD 207, PD 7302 LC, PD 7309 LC, PD 7312 LC, 'Perique' tobacco, PVH03, PVH09, PVH19, PVH50, PVH51, R 610, R 630, R 7-11, R 7-12, RG 17, RG 81, RG H51, RGH 4, RGH 51, RS 1410, Speight 168, Speight 172, Speight 179, Speight 210, Speight 220, Speight 225, Speight 227, Speight 234, Speight G-28, Speight G-70, Speight H-6, Speight H20, Speight NF3, TI 1406, TI 1269, TN 86, TN86LC, TN 90, TN 97, TN97LC, TN D94, TN D950, TR (Tom Rosson) Madole, VA 309, VA359, AA 37-1, B 13P, Xanthi (Mitchell-Mor), Bel-W3, 79-615, Samsun Holmes NN, KTRDC number 2 Hybrid 49, Burley 21, KY 8959, KY 9, MD 609, PG 01, PG 04, PO1, PO2, PO3, RG 11, RG 8, VA 509, AS44, Banket A1, Basma Drama B84/31, Basma I Zichna ZP4/B,

Basma Xanthi BX 2A, Batek, Besuki Jember, C104, Coker 347, Criollo Misionero, Delcrest, Djebel 81, DVH 405, Galpão Comum, HB04P, Hicks Broadleaf, Kabakulak Elassona, Kutsage E1, LA BU 21, NC 2326, NC 297, PVH 2110, Red Russian, Samsun, Saplak, Simmaba, Talgar 28, Wislica, Yayaldag, Prilep HC-72, Prilep P23, Prilep PB 156/1, Prilep P12-2/1, Yaka JK-48, Yaka JB 125/3, TI-1068, KDH-960, TI-1070, TW136, Basma, TKF 4028, L8, TKF 2002, GR141, Basma xanthi, GR149, GR153, Petit Havana.

Further aspects and embodiments of the present disclosure are presented in the following numbered paragraphs.

1. A method of administering or delivering nicotine to a user via inhalation of an aerosol comprising nicotine through an aerosol generating article comprising the steps of: (a) providing an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the aerosol contains levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

2. The method according to paragraph 1, wherein the HPHC other than nicotine in the aerosol generated by the electrically heated tobacco is selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

3. The method according to paragraph 1 or paragraph 2, wherein one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

4. The method according to any of the preceding paragraphs, wherein the levels of any one of carbon monoxide, benzene, acrolein and 1,3-butadiene in the user are lower than the levels in the user when generated from combusted tobacco.

5. The method according to paragraph 4, wherein the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

6. The method according to any of the preceding paragraphs, wherein the level of one or more metabolic enzymes is reduced in the user following inhalation of the aerosol generated from electrically heated tobacco as compared to the level in a user following inhalation of an aerosol generated from combusted tobacco, suitably, wherein the level is reduced to levels that are comparable with smoking abstinence.

7. The method according to any one of the preceding paragraphs, wherein the profile of nicotine delivery via inhalation of the aerosol generated by electrically heated tobacco is substantially the same as that obtained via inhalation of an aerosol generated from combusted tobacco.

8. The method according to paragraph 7, wherein the concentration of nicotine in the blood plasma increases to a maximum concentration within about 9 minutes of inhaling the aerosol from electrically heated tobacco; and/or wherein the $t_{max}$ is about 8 minutes; and/or wherein mean $AUC_{0-\infty}$ and $AUC_{0-t'}$, is about 19 ng.h/mL and about 0.5 ng.h/mL, respectively.

9. The method according to any of the preceding paragraphs, wherein the maximum concentration of nicotine that is delivered to the blood plasma of the user from inhaling the aerosol from electrically heated tobacco is between about 6 and 8 ng/ml of nicotine in plasma; and/or wherein the $t_{max}$ is about 8 minutes; and/or wherein mean $AUC_{0-\infty}$ and $AUC_{0-t'}$, is about 19 ng.h/mL and about 0.5 ng.h/mL, respectively.

10. The method according to any of the preceding paragraphs, wherein the concentration of nicotine that is delivered to the bloodstream of user is greater than about 60% of the concentration of nicotine delivered to the bloodstream of user via combustion of tobacco.

11. The method according to any one of the preceding paragraphs, wherein the electrical heating of the tobacco is controlled electronically over a period of time.

12. The method according to paragraph 11, wherein the aerosol generating article includes a temperature control sensor to avoid overheating the tobacco.

13. The method according to any of the preceding paragraphs, wherein the tobacco is homogenised tobacco material.

14. The method according to paragraph 13, wherein the aerosol-forming substrate comprises a gathered sheet of homogenised tobacco material.

15. The method according to paragraph 14, wherein the sheet is crimped.

16. A method of administering or delivering nicotine to a user via inhalation of an aerosol comprising nicotine through an aerosol generating article comprising the steps of: (a) providing an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma after about 9 minutes after inhalation; (ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (iii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (v) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

17. A method of reducing the absorption of one or more HPHCs other than nicotine in a user inhaling aerosol generated from tobacco comprising the steps of: (a) providing a tobacco product to a user; (b) electrically heating said tobacco product to a temperature of less than about 400 degrees Celsius; (c) allowing the aerosol derived from the electrically heated tobacco to be inhaled by the user and absorbed into the bloodstream of the user; and (d) optionally measuring the levels of nicotine and/or one or more other HPHCs in said user; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

18. Use of an electronic aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein the aerosol contains levels of nicotine that are about

the same as the levels in combusted tobacco; and wherein the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

19. Use of an electronic aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein (i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma about 9 minutes after inhalation; and (ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (iii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (v) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

20. A method of delivering nicotine to a user, wherein the nicotine delivery profile is substantially the same as combusted tobacco and wherein the levels of one or more HPHCs other than nicotine in the bloodstream of the user are lower than the levels from combusted tobacco comprising the use of an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius by a heating element of the aerosol-generating article.

21. An aerosol generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein said aerosol comprises: (i) levels of nicotine are about the same as the levels in combusted tobacco; and (ii) levels of one or more HPHCs other than nicotine that are lower than the level in combusted tobacco.

22. The aerosol according to paragraph 21, wherein the HPHC other than nicotine is selected from the group consisting of: nicotine-free dry particulate matter (NFDPM), carbon monoxide, formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethly ketone, butyraldehyde, benzo[a]pyrene, phenol, m-cresol, o-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, acrylonitrile, benzene, toluene, pyridine, quinoline, styrene, N'-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, nitrogen monoxide (NO), nitrous oxide (NOx), cyanhydric acid, ammonia, arsenic, cadmium, chrome, lead, nickel, selenium and mercury or a combination of one or more thereof or a combination thereof.

23. The aerosol according to paragraph 21 or 22, wherein one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

24. A method of producing an aerosol according to any of paragraphs 21 to 23, comprising the steps of: (i) electrically heating tobacco to a temperature of less than about 400 degrees Celsius; (ii) allowing the electrically heated tobacco to produce an aerosol; and (iii) optionally, isolating or collecting the aerosol.

25. An aerosol-generating article comprising: (i) a heating element that heats tobacco to create an aerosol; and (ii) tobacco that is heated by the heating element the improvement comprising that the heating element electrically heats the tobacco to a temperature of less than about 400 degrees Celsius and the aerosol generated by the aerosol-generating article contains levels of nicotine that are about the same as the levels in combusted tobacco and the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

26. The method or the use or the aerosol-generating article according to any of the preceding paragraphs, wherein the aerosol-generating article is for use with an aerosol-generating device comprising an electric heating element, the aerosol-generating article comprising: (i) tobacco; (ii) a support element located immediately downstream of the aerosol-forming substrate; (iii) an aerosol-cooling element located downstream of the support element; and (iv) an outer wrapper circumscribing the aerosol-forming substrate, the support element and the aerosol-cooling element, wherein the support element abuts the aerosol-forming substrate.

27. A method of determining if a user uses an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing a sample from the user; and (b) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein; wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (ii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iii) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to

1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco is indicative that said user uses the aerosol-generating article.

28. A sample isolated from a user 2 days after using an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2%; and/or (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine; and/or (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

29. The method or the sample according to any of the preceding paragraphs, wherein the levels of carbon monoxide, benzene, acrolein and 1,3-butadiene are determined.

30. A method of monitoring a user consuming nicotine via inhalation of an aerosol comprising nicotine through an aerosol generating article that electrically heats tobacco to a temperature of less than about 400 degrees Celsius, comprising the steps of: (a) providing the user with the aerosol generating article that electrically heats tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine through the aerosol generating article; (c) providing or obtaining one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during consumption by the user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used: (i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and/or (iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and/or (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine; wherein correlation between the samples and the levels in step (c) is indicative that the user is responding favourably to the consumption of nicotine through the device.

31. A method of measuring a user's response to the inhalation of nicotine comprising the steps of: (a) providing the user with an aerosol generating article that electrically heats tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine created by the aerosol generating article; (c) providing or obtaining one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during inhalation by the

user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used: (i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and/or (iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and/or (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

32. The method or the sample according to any of the preceding paragraphs, wherein the levels of at least carbon monoxide, benzene, acrolein and 1,3-butadiene are measured.

33. A method modifying or adapting an aerosol-generating article in which tobacco contained in the aerosol-generating article is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing the aerosol-generating article; (b) making one or more modifications to one or more components parts thereof; and (c) testing the aerosol-generating article to determine if the modification(s) has a beneficial effect on the aerosol-generating article, said testing comprising the steps of: (i) determining the levels one or more HPHCs other than nicotine in the aerosol, wherein a reduction in the levels of one or more HPHCs in the aerosol is indicative that the one or more modifications has a beneficial effect on the aerosol-generating article; and/or (ii) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein in the user after inhaling the aerosol; wherein a reduction in one or more, suitably, all of these levels is indicative that the one or more modifications have a beneficial effect on the aerosol-generating article.

34. A method, a use, an aerosol, or an aerosol-generating article substantially as described herein with reference to the accompanying drawings.

The disclosure is further described in the Examples below, which are provided to describe the disclosure in further detail. These examples, which set forth a preferred mode presently contemplated for carrying out the disclosure, are intended to illustrate and not to limit the disclosure.

## EXAMPLES

### Example 1

A single-center, open-label, randomized, controlled, crossover study to explore the nicotine pharmacokinetic (PK) profile and safety of using an aerosol-generating device (as described in Figures 5 to 7 herein and referred to as THS cigarettes) in which tobacco contained in the aerosol-generating device is heated to a temperature of about 375 degrees Celsius (maximum)

and a range of about 350 degrees Celsius to about 399 degrees Celsius or less (taking account of possible variations in temperature) to create an aerosol compared to conventional cigarettes (CC) following single and *ad libitum* use in smoking, but otherwise healthy users.

The objective of this study is to evaluate the rate and the amount of nicotine absorbed in a user based on the plasma nicotine PK profile following single use of THS cigarettes in comparison to smoking CC, as assessed by the area under the plasma concentration-time curve (AUC) and the maximum plasma concentration ($C_{max}$). A further objective is to evaluate the partial AUC (AUC0-t', where t' is the user-specific time of peak nicotine concentration following CC and area under the concentration-time curve from time 0 extrapolated to time of last quantifiable concentration to infinity [AUC0-∞]) of THS cigarettes compared to CC users following single use. A further objective is to evaluate the time to Cmax (tmax) and half-life (t½) of nicotine with THS cigarettes compared to CC users following single use. A further objective is to compare the peak and trough nicotine concentration between THS cigarettes and CC users following *ad libitum* use. A further objective is to evaluate the levels of exhaled carbon monoxide (CO) and of blood carboxyhemoglobin (COHb) for THS cigarettes compared to CC users on single use and *ad libitum* use.

Materials & Methods

*Study design*

This is a single-center, open-label, randomized, controlled, two-period, two-sequence, cross-over study to explore the nicotine PK profile and safety of THS cigarettes compared to CC following single use in smoking, but otherwise healthy users.

In total, 28 eligible smoking users are randomized on Day 0 into one of the following two sequences: Sequence 1: THS 2.1 → CC (N=14) or Sequence 2: CC → THS 2.1 (N=14).

Type of blinding: open-label

Type of control: conventional CC

*Number of Users (Planned and Analyzed)*

| | |
|---|---|
| Screened: | 78 users |
| Enrolled: | 33 users |
| Randomized: | 28 users |
| Safety population set: | 33 users |
| PK single use analysis set (PKS population): | 28 users |
| PK *ad libitum* use analysis set (PKAL population): | 28 users |

*Diagnosis and Main Criteria for Inclusion*

Female or male, otherwise healthy Caucasian, smokers (a smoking history of at least three years of consecutive smoking prior to screening and a minimum of 10 non-mentholated CC per day with a maximum yield of 1 mg nicotine ISO/CC during the four weeks prior to screening). The user is a current smoker who does not plan to quit smoking in the next 3 months however is ready to accept interruptions of smoking for up to two consecutive days. Users can smoke different brands until admission to the clinic. From Admission to the clinic onwards, however, users are restricted to the user's preferred CC brand. Smoking status is verified with a urinary cotinine test (cotinine ≥200 ng/ml). Randomization quotas are used to ensure that each gender and smoking stratum represented at least 40% of the study population

*Test Product*

As shown in Figures 5 to 7, the aerosol-generating article includes a tobacco heating device, a THS cigarette holder for the use of specially designed THS cigarettes, and THS accessories, including a THS charging unit, a power adaptor and power cords to allow the charge of the holder.

*Reference Products*

Commercially available CC provided by the users according to their preference.

*Duration of Exposure*

The study is performed during a 7-day confinement period (seven overnight stays).

Period 1:
- Day 0: Wash-out;
- Day 1: single product use (THS 2.1/CC)
- Day 2: *ad libitum* product use (THS 2.1/CC).

Period 2:
- Day 3: Wash-out;
- Day 4: single product use (THS 2.1/CC);
- Day 5: *ad libitum* product use (THS 2.1/CC).

*Criteria for Evaluation*

Primary Endpoints:

Nicotine PK after single use of THS cigarette and CC:

- $C_{max.}$
- Area under the concentration-time curve from time zero to time of last quantifiable concentration ($AUC_{0\text{-}last}$).

Secondary Endpoints:

*Pharmacokinetic endpoints:*

- Nicotine PK after single use: $AUC_{0-\infty}$, $t_{max}$, $AUC_{0-t'}$, elimination rate constant and half-life ($t_{½}$).
- Peak and trough nicotine concentration between THS cigarettes and CC users following ad libitum use.

*Biomarker endpoints:*

Levels of exhaled CO and of blood COHb between THS cigarettes and CC users following single and *ad libitum* use

*Sample Size*

A total of 28 smokers are randomized. This sample size is needed to estimate the ratio of geometric means for $C_{max}$ ratio between THS cigarettes and CC with a precision allowing for the 90% confidence interval not exceeding the 0.80 and 1.25 limits, with 80% power and assuming a 5% drop out rate.

*Statistical Methods*

The primary PK endpoints are $AUC_{0-last}$ and $C_{max}$ values for nicotine following single product use. The secondary PK endpoints are $AUC_{0-\infty}$, $AUC_{0-t'}$, $t_{½}$, elimination rate constant and $t_{max}$ following single product use.

An analysis of variance (ANOVA) is conducted on log-transformed (natural log) single use PK parameters. The model includes terms for sequence, user within sequence, period and exposure group as fixed-effect factors. The results of the analysis for each of $AUC_{0-last}$ and $C_{max}$ are presented in terms of adjusted geometric least square (LS) means and 90% confidence intervals (CIs) for the THS cigarettes:CC ratio.

It is assumed that there is no carry-over effect or interaction between user, exposure, and period. Normality is not tested after the log transformation. As the log transformed data are used in the analysis, the reported results are back-transformed.

The $t_{max}$ is analyzed on the original scale using the Wilcoxon Signed-Rank Test. Hodges-Lehmann estimates are presented with 90% CI for the median differences between THS and CC.

Results

*Demography*

Out of the 33 users enrolled, 28 are randomized, and all 28 complete the study. Thirty-three users are exposed to the aerosol generating device (during the product trial) and are therefore included in the safety population. All 28 randomized users meet the inclusion/exclusion criteria, and the sequences are balanced with regard to age, height, weight and Body Mass Index (BMI).

*Primary PK Endpoints*

The mean nicotine concentration curves following single use of the two products are shown in Figure 1. The overall shape of the concentration-time curves appear similar for the two products, but with a lower exposure to nicotine following single use of THS.

Following single use, the extent of the exposure to nicotine is, on average, 23% (90% CI: 15%, 30%) lower for THS compared to CC. Similarly, the maximum nicotine concentrations are, on average, 30% (90% CI: 18% to 40%) lower following single use of THS compared to CC. For both primary endpoints, the lower limit of the 90% CI for the geometric means ratio is less than 80% and the CIs did not contain 100%. Data is shown in Table 2.

*Secondary PK Endpoints*

There is no difference in the $t_{max}$ (90% CI: -1, 2), with both products having a $t_{max}$ of 8 minutes.

The extent of nicotine exposure for THS, as assessed by both mean $AUC_{0-\infty}$ and $AUC_{0-t'}$, is 19.083 ng.h/mL and 0.5262 ng.h/mL, respectively. These estimates result to be 19% (95% CI: 11%, 27%) and 33% (95%CI: 12%, 48%) lower as compared to CC. The average elimination half-life of nicotine is 2.741hours for THS, 11% (95% CI: 2%, 21%) longer than CC.

**Example 2**

A single-center, open-label, randomized, controlled, 2-arm parallel group study to evaluate the exposure to selected smoke constituents in smoking, but otherwise healthy users switching from conventional cigarettes to THS.

The objective of this study is to evaluate the effect of using THS cigarettes on selected primary biomarkers of exposure (BoExp) in smokers switching from conventional cigarettes (CC) to THS cigarettes as compared to those continuing to smoke CC. A further objective is to evaluate the effect of using THS cigarettes in confinement on selected secondary BoExp in smokers switching from CC to THS cigarettes as compared to those continuing to smoke CC. A further objective is to evaluate the effect of using THS cigarettes in a confinement setting on CYP1A2 enzymatic activity in smokers switching from CC to THS cigarettes as compared to those continuing to smoke CC. A further objective is to evaluate the safety of using THS cigarettes during the exposure period, and to evaluate the effect of using THS cigarettes in a confinement setting on 11-DTX-B2 in smokers switching from CC to THS cigarettes as compared to those continuing to smoke CC. A further objective is compare of the results obtained for selected primary and secondary BoExp, 11-DTX-B2, and CYP2A6 in different body matrices.

Materials & Methods

*Study design*

This is a randomized, controlled, open-label, 2-arm, parallel group *ad libitum* smoking study comparing the use of THS cigarettes and CC. Users are confined in a controlled environment for nine days: Admission (Day -2), Baseline (Day -1 and Day 0), Exposure Period (Day 1 to Day 5), Discharge (Day 6). Evaluation of the effects of using THS cigarettes were performed on Day 5. Smoking during confinement is allowed between 06:30 and 23:00.

Randomization is stratified by gender and user reported daily average CC consumption during the four weeks prior to the screening Visit (those smoking 10 to 19 CC per day and those smoking >19 CC per day).

Type of blinding: open-label

Type of control: conventional cigarettes

*Number of Users (Planned and Analyzed)*

| | |
|---|---|
| Enrolled: | 42 users |
| Randomized: | 40 users |
| Safety Population: | 42 users |
| Full Analysis Set (FAS): | 40 users |
| Per Protocol (PP) Population: | 39 users |

*Diagnosis and Main Criteria for Inclusion*

Female or male, otherwise healthy Caucasian, smokers are include with a smoking history of at least three years of consecutive smoking prior to Screening and a minimum of 10 non-mentholated CC per day with a maximum yield of 1 mg nicotine ISO/CC during the four weeks prior to screening. Users can smoke different brands until admission to the clinic. From admission to the clinic onwards, however, users are restricted to the user preferred CC brand. Smoking status is verified with a urinary cotinine test (cotinine ≥200 ng/ml). Randomization quotas are used to ensure that each gender and smoking stratum represented at least 40% of the study population.

*Test Product*

THS as shown in Figures 5 to 7 is composed of the tobacco heating device, the THS cigarette holder for the use of specially designed THS cigarettes and THS accessories, including a THS charging unit, a power adaptor and power cords to allow the charge of the holder.

*Reference Products*

Commercially available CC is provided by the users according to their preference.

*Duration of Exposure Period*

Users use THS for five days following a 2-day baseline period in which they smoke their own brand of CC.

Users randomized to the THS arm are assigned a THS cigarette holder and THS accessories. Users are supplied with THS cigarettes one cigarette at a time, upon request. From Day 1, 06:30 onwards until Day 5, 23:00 users in the THS arm are not allowed to smoke CC.

Users randomized to the CC arm continue smoking their own preferred CC brand from Day 1 06:30 onwards until Day 5 23:00 *ad libitum*.

*Criteria for Evaluation*

The primary endpoints are the exposure to four harmful and potentially harmful constituents (HPHCs) (CO, 1,3-butadiene, acrolein, and benzene) assessed by measuring their respective biomarkers over the 5-day exposure period. The four constituents are several-fold higher in smokers than in smokers abstinent from smoking, and exhibit, on average, an elimination half-life of ≤24 hours. Therefore, the five days of exposure should be sufficient to reach a new steady state (at least five times their elimination half-life). Carbon monoxide is measured by using carboxyhemoglobin in blood as the marker in blood which can be quantitated by spectrophotometry. Benzene is measured by using S-Phenyl-mercapturic acid (S-PMA) in urine as the marker which can be quantitated by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Acrolein is measured by using 3-Hydroxypropyl-mercapturic acid (3-HPMA) in urine as the marker which can be quantitated by via liquid chromatography-tandem mass spectrometry (LC-MS/MS). 1,3-butadiene is measured by using monohydroxybutenyl-mercapturic acid (MHBMA) in urine as the marker which can be quantitated by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

In total, 14 biomarker of HPHCs are assessed in this study (see Table 3), of which 13 are listed in the FDA 18 abbreviated list to be reported.

Carbon monoxide in exhaled breath is measured using the Micro 4 Smokerlyzer. The test is conducted in conjunction with the blood sampling for COHb, where appropriate.

*Additional Endpoints*

- 11-DTX-B2 is measured in urine (spot urine samples and 24 hour urine samples).
- CYP1A2 activity is measured at Day 0 and at Day 5 based on paraxanthine (PX) and caffeine (CAF) plasma molar concentrations, approximately six hours (±15 minutes) after the intake of a cup of coffee.
- CYP2A6 activity is measured in plasma on Day 0 and on Day 5, using the metabolic:molar ratio of trans-3'-hydroxycotinine and cotinine.

- Assessment of cough with a visual analogue scale (VAS), three Likert scales and one open question.
- Smoking behavior: Product use and smoking topography with the SODIM® device.

*Sample Size*

A total of 40 smokers (20 in THS 2.1 arm, 20 in CC arm) are randomized. This sample size is calculated to attain more than 80% power to show a reduction in the THS arm compared to the CC arm, using a two-tailed test with 5% type I error probability.

*Statistical Methods*

BoExp is analyzed on the log-transformed (natural log) data adjusted for creatinine. Estimates of differences between groups are back-transformed to provide relative effects (THS/CC). Values at the end of the exposure period (EoE) on Day 5 are compared between exposure groups by means of a General Linear Model (GLM) adjusted for log transformed baseline values and stratification factors used at randomisation.

Descriptive summary statistics including the number of users (no.), no. of users with missing data, no. of users with results below limit of quantification (BLOQ), mean, standard deviation (SD), geometric mean and associated 95% confidence interval (CI), minimum, first quartile, median, third quartile, maximum and coefficient of variation (CV) are produced for each of the primary BoExp by study arm and overall for absolute values, and changes and percent changes from baseline for each day.

Unless stated otherwise, all statistical tests are two-sided and conducted at the 5% level, and all quoted confidence intervals are two-sided 95% confidence intervals.

Results

*Demography*

Out of the 42 users enrolled, 40 are randomized, and all 40 complete the study. One user is mis-randomized (two users are assigned the same randomization number) and is removed from the per-protocol population. Forty-two users are exposed to THS (during the product trial) and are therefore included in the safety population.

All 40 randomized users meet the inclusion/exclusion criteria, and the groups are balanced with regard to age, height, weight and Body Mass Index (BMI).

*Primary Biomarkers of Exposure*

There are significant decreases in all four primary BoExp. Changes are seen within 24 hours of starting use of THS and the decreases are maintained throughout the study.

*COHb*

In the THS arm, carboxyhemoglobin drops from Baseline by slightly more than four percentage points (-4.19% ±1.2%) on Day 1. On Day 5 the change relative to Baseline is a decrease of 75.2% for THS and an increase of 7.2% for CC. This change is maintained over the five days of exposure. In the CC arm, there is no notable change in carboxyhemoglobin. By Day 1, the level of COHb is below 2% for 19 out of 20 users in the THS arm, which is within the normal range for COHb for non-smokers. At Day 5 the level of COHb is below 2% for all 20 users.user The results are shown in Figure 2A.

*MHBMA*

At the end of exposure period (EoE), the MHBMA urinary concentration adjusted for creatinine is more than 75% decreased from Baseline at Day 5 for THS and is increased 19.5% from Baseline at Day 5 for CC. The change is statistically significant. Changes in MHBMA are seen within 24-hours of starting use of THS, and maintained throughout the exposure. The results are shown in Figure 2B.

*3-HPMA*

At the End of Exposure (EoE), the 3-HPMA urinary concentration adjusted for creatinine is more than -57.9% decreased from Baseline at Day 5 for THS 2.1 and is increased 11.4% from Baseline at Day 5 for CC. The change is statistically significant. Changes in 3-HPMA are seen within 24-hours of starting use of THS, and remained reduced through the exposure period. The results are shown in Figure 2C.

*S-PMA*

At the End of Exposure (EoE), the MHBMA urinary concentration adjusted for creatinine is more than -88% decreased from Baseline at Day 5 for THS and is increased 26.4% from Baseline at Day 5 for CC. The change is statistically significant. Changes in S-PMA are seen within 24-hours of starting use of THS, and remained low for the duration of the study. The results are shown in Figure 2D.

The results are summarised in Table 5.

*CYP1A2 Activity*

Levels of CYP1A2 can be measured using methods known in the art, for example, see *Clinical Pharmacology & Therapeutics* (2011) **90**, 117-125. CYP1A2 activity, decreases approximately 25% in the THS arm and remains the same in the CC arm. The results are shown in Figure 3.

**Example 3**

Figures 4A and 4B illustrate the chemical analysis of aerosol (smoke) produced via combustion of tobacco (MM-2008 median) versus heating of tobacco according to the present disclosure using menthol flavoured tobacco (platform 1 menthol) and regular tobacco (platform 1 regular). As can be seen in this Figure the levels of many HPHCs are reduced in aerosol produced by the heating of tobacco as compared to aerosol produced by combusting tobacco. The HPHCs are measured in aerosol (smoke) using methods that are well known in the art.

Any publication cited or described herein provides relevant information disclosed prior to the filing date of the present application. Statements herein are not to be construed as an admission that the inventors are not entitled to antedate such disclosures. All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the disclosure will be apparent to those skilled in the art without departing from the scope and spirit of the disclosure. Although the disclosure has been described in connection with specific preferred embodiments, it should be understood that the disclosure as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the disclosure which are obvious to those skilled the art and related fields are intended to be within the scope of the following claims.

**TABLE 1**

**Examples of smoke constituent biomarkers of exposure**

| Smoke constituent [smoke phase] | Biomarker [Matrix] | Biomarker $t_{1/2\beta}$ | Organ Class toxicity |
|---|---|---|---|
| 1,3-Butadiene [gas] | Monohydroxybutenyl-mercapturic acid (MHBMA) [Urine(a)] | 4 to 16 h | CA, RT, RDT |
| 1-Aminonaphthalene [particulate] | 1-Aminonaphthalene (1-NA) [Urine(a)] | Not described | CA |
| 2-Aminonaphthalene [particulate] | 2-Aminonaphthalene (2-NA) [Urine(a)] | 9 h | CA |
| 4-Aminobiphenyl [particulate] | 4-Aminobiphenyl (4-ABP) [Urine(a)] | 26 h | CA |
| Acrolein [gas] | 3-Hydroxypropyl-mercapturic acid (3-HPMA) [Urine(a)] | 10 h | RT, CT |
| Acrylonitrile [gas] | 2-Cyanoethylmercapturic acid (CEMA) [Urine(a)] | 17 h | CA, RT |
| Benzene [gas] | S-Phenyl-mercapturic acid (S-PMA) [Urine(a)] | 9 to 15 h | CA, CT, RDT |
| Benzo[a]pyrene [particulate] | 3-Hydroxybenzopyrene [Urine(a)] | 3 to 4 h | CA |
| Carbon monoxide [gas] | Carboxyhemoglobin (COHb) [Blood(b)] | 1 to 6 h | RDT, CT |
| Crotonaldehyde [gas] | 3-Hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA) [Urine(a)] | 2 days | CA |
| Ethylene Oxide [gas] | 2-Hydroxyethyl-mercapturic acid (HEMA) [Urine(a)] | 5 h | CA, RT, RDT |
| Nicotine [particulate] | Nicotine (NIC-P) [Plasma(a)] | 1 to 2 h | RDT, AD |
| | Cotinine (COT-P)<br>3-OH Cotinine (3OHCOTP) [Plasma(a)] | 16 to 18 h<br>- | |
| | Nicotine equivalents (NEq) [Urine(a)] | 16 h (estimated) | |
| NNK [particulate] | Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol | 10 to 18 days | CA |

**Examples of smoke constituent biomarkers of exposure**

| Smoke constituent [smoke phase] | Biomarker [Matrix] | Biomarker $t_{1/2\beta}$ | Organ Class toxicity |
|---|---|---|---|
| | (NNAL) [Urine[(a)]] | | |
| NNN [particulate] | Total N-nitrosonornicotine (NNN) [Urine[(a)]] | 15 h | CA |
| Pyrene [particulate] | Total 1-hydroxypyrene (1-OHP) [Urine[(a)]] | 6 to 20 h | Nontoxic (surrogate for exposure to polycyclic aromatic hydrocarbons) |
| *o*-Toluidine [gas] | *o*-Toluidine (*o*-TOL) [Urine[(a)]] | 10 to 16 h | CA |
| Toluene [gas] | S-benzyl-mercapturic acid (S-BMA) [urine[a]] | 9 h | RT, RDT |

Analytical methods: [(a)] liquid chromatography-tandem mass spectrometry (LC-MS/MS) [(b)] Spectrophotometry

Organ Class toxicity (Federal Register 2012 Vol 77; no. 64)): AD: addictive; CA: carcinogen; CT: cardiovascular toxicant; RDT: reproductive and developmental toxicant; RT: respiratory toxicant

**TABLE 2**

| PK parameter (unit) | Product exposure | Number of users | Geometric means | Geometric means ratio (THS 2.1/CC) (%) | 90% CIs (%) Lower | 90% CIs (%) Upper | CV (%) |
|---|---|---|---|---|---|---|---|
| $AUC_{0\text{-last}}$ (ng.h/mL) | THS 2.1 | 28 | 17.659 | 77.41 | 70.46 | 85.04 | 20.85 |
| | CC | 28 | 22.813 | | | | |
| $C_{max}$ (ng/mL) | THS2.1 | 28 | 8.369 | 70.25 | 60.01 | 82.23 | 35.60 |
| | CC | 28 | 11.914 | | | | |

**TABLE 3**

| Exposure marker | Smoke constituent[smoke phase] | Matrix |
|---|---|---|
| Monohydroxybutenyl mercapturic acid (MHBMA) | 1,3-butadiene[gas] | Urine |
| 3-hydroxypropylmercapturic acid (3-HPMA) | acrolein[gas] | Urine |
| *S*-phenylmercapturic acid (S-PMA) | benzene[gas] | Urine |
| Carboxyhemoglobin (COHb) | CO[gas] | Blood |
| Carbon monoxide (CO) | CO[gas] | Exhaled breath |
| 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) | 4 (methylnitrosamino)-1-(3-pyridyl)-1butadone (NNK)[particulate] | Urine |
| Total 1-hydroxypyrene (1-OHP) | Pyrene[particulate] | Urine |
| Total N-nitrosonornicotine (NNN) | N-nitrosonornicotine[particulate] | Urine |
| 4-aminobiphenyl (4-ABP) | 4-aminobiphenyl [particulate] | Urine |
| 2-aminonaphthalene (2-NA) | 2-aminonaphtalene[particulate] | Urine |
| o-toluidine (o-tol) | o-toluidine[gas] | Urine |
| Nicotine equivalents (NEQ)<br>free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-glucuronide | Nicotine[particulate] | Urine |
| Nicotine | Nicotine[particulate] | Plasma |
| Cotinine | Nicotine[particulate] | Plasma |
| 2-cyanoethylmercapturic acid (CEMA) | Acrylonitrile[gas] | Urine |

## TABLE 4

| | | THS Regular | | | THS Menthol | | | 3R4F | | | % of 3R4F | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HPHC** | **Unit** | **Mean** | **± SD** | **n** | **Mean** | **± SD** | **n** | **Mean** | **± SD** | **n** | **Regular** | **Menthol** |
| Nicotine | mg/mg nic. | 1.00 | 0.07 | 25 | 1.00 | 0.10 | 29 | 1.00 | 0.05 | 299 | 100 | 100 |
| Carbon monoxide | mg/mg nic. | 0.39 | 0.04 | 25 | 0.35 | 0.12 | 29 | 14.84 | 0.71 | 292 | 2.65 | 2.35 |
| Formaldehyde | µg/mg nic. | 2.72 | 0.43 | 20 | 4.55 | 0.60 | 20 | 27.93 | 4.19 | 54 | 9.72 | 16.29 |
| Acetaldehyde | µg/mg nic. | 130.48 | 26.3 | 20 | 169.63 | 12.3 | 20 | 809.74 | 81.2 | 54 | 16.11 | 20.95 |
| Acrolein | µg/mg nic. | 5.35 | 1.21 | 20 | 8.22 | 1.07 | 20 | 78.80 | 7.84 | 54 | 6.78 | 10.43 |
| Crotonaldehyde | µg/mg nic. | 2.03 | 0.53 | 20 | 2.89 | 0.48 | 20 | 38.27 | 5.04 | 54 | 5.30 | 7.55 |
| Benzo[a]pyrene | ng/mg nic. | 0.93 | 0.03 | 4 | 1.02 | 0.03 | 3 | 7.27 | 0.83 | 33 | 12.74 | 14.05 |
| 1,3-butadiene | µg/mg nic. | 0.22 | 0.02 | 20 | 0.36* | NA | 0 | 29.46 | 6.02 | 23 | 0.74 | 1.24 |
| Isoprene | µg/mg nic. | 1.66 | 0.14 | 20 | 1.98 | 0.20 | 20 | 428.21 | 66.07 | 22 | 0.39 | 0.46 |
| Acrylonitrile | µg/mg nic. | 0.11 | 0.03 | 20 | 0.13 | 0.02 | 17 | 13.53 | 1.20 | 24 | 0.83 | 0.97 |
| Benzene | µg/mg nic. | 0.45 | 0.03 | 20 | 0.53 | 0.04 | 20 | 45.89 | 4.97 | 23 | 0.98 | 1.15 |
| Toluene | µg/mg nic. | 1.55 | 0.18 | 20 | 1.96 | 0.19 | 20 | 84.40 | 8.26 | 24 | 1.84 | 2.33 |
| N-nitrosonornicotine | ng/mg nic. | 4.70 | 0.31 | 4 | 5.19 | 0.73 | 3 | 140.34 | 11.66 | 26 | 3.35 | 3.70 |
| NNK | ng/mg nic. | 4.04 | 0.27 | 4 | 4.47 | 0.63 | 3 | 110.93 | 11.32 | 26 | 3.65 | 4.03 |
| 1-aminonaphthalene | ng/mg nic. | 0.07 | 0.01 | 4 | 0.10 | 0.02 | 4 | 10.94 | 1.27 | 22 | 0.67 | 0.87 |
| 2-aminonaphthalene | ng/mg nic. | 0.03 | 0.01 | 4 | 0.03 | 0.00 | 2 | 7.91 | 0.89 | 24 | 0.39 | 0.33 |
| 4-aminobiphenyl | ng/mg nic. | 0.01* | NA | 0 | 0.04* | NA | 0 | 1.75 | 0.25 | 24 | 0.59 | 2.20 |
| Ammonia | µg/mg nic. | 10.25 | 0.45 | 20 | 11.11 | 0.66 | 20 | 18.12 | 1.62 | 33 | 56.55 | 61.29 |

**TABLE 5**

Primary Biomarkers of Exposure on Day 5 - Change from Baseline (%)

| Parameter | THS 2.1 | | | CC | | |
|---|---|---|---|---|---|---|
| | Mean | SD | Median | Mean | SD | Median |
| CARBOXYHEMOGLOBIN | -75.2 | 6.0 | -76.9 | 7.5 | 22.3 | 1.5 |
| MHBMA (ADJ CREAT) | -77.8 | 40.3 | -91.1 | 19.5 | | |
| 3-HPMA (ADJ CREAT) | -57.9 | 20.3 | -58.4 | 11.4 | 52.1 | 4.2 |
| S-PMA (ADJ CREAT) | -88.0 | 9.7 | -89.2 | 26.4 | 38.9 | 15.7 |

**CLAIMS:**

1. A method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of:

(a) providing an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and

(b) allowing a user to inhale the aerosol derived from the electrically heated tobacco;

wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and

wherein the aerosol contains levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

2. The method according to claim 1, wherein one or more HPHCs other than nicotine are not detectable or are not appreciably detectable in the aerosol generated by the electrically heated tobacco, said HPHCs being selected from the group consisting of: m-cresol, p-cresol, 1,3 butadiene, isoprene, acrylonitrile, benzene, 1-aminonaphthalene, 2-aminonaphthalene, 3-aminobiphenyl, 4-aminobiphenyl, cyanhydric acid and cadmium or a combination of one or more thereof or a combination thereof.

3. The method according to any of the preceding claims, wherein 4-aminobiphenyl, 2-aminonaphthalene and 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1ng/mg nicotine; wherein carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine; wherein isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine; wherein N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine; wherein acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine; wherein ammonia is present in the aerosol at between about 9 and 11 ng/mg nicotine; and wherein acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine.

4. The method according to any of the preceding claims, wherein the levels of any one of carbon monoxide, benzene, acrolein and 1,3-butadiene or biomarkers thereof in the user of the

aerosol-generating device are lower than the levels in the user when generated from combusted tobacco, suitably, wherein

the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or

the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

5. The method according to any one of the preceding claims, wherein the profile of nicotine delivery via inhalation of the aerosol generated by electrically heated tobacco is substantially the same as that obtained via inhalation of an aerosol generated from combusted tobacco, suitably, wherein the concentration of nicotine in the blood plasma increases to a maximum concentration within about 9 minutes of inhaling the aerosol from electrically heated tobacco; and/or wherein the $t_{max}$ is between about 7 and 9 minutes; and/or wherein mean $AUC_{0-\infty}$ and $AUC_{0-t'}$, is between about 18 and 20 ng.h/mL and between about 0.5 and 0.6 ng.h/mL, respectively.

6. The method of any of the preceding claims, wherein the heating element that electrically heats the tobacco is inserted into the tobacco and wherein a continuous supply of energy is supplied to the heating element, said continuous supply of energy being monitored during use of the device.

7. A method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of:

(a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and

(b) allowing a user to inhale the aerosol derived from the electrically heated tobacco;

wherein

(i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma after about 9 minutes after inhalation;

(ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or

(iii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

(iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

(v) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

8. Use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the level of one or more HPHCs other than nicotine in the aerosol is lower than the level in combusted tobacco.

9. Use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius; wherein

(i) the nicotine concentration in the user is between about 6 and 8 ng/ml in plasma about 9 minutes after inhalation; and

(ii) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or

(iii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

(iv) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

(v) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco.

10. An aerosol generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein said aerosol comprises:

(i) levels of nicotine are about the same as the levels in combusted tobacco; and

(ii) wherein 4-aminobiphenyl, 2-aminonaphthalene and 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1ng/mg nicotine; wherein carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine; wherein isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine; wherein N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine; wherein acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine; wherein ammonia is present in the aerosol at between about 9 and 11 ng/mg nicotine; and wherein acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine.

11. A method of identifying a user using an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of:

(a) providing a sample from the user; and

(b) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein;

wherein

(i) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or

(ii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

(iii) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or

(iv) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco is indicative that said user uses the aerosol-generating device.

12. The method according to claim 10, wherein the user is identified from a pool of two or more users.

13. A sample obtained from a user at least 2 days after using an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, wherein

(i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2%; and/or

(ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine; and/or

(iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine; and/or

(iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

14. A method of monitoring a user consuming nicotine via inhalation of an aerosol comprising nicotine through an aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius, comprising the steps of:

(a) providing the user with the aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius;

(b) allowing the user to inhale the aerosol comprising nicotine through the aerosol generating device;

(c) providing, obtaining or collecting one or more samples from the user, which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during consumption by the user;

(d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and

(e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used:

(i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or

(ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and/or

(iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and/or

(iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine;

wherein correlation between the samples and the levels in step (e) is indicative that the user is exposed to levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

15. A method of modifying an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of:

(a) providing the aerosol-generating device;

(b) making one or more modifications to one or more component parts of the aerosol-generating device; and

(c) testing the modified aerosol-generating device to determine if the modification(s) has a beneficial effect on the aerosol-generating device, said testing comprising the steps of:

(i) determining the levels one or more HPHCs other than nicotine in the aerosol, wherein a reduction in the levels of one or more HPHCs in the aerosol is indicative that the one or more modifications have a beneficial effect on the aerosol-generating device; and/or

(ii) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein in the user after inhaling the aerosol; wherein a reduction in one or more, suitably, all of these levels is indicative that the one or more modifications have a beneficial effect on the aerosol-generating device.

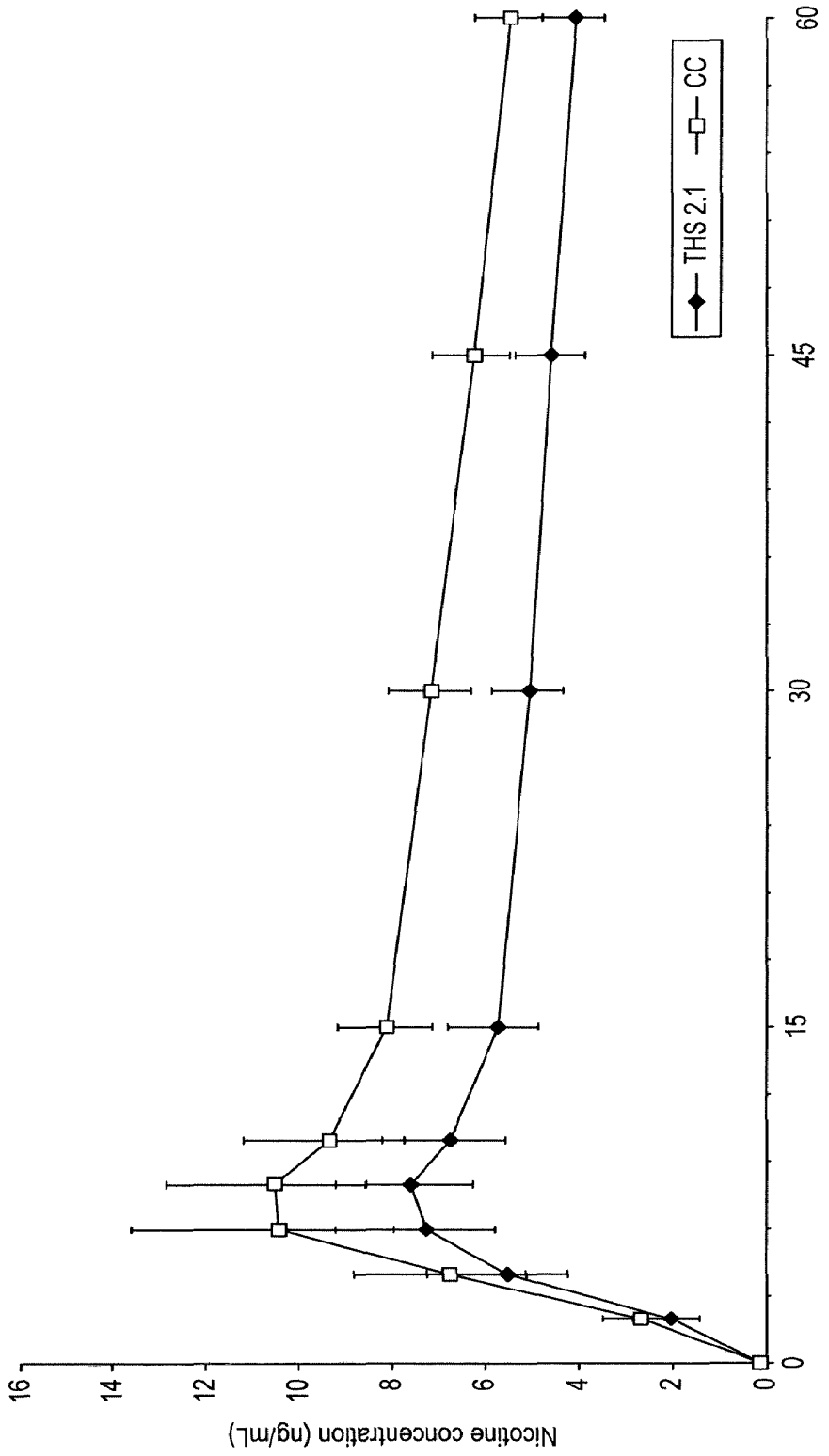

Nicotine concentration (ng/mL)
0
2
4
6
8
10
12
14
16
0
15
30
45
60
Time from $T_0$ (minutes)
THS 2.1
CC

FIG. 1

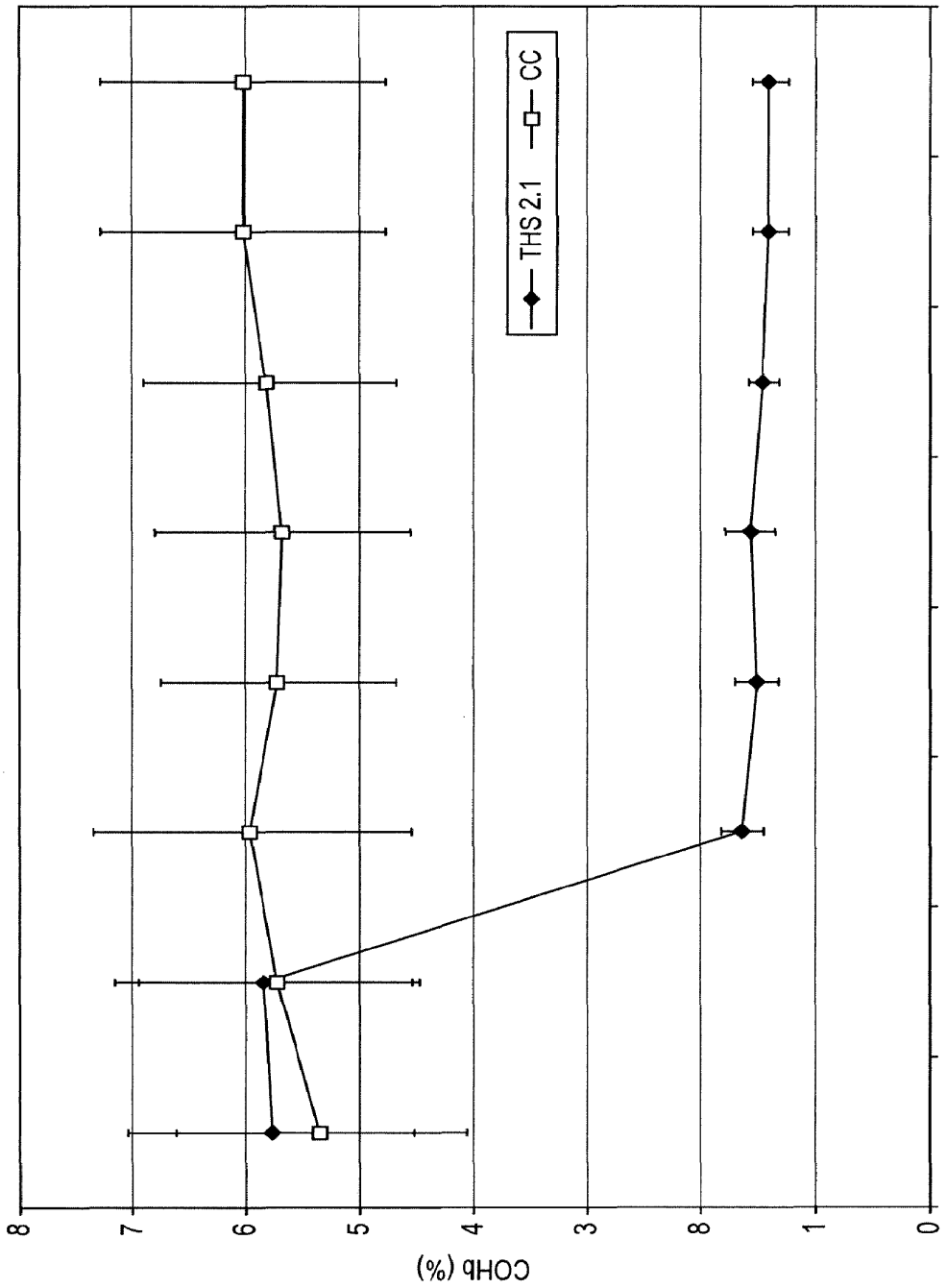

THS 2.1
CC
COHb (%)
8
7
6
5
4
3
8
1
0
Day -1
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
EoE
Study day

FIG. 2A

1763

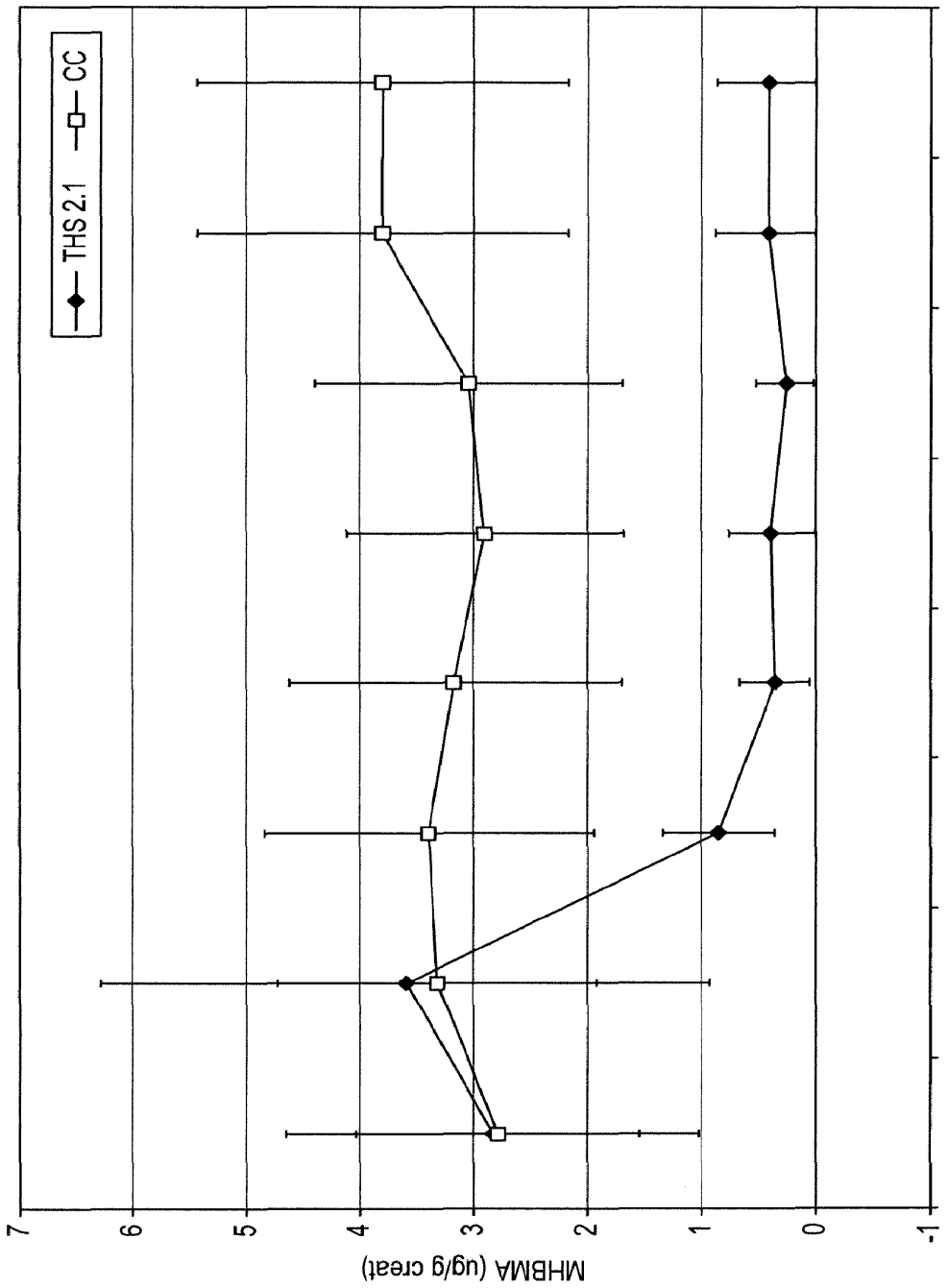

THS 2.1
CC
MHBMA (ug/g creat)
7
6
5
4
3
2
1
0
-1
Day -1
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
EoE
Study day

FIG. 2B

1764

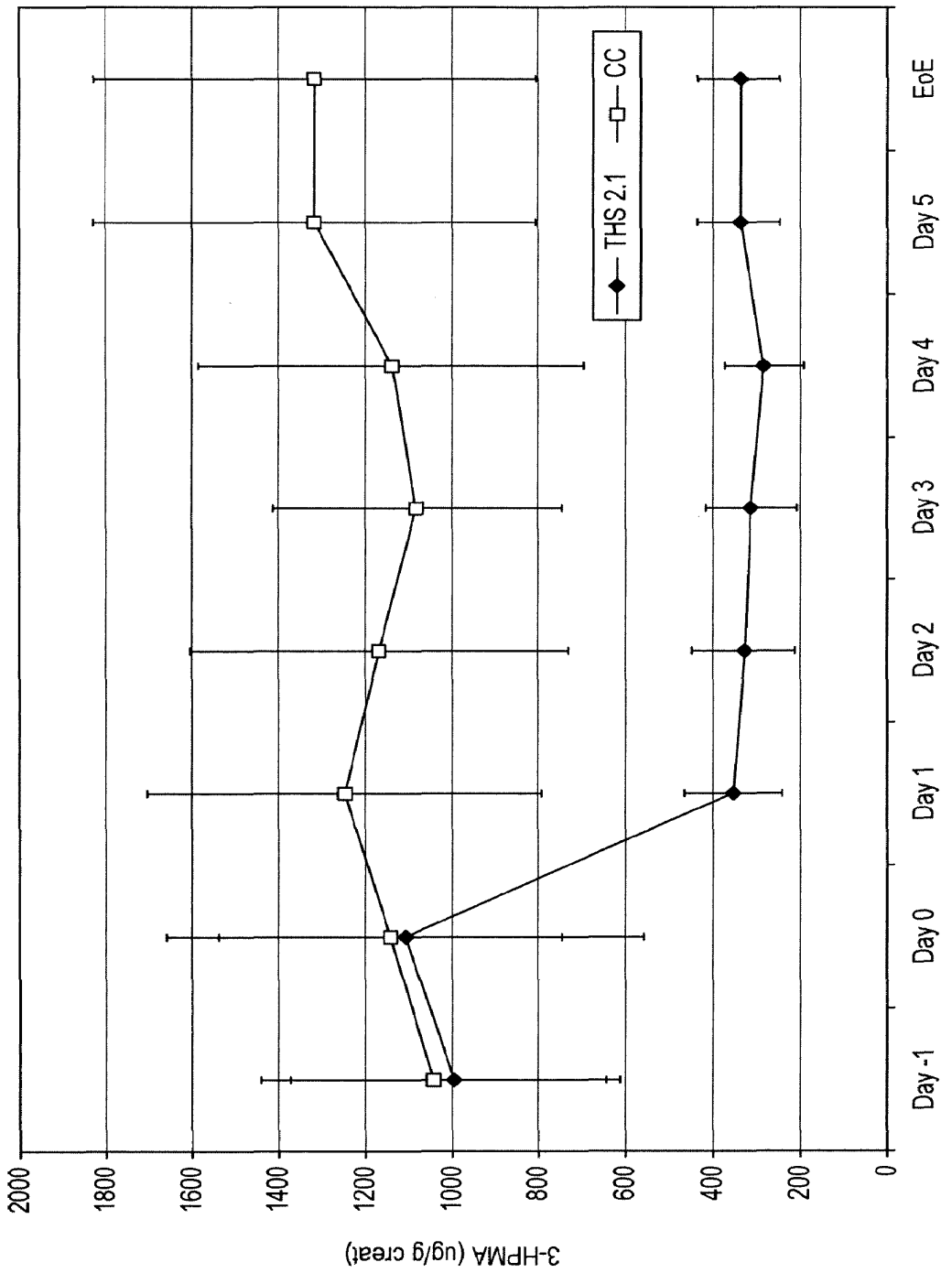

3-HPMA (ug/g creat)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Day -1
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
EoE
Study day
THS 2.1
CC

FIG. 2C

1765

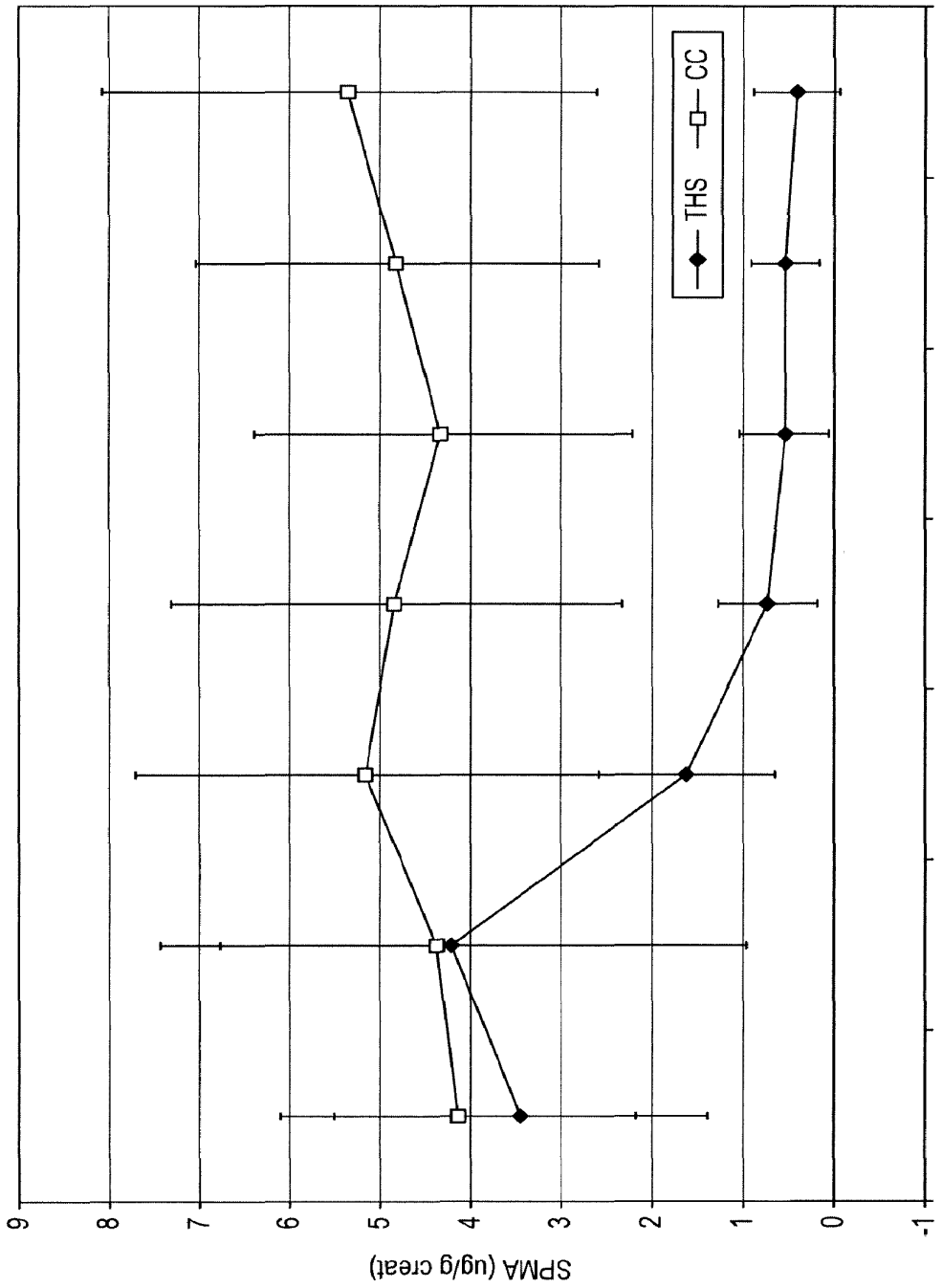

SPMA (ug/g creat)
9
8
7
6
5
4
3
2
1
0
-1
Day -1
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Study day
THS
CC

FIG. 2D

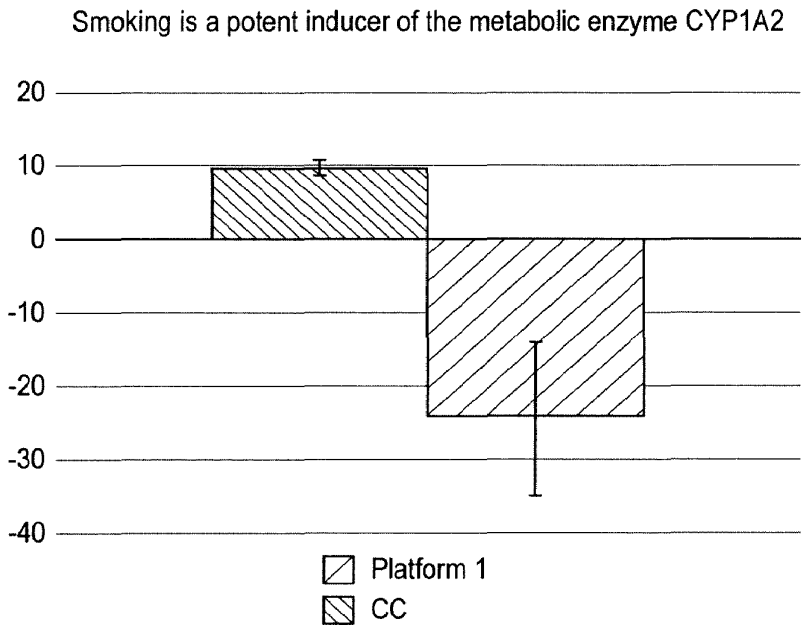

Smoking is a potent inducer of the metabolic enzyme CYP1A2
20
10
0
-10
-20
-30
-40
Platform 1
CC
On switching to Platform 1 the change in CYP1A2 activity
is comparable to smoking abstinence (30%)

*FIG. 3*

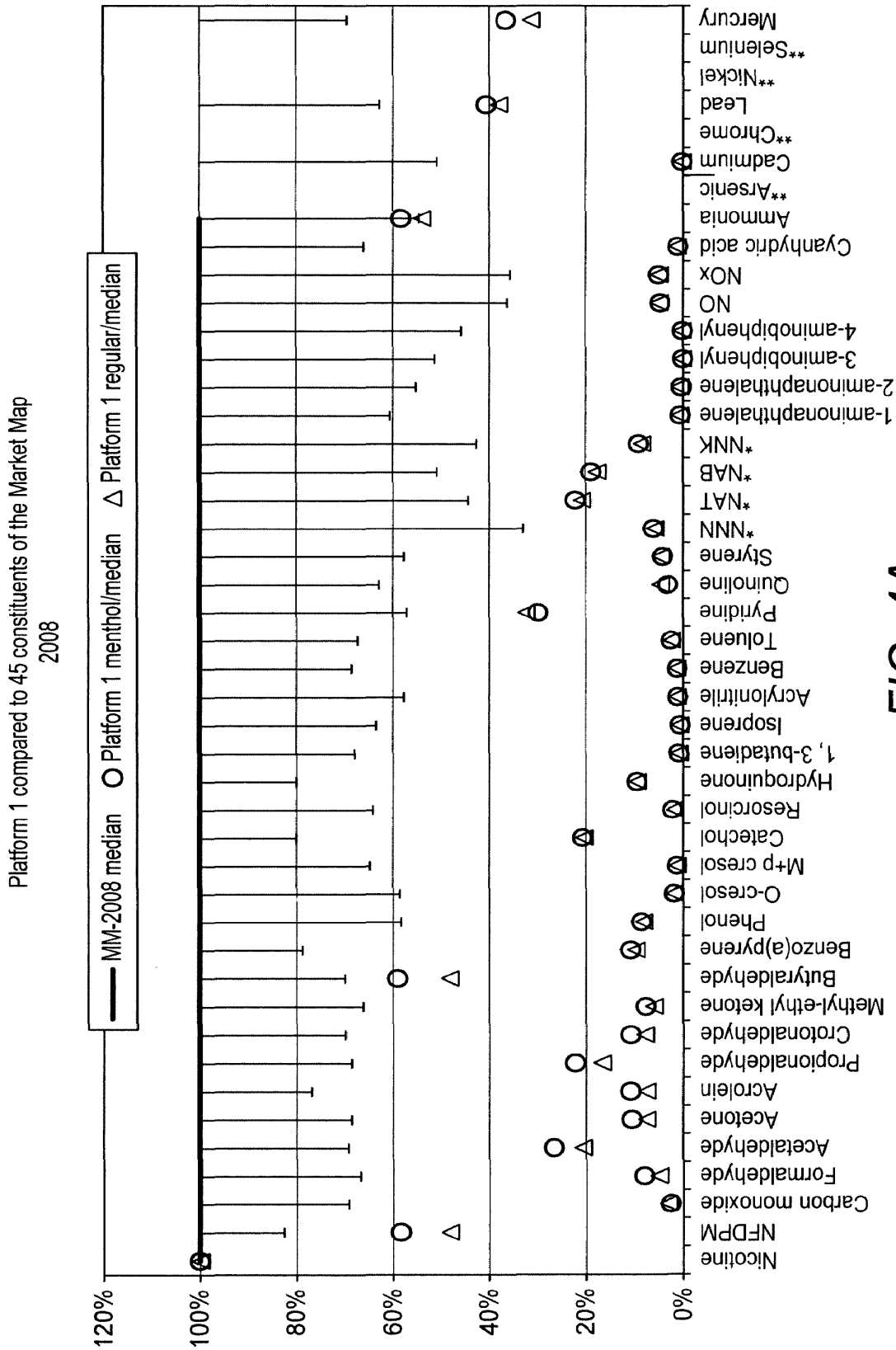

Platform 1 compared to 45 constituents of the Market Map
2008
MM-2008 median
Platform 1 menthol/median
Platform 1 regular/median
120%
100%
80%
60%
40%
20%
0%
Nicotine
NFDPM
Carbon monoxide
Formaldehyde
Acetaldehyde
Acetone
Acrolein
Propionaldehyde
Crotonaldehyde
Methyl-ethyl ketone
Butyraldehyde
Benzo(a)pyrene
Phenol
O-cresol
M+p cresol
Catechol
Resorcinol
Hydroquinone
1, 3-butadiene
Isoprene
Acrylonitrile
Benzene
Toluene
Pyridine
Quinoline
Styrene
*NNN
*NAT
*NAB
*NNK
1-aminonaphthalene
2-aminonaphthalene
3-aminobiphenyl
4-aminobiphenyl
NO
NOx
Cyanhydric acid
Ammonia
**Arsenic
Cadmium
**Chrome
Lead
**Nickel
**Selenium
Mercury

FIG. 4A

1768

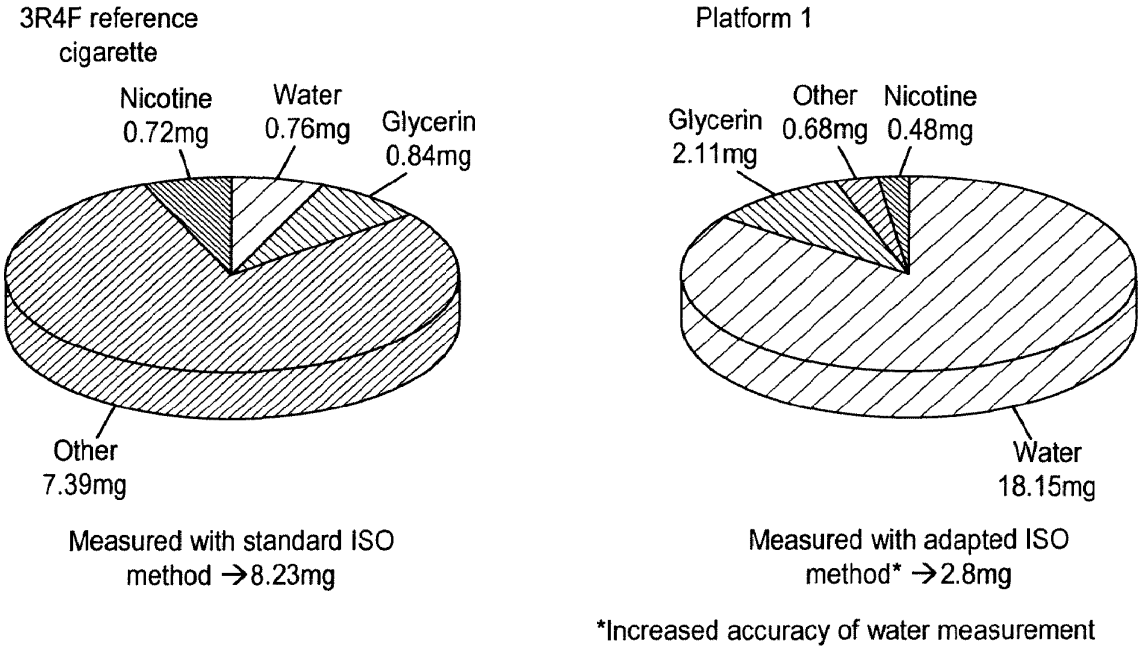

3R4F reference cigarette
Nicotine 0.72mg
Water 0.76mg
Glycerin 0.84mg
Other 7.39mg
Measured with standard ISO method →8.23mg
Platform 1
Glycerin 2.11mg
Other 0.68mg
Nicotine 0.48mg
Water 18.15mg
Measured with adapted ISO method* →2.8mg
*Increased accuracy of water measurement

FIG. 4B

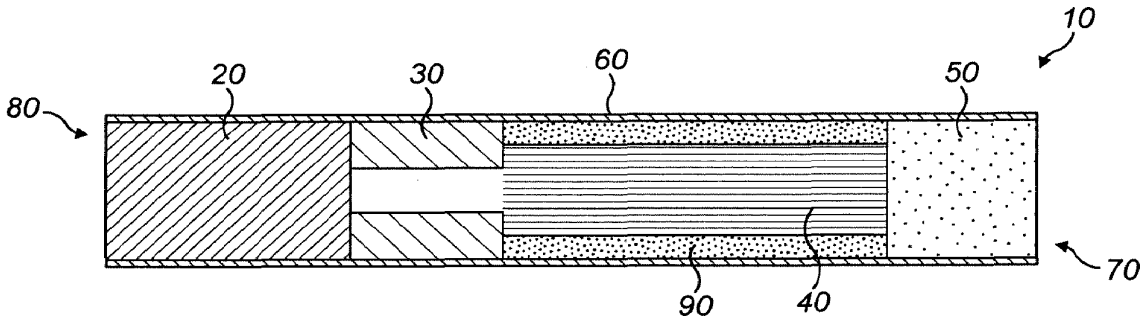

10
20
30
60
50
80
70
90
40

FIG. 5

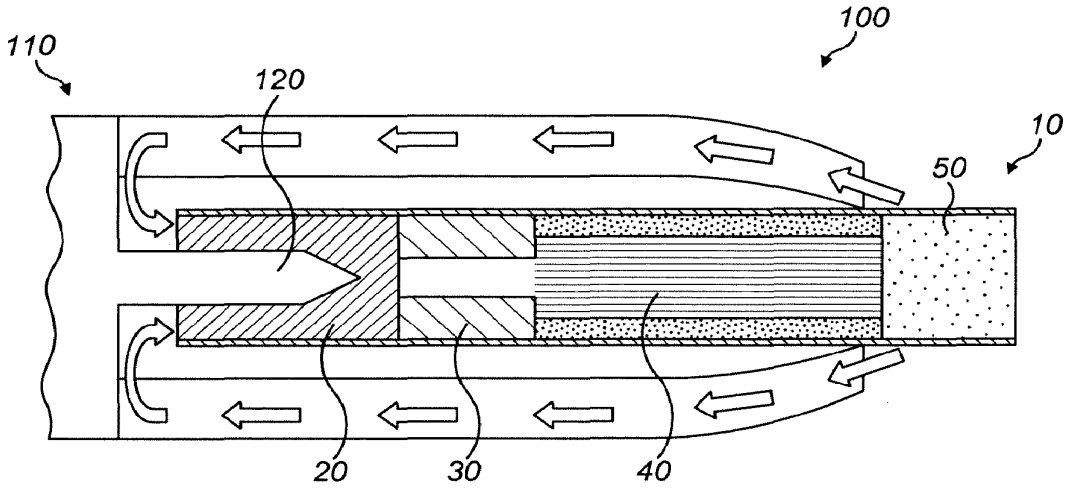



FIG. 6

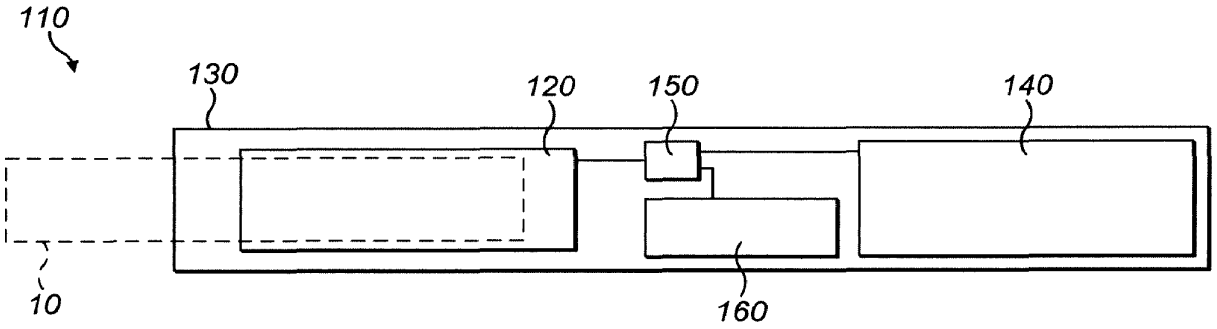



FIG. 7

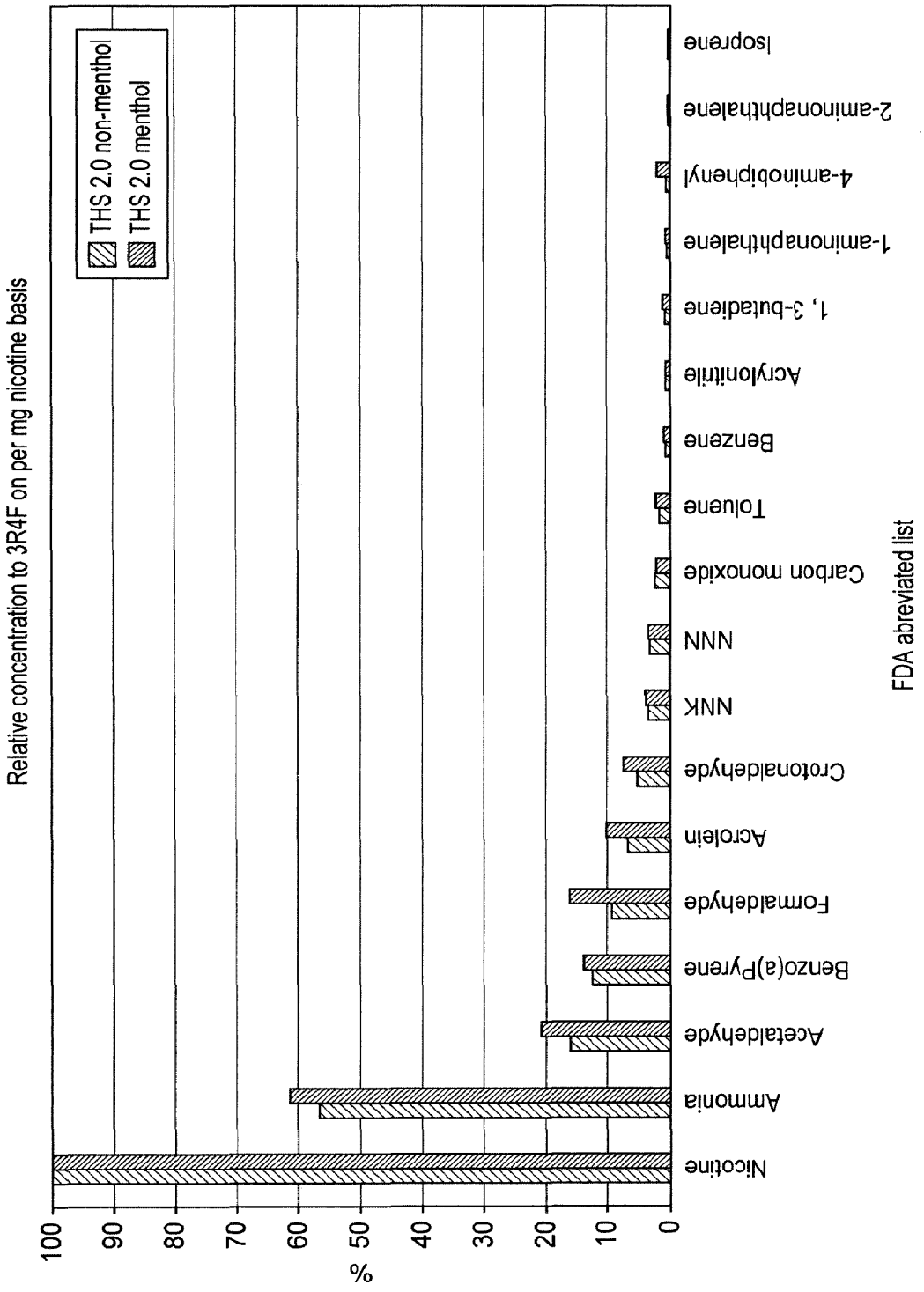

Relative concentration to 3R4F on per mg nicotine basis
THS 2.0 non-menthol
THS 2.0 menthol
100
90
80
70
60
50
40
30
20
10
0
%
Nicotine
Ammonia
Acetaldehyde
Benzo(a)Pyrene
Formaldehyde
Acrolein
Crotonaldehyde
NNK
NNN
Carbon monoxide
Toluene
Benzene
Acrylonitrile
1, 3-butadiene
1-aminonaphthalene
4-aminobiphenyl
2-aminonaphthalene
Isoprene
FDA abreviated list

FIG. 8

1771

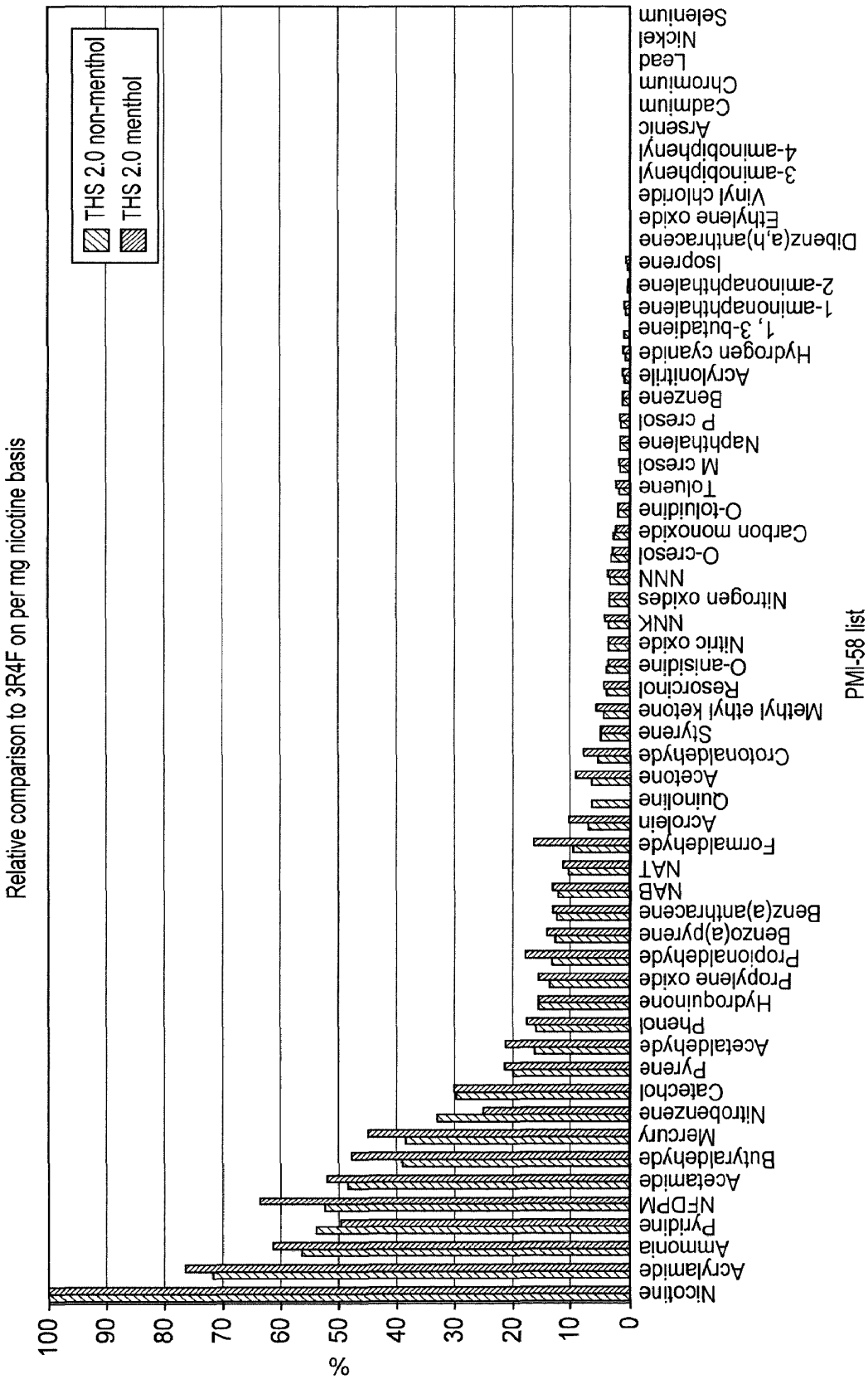

Relative comparison to 3R4F on per mg nicotine basis
THS 2.0 non-menthol
THS 2.0 menthol
%
100
90
80
70
60
50
40
30
20
10
0
Nicotine
Acrylamide
Ammonia
Pyridine
NFDPM
Acetamide
Butyraldehyde
Mercury
Nitrobenzene
Catechol
Pyrene
Acetaldehyde
Phenol
Hydroquinone
Propylene oxide
Propionaldehyde
Benzo(a)pyrene
Benz(a)anthracene
NAB
NAT
Formaldehyde
Acrolein
Quinoline
Acetone
Crotonaldehyde
Styrene
Methyl ethyl ketone
Resorcinol
O-anisidine
Nitric oxide
NNK
Nitrogen oxides
NNN
O-cresol
Carbon monoxide
O-toluidine
Toluene
M cresol
Naphthalene
P cresol
Benzene
Acrylonitrile
Hydrogen cyanide
1, 3-butadiene
1-aminonaphthalene
2-aminonaphthalene
Isoprene
Dibenz(a,h)anthracene
Ethylene oxide
Vinyl chloride
3-aminobiphenyl
4-aminobiphenyl
Arsenic
Cadmium
Chromium
Lead
Nickel
Selenium
PMI-58 list

FIG. 9

1772

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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(54) Title: IMPROVED AEROSOL FROM TOBACCO

(57) Abstract: In one aspect, there is provided a method of administering nicotine to a user via inhalation of the nicotine through an aerosol generating device comprising the steps of: (a) providing an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius; and (b) allowing the user to inhale the aerosol derived from the electrically heated tobacco; wherein the aerosol contains levels of nicotine that are about the same as the levels in combusted tobacco; and wherein the level of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine in the aerosol is lower than the level in combusted tobacco.

# INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A24F47/00
ADD.

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)
A24F

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 practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | paragraph [0001]<br>paragraph [0012] - paragraph [0014]<br>paragraph [0023] | 6 |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 May 2014 | 20/03/2015 |

| Name and mailing address of the ISA/ | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Dimoula, Kerasina |

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Form PCT/ISA/210 (second sheet) (April 2005)

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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| A | column 4, line 45 - line 57<br>column 6, line 1 - line 21<br>column 6, line 58 - column 7, line 17<br>column 12, line 35 - line 50 | 6 |
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| A | US 6 095 153 A (KESSLER STEPHEN B [US] ET AL) 1 August 2000 (2000-08-01)<br>the whole document | 1-3,6,8 |
| | --- | |

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/051818

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6, 8, 10

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 8, 10

A method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of:(a) providing an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing a user to inhale the aerosol derived from the electrically heated tobacco, wherein the levels of nicotine and HPHCs in the aerosol are within a specified range.
Use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein the levels of nicotine and HPHCs in the aerosol are within a specified range.
An aerosol generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein said aerosol comprises:(i) levels of nicotine are about the same as the levels in combusted tobacco; and (ii) wherein 4-aminobiphenyl, 2-aminonaphthalene and 1-aminonaphthalene are present in the aerosol at up to or less than about 0.1 ng/mg nicotine; wherein carbon monooxide, 1,3-butadiene, benzene, benzo[a]prene and acrylonitrile are present in the aerosol at between about 0.4 and 0.11 ng/mg nicotine; wherein isoprene, toluene, formaldehyde and crotonaldehyde are present in the aerosol at between about 1.5 and 3 ng/mg nicotine, wherein N-nitrosonornicotine and NNK are present in the aerosol at between about 3.1 and 5 ng/mg nicotine; wherein acrolein is present in the aerosol at between about 4 and 7 ng/mg nicotine; wherein ammonia is present in the aerosol at between about 9 and 11 ng/mg nicotine; and wherein acetaldehyde is present in the aerosol at between about 100 and 160 ng/mg nicotine.

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2. claims: 7, 9

A method of inhaling an aerosol comprising nicotine through an aerosol generating device comprising the steps of:(a) providing an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol; and (b) allowing a user to inhale the aerosol derived from the electrically heated tobacco, wherein the levels of a number of compounds in the user plasma, blood and urine are within a specified range.
Use of an aerosol-generating device for delivering nicotine in an aerosol to a user, wherein the aerosol is generated by electrically heating tobacco to a temperature of less than about 400 degrees Celsius, wherein the levels of a number of compounds in the user plasma, blood and urine are within a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

specified range.

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3. claims: 11-13

A method of identifying a user using an aerosol-generating device in which tobacco contained therein is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing a sample from the user; and (b) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein; wherein (i) the carboxyhemoglobin (carbon monoxide marker) level in the user is between about 1-2%, suitably about 1.5% in blood after 1 day of consuming aerosol generated from electrically heated tobacco; and/or (ii) the S-PMA (benzene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine, suitably about 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iii) the 3-HPMA (acrolein marker) level in the user is between about 200 to 400 micro.g/g creatinine, suitably, about 300 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is about 0.1 to 1 micro.g/g creatinine, suitably 0.5 micro.g/g creatinine in urine after 2 days of consuming aerosol generated from electrically heated tobacco is indicative that said user uses the aerosol-generating device.
A sample obtained from a user at least 2 days after using an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, wherein(i) the carboxyhemoglobin (carbon monoxide marker) level in the sample is between about 1%-2%; and/or (ii) the S-PMA (benzene marker) level in the user is to between about 0.1 to 1 micro.g/g creatinine; and/or (iii) the 3-HPMA (acrolein marker) level in the user is about 200 to 400 micro.g/g creatinine; and/or (iv) the MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine.

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4. claim: 14

A method of monitoring a user consuming nicotine via inhalation of an aerosol comprising nicotine through an aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius, comprising the steps of: (a) providing the user with the aerosol generating device that electrically heats tobacco to a temperature of less than about 400 degrees Celsius; (b) allowing the user to inhale the aerosol comprising nicotine through the aerosol generating device; (c) providing, obtaining or collecting one or more samples from the user,

which may be the same or different types of sample and which may optionally be a plurality of samples taken at time intervals during consumption by the user; (d) measuring the levels of two or more of at least nicotine, carbon monoxide, acrolein or benzene therein, either directly or in a biomarker thereof; and (e) comparing the levels measured in step (b) with the following levels or equivalent levels if different types of samples are used: (i) a carboxyhemoglobin (carbon monoxide marker) level in the sample of between about 1%-2% in blood; and/or (ii) a S-PMA (benzene marker) level in the user of between about 0.1 to 1 micro.g/g creatinine; and/or (iii) a 3-HPMA (acrolein marker) level in the user of about 200 to 400 micro.g/g creatinine; and/or (iv) a MHBMA (1,3-butadiene marker) level in the user is between about 0.1 to 1 micro.g/g creatinine; wherein correlation between the samples and the levels in step (e) is indicative that the user is exposed to levels of one or more harmful or potentially harmful constituents (HPHCs) other than nicotine that are lower than the levels in combusted tobacco.

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5. claim: 15

A method of modifying an aerosol-generating device in which tobacco contained in the aerosol-generating device is electrically heated to a temperature of less than about 400 degrees Celsius to create an aerosol, said method comprising the steps of: (a) providing the aerosol-generating device; (b) making one or more modifications to one or more component parts of the aerosol-generating device; and (c) testing the modified aerosol-generating device to determine if the modification(s) has a beneficial effect on the aerosol-generating device, said testing comprising the steps of:(i) determining the levels one or more HPHCs other than nicotine in the aerosol, wherein a reduction in the levels of one or more HPHCs in the aerosol is indicative that the one or more modifications have a beneficial effect on the aerosol-generating device; and/or (ii) determining the levels of one or more of at least carbon monoxide, benzene, acrolein and 1,3-butadiene therein in the user after inhaling the aerosol, wherein a reduction in one or more, suitably, all of these levels is indicative that the one or more modifications have a beneficial effect on the aerosol-generating device.

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Information on patent family members

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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— *with international search report (Art. 21(3))*

(54) **Title**: AEROSOL-GENERATING DEVICE COMPRISING MULTIPLE SOLID-LIQUID PHASE-CHANGE MATERIALS

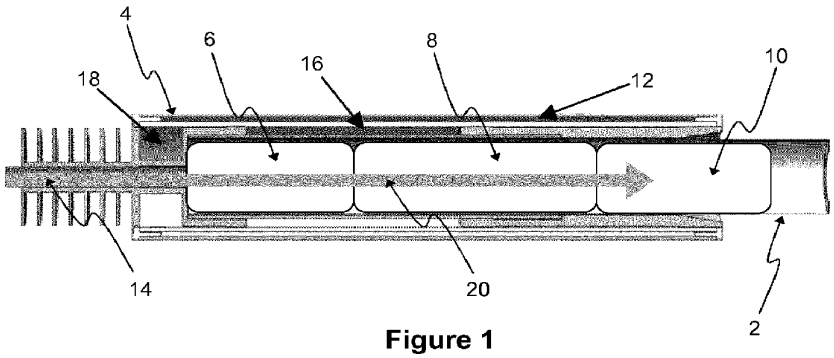



**Figure 1**

(57) **Abstract**: An aerosol-generating device (4) for use in an aerosol-generating system and an aerosol-generating system comprising an aerosol-generating device (4) and an aerosol-generating article (2). The aerosol-generating device (4) comprises: a cavity configured to receive an aerosol-generating article (2); a first solid-liquid phase-change material (16) positioned about a perimeter of the cavity; and heating means (14) configured to heat the first solid-liquid phase-change material (16) to a temperature above the melting point of the first solid-liquid phase-change material (16). The aerosol-generating device (4) further comprises: a second solid-liquid phase-change material (18), wherein the melting point of the second solid-liquid phase-change material (18) is higher than the melting point of the first solid-liquid phase-change material (16).

WO 2014/139611 A1

# AEROSOL-GENERATING DEVICE COMPRISING MULTIPLE SOLID-LIQUID PHASE-CHANGE MATERIALS

The present invention relates to an aerosol-generating device for use in an aerosol-generating system and an aerosol-generating system comprising an aerosol-generating device and an aerosol-generating article. In particular, the present invention relates to an aerosol-generating device and an aerosol-generating system for generating an aerosol comprising nicotine salt particles.

WO 2008/121610 A1, WO 2010/107613 A1 and WO 2011/034723 A1 disclose devices for delivering nicotine to a user comprising a volatile acid, such as pyruvic acid, or other volatile delivery enhancing compound source and a nicotine source. The volatile delivery enhancing compound is reacted with nicotine in the gas phase to form an aerosol of nicotine salt particles that is inhaled by the user.

At room temperature pyruvic acid and nicotine are both sufficiently volatile to form respective vapours that react with one another in the gas phase to form nicotine pyruvate salt particles. However, the vapour pressure of pyruvic acid at a given temperature is substantially greater than that of nicotine leading to a difference in the vapour concentration of the two reactants. Differences between the vapour concentration of the volatile delivery enhancing compound and nicotine in devices of the type disclosed in WO 2008/121610 A1, WO 2010/107613 A1 and WO 2011/034723 A1 can disadvantageously lead to the delivery of unreacted volatile delivery enhancing compound to a user.

It is desirable to produce a maximum quantity of nicotine salt particles for delivery to a user using a minimum quantity of reactants. Consequently, it would be desirable to provide an aerosol-generating system of the type disclosed in WO 2008/121610 A1, WO 2010/107613 A1 and WO 2011/034723 A1 in which the quantity of unreacted volatile delivery enhancing agent is minimised.

It would be especially desirable to provide an aerosol-generating system of the type disclosed in WO 2008/121610 A1, WO 2010/107613 A1 and WO 2011/034723 A1 in which the consistency of nicotine salt particle delivery to a user is improved.

According to the invention there is provided an aerosol-generating device for use in an aerosol-generating system, the aerosol-generating device comprising: a cavity configured to receive an aerosol-generating article; a first solid-liquid phase-change material positioned about a perimeter of the cavity; heating means configured to heat the first solid-liquid phase-change material to a temperature above the melting point of the first solid-liquid phase-change material; and a second solid-liquid phase-change material, wherein the melting point of the second solid-liquid phase-change material is higher than the melting point of the first solid-liquid phase-change material.

According to the invention there is also provided an aerosol-generating system comprising an aerosol-generating device according to the invention and an aerosol-generating article.

In particular, there is provided an aerosol-generating system comprising an aerosol-generating device according to the invention and an aerosol-generating article, the aerosol-generating article comprising: a first compartment comprising a volatile delivery enhancing compound source and second compartment comprising a nicotine source.

As used herein, the term "aerosol-generating device" refers to a device that interacts with an aerosol-generating article to generate an aerosol that is directly inhalable into a user's lungs thorough the user's mouth.

As used herein, the term "aerosol-generating article" refers to an article comprising an aerosol-forming substrate capable of releasing volatile compounds, which can form an aerosol. In certain embodiments, the aerosol-generating article may comprise an aerosol-forming substrate capable of releasing upon heating volatile compounds, which can form an aerosol.

As used herein, the terms "upstream", "downstream", "proximal" and "distal" are used to describe the relative positions of components, or portions of components, of aerosol-generating devices and aerosol-generating articles of aerosol-generating systems according to the invention.

The aerosol-generating article comprises a proximal end through which, in use, an aerosol exits the aerosol-generating article. The proximal end may also be referred to as the mouth end. In use, a user draws on the proximal or mouth end of the aerosol-generating article in order to inhale an aerosol generated by the aerosol-generating article. The aerosol-generating article comprises a distal end opposed to the proximal or mouth end. The proximal or mouth end of the aerosol-generating article may also be referred to as the downstream end and the distal end of the aerosol-generating article may also be referred to as the upstream end. Components, or portions of components, of the aerosol-generating article may be described as being upstream or downstream of one another based on their relative positions between the proximal or downstream end and the distal or upstream end of the aerosol-generating article.

The upstream and downstream ends of the aerosol-generating article are defined with respect to the airflow when a user draws on the proximal or mouth end of the aerosol-generating article. Air is drawn into the aerosol-generating article at the distal or upstream end, passes downstream through the aerosol-generating article and exits the aerosol-generating article at the proximal or downstream end.

As used herein, the term "longitudinal" is used to describe the direction between the downstream or proximal end and the opposed upstream or distal end and the term "transverse" is used to describe the direction perpendicular to the longitudinal direction.

Aerosol-generating devices according to the invention comprise a first solid-liquid phase-change material that is solid at ambient temperature. In use, when heated to its melting point by the heating means of the aerosol-generating device, the first solid-liquid phase-change material absorbs thermal energy as it changes phase from a solid to a liquid. Upon subsequent cooling, the first solid-liquid phase-change material releases the absorbed thermal energy as it changes phase from a liquid to a solid.

The thermal energy released by the first solid-liquid phase-change material as it solidifies heats an aerosol-generating article received in the cavity of the aerosol-generating device to an operating temperature above ambient temperature.

In certain preferred embodiments, aerosol-generating devices according to the invention are used in cooperation with aerosol-generating articles comprising a first compartment comprising a volatile delivery enhancing compound source and second compartment comprising a nicotine source. In such embodiments, the thermal energy released by the first solid-liquid phase-change material as it solidifies heats one or both of the first compartment and the second compartment of the aerosol-generating article to an operating temperature above ambient temperature. This increases the vapour pressure of one or both of the volatile delivery enhancing compound and the nicotine, leading to a higher concentration of respective vapours available for reaction. This advantageously results in the production of a higher quantity of nicotine salt particles for delivery to a user.

Aerosol-generating devices according to the invention comprise a cavity configured to receive an aerosol-generating article.

Preferably, the cavity of the aerosol-generating device is substantially cylindrical.

The cavity of the aerosol-generating device may have a transverse cross-section of any suitable shape. For example, the cavity may be of substantially circular, elliptical, triangular, square, rhomboidal, trapezoidal, pentagonal, hexagonal or octagonal transverse cross-section.

Preferably, the cavity of the aerosol-generating device has a transverse cross-section of substantially the same shape as the transverse cross-section of the aerosol-generating article to be received in the cavity.

In certain embodiments, the cavity of the aerosol-generating device may have a transverse cross-section of substantially the same shape and dimensions as the transverse cross-section of the aerosol-generating article to be received in the cavity in order to maximize conductive thermal transfer from the aerosol-generating device to the aerosol-generating article.

As used herein, the term "transverse cross-section" is used to describe the cross-section of the cavity and the aerosol-generating article perpendicular to the major axis of the cavity and the aerosol-generating article, respectively.

Preferably, the cavity of the aerosol-generating device is of substantially circular transverse cross-section or of substantially elliptical transverse cross-section. Most preferably,

the cavity of the aerosol-generating device is of substantially circular transverse cross-section.

Preferably, the length of the cavity of the aerosol-generating device is less than the length of the aerosol-generating article so that when the aerosol-generating article is received in the cavity of the aerosol-generating device the proximal or downstream end of the aerosol-generating article projects from the cavity of the aerosol-generating device.

As used herein, by "length" is meant the maximum longitudinal dimension between the distal or upstream end and the proximal or downstream end of the cavity and the aerosol-generating article.

Preferably, the cavity of the aerosol-generating device has a diameter substantially equal to or slightly greater than the diameter of the aerosol-generating article.

As used herein, by "diameter" is meant the maximum transverse dimension of the cavity and the aerosol-generating article.

The first solid-liquid phase-change material is positioned about the perimeter of the cavity of the aerosol-generating device so that thermal energy released by the first solid-liquid phase-change material as it changes phase from a liquid to a solid heats an aerosol-generating article received in the cavity.

The first solid-liquid phase-change material may extend fully or partially around the circumference of the cavity. Preferably, the first solid-liquid phase-change material extends fully around the circumference of the cavity.

The first solid-liquid phase-change material may extend fully or partially along the length of the cavity.

The first solid-liquid phase-change material may be any suitable material having a melting point in a desired operating temperature range of the aerosol-generating system and a high latent heat of fusion.

Preferably, the first solid-liquid phase-change material has a melting point of between about 30 degrees Celsius and about 70 degrees Celsius. In certain embodiments, the first solid-liquid phase-change material may have a melting point of between about 40 degrees Celsius and about 60 degrees Celsius.

Preferably, the first solid-liquid phase-change material has a latent heat of fusion of at least about 150 kJ/kg, more preferably at least 200 kJ/kg, most preferably at least 250 kJ/kg.

Preferably, the first solid-liquid phase-change material has a thermal conductivity of at least about 0.5 $W.m^{-1}.K$.

Preferably, the first solid-liquid phase-change material undergoes small volumetric changes on phase change from a solid to a liquid and from a liquid to a solid.

Preferably, the first solid-liquid phase-change material has a low vapour pressure in the desired operating temperature range of the aerosol-generating system.

Preferably, the first solid-liquid phase-change material is non-flammable.

Examples of suitable first solid-liquid phase-change materials for use in aerosol-generating devices according to the invention include, but are not limited to: organic phase-change materials, such as fatty acids and paraffins; and inorganic phase-change materials, such as inorganic salt hydrates.

Suitable fatty acids for use as the first solid-liquid phase-change material include, but are not limited to: lauric acid and myristic acid. Suitable paraffins for use as the first solid-liquid phase-change material include, but are not limited to: icosane, pentacosane, hexacosane, heptacosane, octasosane, nonacosane, n-triacontane, hentriacontane, dotriacontane and tritriacontane.

In preferred embodiments, the first solid-liquid phase-change material is an inorganic salt hydrate. Suitable inorganic salt hydrates for use as the first solid-liquid phase-change material include, but are not limited to: phosphoric acid disodium salt dodecahydrate, calcium nitrate tetrahydrate, sodium thiosulfate pentahydrate and sodium acetate trihydrate.

In particularly preferred embodiments, the first solid-liquid phase-change material is sodium acetate trihydrate.

The amount of first solid-liquid phase-change material in the aerosol-generating device should be sufficient for the first solid-liquid phase-change material to release enough thermal energy as it changes phase from a liquid to a solid to heat the aerosol-generating article to a desired operating temperature range of the aerosol-generating system.

Preferably, the first solid-liquid phase-change material in the aerosol-generating device is configured to release at least about 250 J of thermal energy, more preferably at least about 500 J of thermal energy, as it changes phase from a liquid to a solid.

In certain preferred embodiments, the first solid-liquid phase-change material in the aerosol-generating device is configured to release at between about 250 J and about 1500 J of thermal energy, more preferably between about 500 J and about 1250 J of thermal energy, as it changes phase from a liquid to a solid.

Preferably, the first solid-liquid phase-change material is configured to heat an aerosol-generating article received in the cavity of the aerosol-generating device to at least about 40 degrees Celsius. More preferably, the first solid-liquid phase-change material is configured to heat an aerosol-generating article received in the cavity of the aerosol-generating device to at least about 40 degrees Celsius within about 10 seconds to about 15 seconds.

In certain preferred embodiments, the first solid-liquid phase-change material is configured to heat an aerosol-generating article received in the cavity of the aerosol-generating device to between about 40 degrees Celsius and 60 degrees Celsius. In certain particularly preferred embodiments, the first solid-liquid phase-change material is configured to heat an aerosol-generating article received in the cavity of the aerosol-generating device to between

about 40 degrees Celsius and 60 degrees Celsius within about 10 seconds to about 15 seconds.

Preferably, the first solid-liquid phase-change material is configured to release thermal energy for between about 3 minutes and about 10 minutes as it changes phase from a liquid to a solid.

To reduce the risk of overheating of the first solid-liquid phase-change material by the heating means of the aerosol-generating device, the aerosol-generating device further comprises a second solid-liquid phase-change material, wherein the melting point of the second solid-liquid phase-change material is higher than the melting point of the first solid-liquid phase-change material.

The inclusion of a second solid-liquid phase-change material is particularly advantageous where the heating means of the aerosol-generating device comprises a heat sink or heat exchanger configured to transfer thermal energy from an external heat source to the first solid-liquid phase-change material.

In use, once the first solid-liquid phase-change material has changed phase from a solid to a liquid, the first solid-liquid phase-change material may continue to absorb additional thermal energy from the heating means. This will cause the temperature of the first solid-liquid phase-change material to continue to rise above its melting point and in the absence of a second solid-liquid phase-change material could result in overheating of the first solid-liquid phase-change material.

However, where the aerosol-generating device comprises a second solid-liquid phase-change material with a higher melting point than the first solid-liquid phase-change material, the second solid-liquid phase-change material undergoes a phase change from solid to liquid when the temperature of the first solid-liquid phase-change material reaches the melting point of the second solid-liquid phase-change material. As it undergoes the phase change from solid to liquid the second solid-liquid phase-change material absorbs thermal energy. The second solid-liquid phase-change material thereby buffers the amount of additional thermal energy absorbed by the first solid-liquid phase-change material. This reduces the risk of overheating of the first solid-liquid phase-change material.

By reducing the risk of overheating of the first solid-liquid phase-change material, the inclusion of a second solid-liquid phase-change material advantageously increases the operational lifetime of the aerosol-generating device.

Preferably, the melting point of the second solid-liquid phase-change material is between 15 degrees Celsius and 25 degrees Celsius higher than the melting point of the first solid-liquid phase-change material.

Preferably, the second solid-liquid phase-change material has a melting point of between about 70 degrees Celsius and about 90 degrees Celsius.

Preferably, the second solid-liquid phase-change material has a latent heat of fusion of at least about 150 kJ/kg, more preferably at least 200 kJ/kg.

Preferably, the second solid-liquid phase-change material undergoes small volumetric changes on phase change from a solid to a liquid and from a liquid to a solid.

Preferably, the second solid-liquid phase-change material has a low vapour pressure in the desired operating temperature range of the aerosol-generating system.

Preferably, the second solid-liquid phase-change material is non-flammable.

Examples of suitable second solid-liquid phase-change materials for use in aerosol-generating devices according to the invention include, but are not limited to: organic phase-change materials, such as paraffins; and inorganic phase-change materials, such as inorganic salt hydrates.

Suitable paraffins for use as the second solid-liquid phase-change material include, but are not limited to: triatriacontane, tetratriacontane, pentatriacontane, hexatriacontane, heptatriacontane, octatriacontane, nonatriacontane, tertracontane, hentetracontane and dotetracontane.

Suitable inorganic salt hydrates for use as the second solid-liquid phase-change material include, but are not limited to: magnesium nitrate hexahydrate and magnesium chloride hexahydrate.

In preferred embodiments, the second solid-liquid phase-change material is a paraffin.

In particularly preferred embodiments, the second solid-liquid phase-change material is hexatriacontane.

The second solid-liquid phase-change material is in thermal contact with the first solid-liquid phase-change material and the heating means.

Preferably, thermal energy is transferred from the heating means to the first solid-liquid phase-change material via the second solid-liquid phase-change material.

The second solid-liquid phase-change material may be positioned upstream of the cavity and the first solid-liquid phase-change material.

Alternatively, the second solid-liquid phase-change material may be positioned about the perimeter of the cavity. In such embodiments, the second solid-liquid phase-change material may be upstream of the first solid-liquid phase-change material, downstream of the first solid-liquid phase-change material or may circumscribe the first solid-liquid phase-change material.

The heating means of the aerosol-generating device is configured to heat the first solid-liquid phase-change material to a temperature above the melting point of the first solid-liquid phase-change material.

The heating means may be a non-electrical heating means.

In certain preferred embodiments the heating means comprises a heat sink or heat exchanger configured to transfer thermal energy from an external heat source to the first solid-

liquid phase-change material. The heat sink or heat exchanger may be formed of any suitable thermally conductive material. Suitable materials include, but are not limited to, metals, such as aluminium and copper.

In certain particularly preferred embodiments, the heating means comprises a heat sink or heat exchanger configured to transfer thermal energy from a blue flame or torch lighter or other lighter to the first solid-liquid phase-change material. In such embodiments, a user may advantageously use a lighter to activate the aerosol-generating system in a manner similar to lighting a cigarette or other conventional smoking article.

The heat sink or heat exchanger is in thermal contact with the first solid-liquid phase-change material. The heat sink or heat exchanger is also in thermal contact with the second solid-liquid phase-change material. In such embodiments, the heat sink or heat exchanger, first solid-liquid phase-change material and second solid-liquid phase-change material are preferably configured so that thermal energy is transferred from the heat sink or heat exchanger to the second phase solid-liquid phase-change material and then from the second solid-liquid phase-change material to the first solid-liquid phase-change material.

The heat sink or heat exchanger preferably extends downstream from the distal or upstream end of the aerosol-generating device to the first solid-liquid phase-change material.

In certain preferred embodiments, the heat sink or heat exchanger surrounds the first solid-liquid phase-change material. For example, the heat sink or heat exchanger may comprise a hollow thermally conductive tube that surrounds the first solid-liquid phase-change material.

Alternatively or in addition, the heat sink or heat exchanger may surround the second solid-liquid phase-change material.

The heating means may be an electrical heating means powered by an electric power supply.

Where the heating means is an electric heating means, the aerosol-generating device may further comprise an electric power supply and a controller comprising electronic circuitry configured to control the supply of electric power from the electric power supply to the electric heating means. Any suitable electronic circuitry may be used in order to control the supply of power to the electric heating means. The electronic circuitry may be programmable.

Alternatively, the electrical heating means may be powered by an external electric power supply.

The electric power supply may be a DC voltage source. In preferred embodiments, the electric power supply is a battery. For example, the electric power supply may be a Nickel-metal hydride battery, a Nickel cadmium battery, or a Lithium based battery, for example a Lithium-Cobalt, a Lithium-Iron-Phosphate or a Lithium-Polymer battery. The electric power supply may alternatively be another form of electric charge storage device such as a capacitor.

The electric power supply may require recharging and may have a capacity that allows for the storage of enough electrical energy for use of the aerosol-generating device with one or more aerosol-generating articles.

The aerosol-generating device may comprise a heating means comprising one or more heating elements. The one or more heating elements may extend fully or partially along the length of the cavity of the aerosol-generating device. The one or more heating elements may extend fully or partially around the circumference of the cavity of the aerosol-generating device.

The aerosol-generating device may further comprise a controller configured to independently control a supply of power to the one or more heating elements.

In one preferred embodiment the heating means comprises one or more heating elements that are heated electrically. However, other heating schemes may be used to heat the one or more heating elements. For example, the one or more heating elements may be heated by conduction from another heat source. Alternatively, the one or more heating elements may be infra-red heating elements or inductive heating elements.

In a particularly preferred embodiment, the heating means comprises one or more heating elements comprising an electrically resistive material. Each heating element may comprise a non-elastic material, for example a ceramic sintered material, such as alumina ($Al_2O_3$) and silicon nitride ($Si_3N_4$), or printed circuit board or silicon rubber. Alternatively, each heating element may comprise an elastic, metallic material, for example an iron alloy or a nickel-chromium alloy. The one or more heating elements may be flexible heating foils on a dielectric substrate, such as polyimide. Alternatively, the one or more heating elements may be metallic grid or grids, flexible printed circuit boards, or flexible carbon fibre heaters.

Other suitable electrically resistive materials include but are not limited to: semiconductors such as doped ceramics, electrically "conductive" ceramics (such as, for example, molybdenum disilicide), carbon, graphite, metals, metal alloys and composite materials made of a ceramic material and a metallic material. Such composite materials may comprise doped or undoped ceramics. Examples of suitable doped ceramics include doped silicon carbides. Examples of suitable metals include titanium, zirconium, tantalum and metals from the platinum group. Examples of suitable metal alloys include stainless steel, nickel-, cobalt-, chromium-, aluminium- titanium- zirconium-, hafnium-, niobium-, molybdenum-, tantalum-, tungsten-, tin-, gallium- and manganese- alloys, and super-alloys based on nickel, iron, cobalt, stainless steel, Timetal® and iron-manganese-aluminium based alloys. Timetal® is a registered trade mark of Titanium Metals Corporation, 1999 Broadway Suite 4300, Denver, Colorado. In composite materials, the electrically resistive material may optionally be embedded in, encapsulated or coated with an insulating material or vice-versa, depending on the kinetics of energy transfer and the external physicochemical properties required.

The aerosol-generating device may further comprise a temperature sensor configured to sense the temperature of the first solid-liquid phase-change material of the aerosol-generating device.

In such embodiments, the aerosol-generating device may comprise a controller configured to control a supply of power to the one or more heating elements based on the temperature of the first solid-liquid phase-change material sensed by the temperature sensor.

The heating means may comprise one or more heating elements formed using a metal having a defined relationship between temperature and resistivity. In such embodiments, the metal may be formed as a track between two layers of suitable insulating materials. Heating elements formed in this manner may be used to both heat and monitor the temperature of the first solid-liquid phase-change material of the aerosol-generating device.

The aerosol-generating device may further comprise a housing containing the cavity, first solid-liquid phase-change material, heating means and second solid-liquid phase-change material, controller, and power source.

Preferably, the housing of the aerosol-generating device is substantially cylindrical.

The housing of the aerosol-generating device may be designed to be grasped or held by a user.

In a preferred embodiment, the aerosol-generating device is a cylindrical heating sleeve.

The heating means, first solid-liquid phase-change material and second solid-liquid phase-change material may be spaced from the housing by an air gap or a layer of insulation.

Aerosol-generating devices according to the invention are preferably configured to receive an aerosol-generating article comprising a first compartment comprising a volatile delivery enhancing compound source and a second compartment comprising a nicotine source. However, it will be appreciated that aerosol-generating devices according to the invention may be configured to receive other types of aerosol-generating article.

The first compartment and the second compartment of the aerosol-generating article may abut one another. Alternatively, the first compartment and the second compartment of the aerosol-generating article may be spaced apart from one another.

The first compartment of the aerosol-generating article may be sealed by one or more frangible barriers. In a preferred embodiment, the first compartment is sealed by a pair of opposed transverse frangible barriers.

Alternatively or in addition, the second compartment of the aerosol-generating article may be sealed by one or more frangible barriers. In a preferred embodiment, the second compartment is sealed by a pair of opposed transverse frangible barriers.

The one or more frangible barriers may be formed from any suitable material. For example, the one or more frangible barriers may be formed from a metal foil or film.

In such embodiments, the aerosol-generating device preferably further comprises a

piercing member positioned within the cavity of the aerosol-generating device for piercing the one or more frangible barriers sealing one or both of the first compartment and the second compartment of the aerosol-generating article. The piercing member may be formed from any suitable material.

The volume of the first compartment and the second compartment may be the same or different. In a preferred embodiment, the volume of the second compartment is greater than the volume of the first compartment.

As described further below, the first compartment and the second compartment may be arranged in series or parallel within the aerosol-generating article.

As used herein, by "series" it is meant that the first compartment and the second compartment are arranged within the aerosol-generating article so that in use an air stream drawn through the aerosol-generating article passes through one of the first compartment and the second compartment and then passes through the other of the first compartment and the second compartment. Volatile delivery enhancing compound vapour is released from the volatile delivery enhancing compound source in the first compartment into the air stream drawn through the aerosol-generating article and nicotine vapour is released from the nicotine source in the second compartment into the air stream drawn through the aerosol-generating article. The volatile delivery enhancing compound vapour reacts with the nicotine vapour in the gas phase to form an aerosol, which is delivered to a user.

Where the first compartment and the second compartment are arranged in series within the aerosol-generating article, the second compartment may be downstream of the first compartment so that in use an air stream drawn through the aerosol-generating article passes through the first compartment and then passes through the second compartment.

In such embodiments, the volatile delivery enhancing compound vapour may react with the nicotine vapour in the second compartment. In such embodiments the aerosol-generating article may further comprise a third compartment downstream of the second compartment and the volatile delivery enhancing compound vapour may alternatively or in addition react with the nicotine vapour in the third compartment to form an aerosol.

Alternatively, where the first compartment and the second compartment are arranged in series within the aerosol-generating article, the second compartment may be upstream of the first compartment so that in use an air stream drawn through the aerosol-generating article passes through the second compartment and then passes through the first compartment.

In such embodiments, the nicotine vapour may react with the volatile delivery enhancing compound vapour in the first compartment. In such embodiments the aerosol-generating article may further comprise a third compartment downstream of the first compartment and the volatile nicotine vapour may alternatively or in addition react with the volatile delivery enhancing compound vapour in the third compartment to form an aerosol.

Where the first compartment and the second compartment are arranged in series within the aerosol-generating article, the aerosol-generating device may further comprise a piercing member positioned centrally within the cavity of the aerosol-generating device, along the major axis of the cavity, for piercing the first and second compartments of the aerosol-generating article.

As used herein, by "parallel" it is meant that the first compartment and the second compartment are arranged within the aerosol-generating article so that in use a first air stream drawn through the aerosol-generating article passes through the first compartment and a second air stream drawn through the aerosol-generating article passes through the second compartment. Volatile delivery enhancing compound vapour is released from the volatile delivery enhancing compound source in the first compartment into the first air stream drawn through the aerosol-generating article and nicotine vapour is released from the nicotine source in the second compartment into the second air stream drawn through the aerosol-generating article. The volatile delivery enhancing compound vapour in the first air stream reacts with the nicotine vapour in the second air stream in the gas phase to form an aerosol, which is delivered to a user.

In such embodiments the aerosol-generating article may further comprise a third compartment downstream of the first compartment and the second compartment and the volatile delivery enhancing compound vapour in the first air stream may mix and react with the nicotine vapour in the second air stream in the third compartment to form an aerosol.

Where the first compartment and the second compartment of the aerosol-generating article are arranged in parallel within the aerosol-generating article, the aerosol-generating device may further comprise a piercing member comprising a first piercing element positioned within the cavity of the aerosol-generating device for piercing the first compartment of the aerosol-generating article and a second piercing element positioned within the cavity of the aerosol-generating device for piercing the second compartment of the aerosol-generating article.

In particularly preferred embodiments, the aerosol-generating article comprises: a housing comprising: an air inlet; a first compartment in communication with the air inlet, the first compartment comprising a first one of a volatile delivery enhancing compound source and a nicotine source; a second compartment in communication with the first compartment, the second compartment comprising a second one of the volatile delivery enhancing compound source and the nicotine source; and an air outlet, wherein the air inlet and the air outlet are in communication with each other and configured so that air may pass into the housing through the air inlet, through the housing and out of the housing through the air outlet.

As used herein, the term "air inlet" is used to describe one or more apertures through which air may be drawn into the aerosol-generating article.

As used herein, the term "air outlet" is used to describe one or more apertures through which air may be drawn out of the aerosol-generating article.

In such embodiments, the first compartment and the second compartment are arranged in series from air inlet to air outlet within the housing. That is, the first compartment is downstream of the air inlet, the second compartment is downstream of the first compartment and the air outlet is downstream of the second compartment. In use, a stream of air is drawn into the housing through the air inlet, downstream through the first compartment and the second compartment and out of the housing through the air outlet.

In such embodiments, the first compartment may comprise the volatile delivery enhancing compound source and the second compartment may comprise the nicotine source.

Alternatively, in such embodiments, the first compartment may comprise the nicotine source and the second compartment may comprise the volatile delivery enhancing compound source.

The aerosol-generating article may further comprise a third compartment in communication with: the second compartment; and the air outlet. In use in such embodiments, a stream of air is drawn into the housing through the air inlet, downstream through the first compartment, the second compartment and the third compartment and out of the housing through the air outlet.

The aerosol-generating article may further comprise a mouthpiece in communication with: the second compartment, or the third compartment, where present; and the air outlet. In use in such embodiments, a stream of air is drawn into the housing through the air inlet, downstream through the first compartment, the second compartment, the third compartment, where present, and the mouthpiece and out of the housing through the air outlet.

In other preferred embodiments, the aerosol-generating article comprises: a housing comprising: an air inlet; a first compartment in communication with the air inlet, the first compartment comprising a volatile delivery enhancing compound source; a second compartment in communication with the air inlet, the second compartment comprising a nicotine source; and an air outlet, wherein the air inlet and the air outlet are in communication with each other and configured so that air may pass into the housing through the air inlet, through the housing and out of the housing through the air outlet.

In such embodiments, the first compartment and the second compartment are arranged in parallel from air inlet to air outlet within the housing. The first compartment and the second compartment are both downstream of the air inlet and upstream of the air outlet. In use, a stream of air is drawn into the housing through the air inlet, a first portion of the stream of air is drawn downstream through the first compartment and a second portion of the stream of air is drawn downstream through the second compartment.

The aerosol-generating article may further comprise a third compartment in communication with: one or both of the first compartment and the second compartment; and the air outlet.

The aerosol-generating article may further comprise a mouthpiece in communication with: the first compartment and the second compartment, or the third compartment, where present; and the air outlet.

In further preferred embodiments, the aerosol-generating article comprises: a housing comprising: a first air inlet; a second air inlet; a first compartment in communication with the first air inlet, the first compartment comprising a volatile delivery enhancing compound source; a second compartment in communication with the second air inlet, the second compartment comprising a nicotine source; and an air outlet, wherein the first air inlet, the second air inlet and the air outlet are in communication with each other and configured so that air may pass into the housing through the first air inlet, through the housing and out of the housing through the air outlet and air may pass into the housing through the first air inlet, through the housing and out of the housing through the air outlet.

In such embodiments, the first compartment and the second compartment are arranged in parallel within the housing. The first compartment is downstream of the first air inlet and upstream of the air outlet and the second compartment is downstream of the second air inlet and upstream of the air outlet. In use, a first stream of air is drawn into the housing through the first air inlet and downstream through the first compartment and a second stream of air is drawn into the housing through the second air inlet and downstream through the second compartment.

The aerosol-generating article may further comprise a third compartment in communication with: one or both of the first compartment and the second compartment; and the air outlet.

The aerosol-generating article may further comprise a mouthpiece in communication with: the first compartment and the second compartment, or the third compartment, where present; and the air outlet.

The housing of the aerosol-generating article may simulate the shape and dimensions of a tobacco smoking article, such as a cigarette, a cigar, a cigarillo or a pipe, or a cigarette pack. In a preferred embodiment, the housing simulates the shape and dimensions of a cigarette.

Where present, the third compartment may comprise one or more aerosol-modifying agents. For example, the third compartment may comprise an adsorbent, such as activated carbon, a flavourant, such as menthol, or a combination thereof.

Where present, the mouthpiece may comprise a filter. The filter may have a low particulate filtration efficiency or very low particulate filtration efficiency. Alternatively, the mouthpiece may comprise a hollow tube.

The first compartment of the aerosol-generating article comprises a volatile delivery enhancing compound source. As used herein, by "volatile" it is meant the delivery enhancing compound has a vapour pressure of at least about 20 Pa. Unless otherwise stated, all vapour pressures referred to herein are vapour pressures at 25°C measured in accordance with ASTM E1194 – 07.

Preferably, the volatile delivery enhancing compound has a vapour pressure of at least about 50 Pa, more preferably at least about 75 Pa, most preferably at least 100 Pa at 25°C.

Preferably, the volatile delivery enhancing compound has a vapour pressure of less than or equal to about 400 Pa, more preferably less than or equal to about 300 Pa, even more preferably less than or equal to about 275 Pa, most preferably less than or equal to about 250 Pa at 25°C.

In certain embodiments, the volatile delivery enhancing compound may have a vapour pressure of between about 20 Pa and about 400 Pa, more preferably between about 20 Pa and about 300 Pa, even more preferably between about 20 Pa and about 275 Pa, most preferably between about 20 Pa and about 250 Pa at 25°C.

In other embodiments, the volatile delivery enhancing compound may have a vapour pressure of between about 50 Pa and about 400 Pa, more preferably between about 50 Pa and about 300 Pa, even more preferably between about 50 Pa and about 275 Pa, most preferably between about 50 Pa and about 250 Pa at 25°C.

In further embodiments, the volatile delivery enhancing compound may have a vapour pressure of between about 75 Pa and about 400 Pa, more preferably between about 75 Pa and about 300 Pa, even more preferably between about 75 Pa and about 275 Pa, most preferably between about 75 Pa and about 250 Pa at 25°C.

In yet further embodiments, the volatile delivery enhancing compound may have a vapour pressure of between about 100 Pa and about 400 Pa, more preferably between about 100 Pa and about 300 Pa, even more preferably between about 100 Pa and about 275 Pa, most preferably between about 100 Pa and about 250 Pa at 25°C.

The volatile delivery enhancing compound may comprise a single compound. Alternatively, the volatile delivery enhancing compound may comprise two or more different compounds.

Where the volatile delivery enhancing compound comprises two or more different compounds, the two or more different compounds in combination have a vapour pressure of at least about 20 Pa at 25°C.

Preferably, the volatile delivery enhancing compound is a volatile liquid.

The volatile delivery enhancing compound may comprise a mixture of two or more different liquid compounds.

The volatile delivery enhancing compound may comprise an aqueous solution of one or more compounds. Alternatively the volatile delivery enhancing compound may comprise a non-aqueous solution of one or more compounds.

The volatile delivery enhancing compound may comprise two or more different volatile compounds. For example, the volatile delivery enhancing compound may comprise a mixture of two or more different volatile liquid compounds.

Alternatively, the volatile delivery enhancing compound may comprise one or more non-volatile compounds and one or more volatile compounds. For example, the volatile delivery enhancing compound may comprise a solution of one or more non-volatile compounds in a volatile solvent or a mixture of one or more non-volatile liquid compounds and one or more volatile liquid compounds.

In one embodiment, the volatile delivery enhancing compound comprises an acid. The volatile delivery enhancing compound may comprise an organic acid or an inorganic acid. Preferably, the volatile delivery enhancing compound comprises an organic acid, more preferably a carboxylic acid, most preferably an alpha-keto or 2-oxo acid.

In a preferred embodiment, the volatile delivery enhancing compound comprises an acid selected from the group consisting of 3-methyl-2-oxopentanoic acid, pyruvic acid, 2-oxopentanoic acid, 4-methyl-2-oxopentanoic acid, 3-methyl-2-oxobutanoic acid, 2-oxooctanoic acid and combinations thereof. In a particularly preferred embodiment, the volatile delivery enhancing compound comprises pyruvic acid.

In a preferred embodiment, the volatile delivery enhancing compound source comprises a sorption element and a volatile delivery enhancing compound sorbed on the sorption element.

As used herein, by "sorbed" it is meant that the volatile delivery enhancing compound is adsorbed on the surface of the sorption element, or absorbed in the sorption element, or both adsorbed on and absorbed in the sorption element. Preferably, the volatile delivery enhancing compound is adsorbed on the sorption element.

The sorption element may be formed from any suitable material or combination of materials. For example, the sorption element may comprise one or more of glass, stainless steel, aluminium, polyethylene (PE), polypropylene, polyethylene terephthalate (PET), polybutylene terephthalate (PBT), polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), and BAREX®.

In a preferred embodiment, the sorption element is a porous sorption element.

For example, the sorption element may be a porous sorption element comprising one or more materials selected from the group consisting of porous plastic materials, porous polymer fibres and porous glass fibres.

The sorption element is preferably chemically inert with respect to the volatile delivery enhancing compound.

The sorption element may have any suitable size and shape.

In one preferred embodiment, the sorption element is a substantially cylindrical plug. In one particularly preferred embodiment, the sorption element is a porous substantially cylindrical plug.

In another preferred embodiment, the sorption element is a substantially cylindrical hollow tube. In another particularly preferred embodiment, the sorption element is a porous substantially cylindrical hollow tube.

The size, shape and composition of the sorption element may be chosen to allow a desired amount of volatile delivery enhancing compound to be sorbed on the sorption element.

In a preferred embodiment, between about 20 µl and about 200 µl, more preferably between about 40 µl and about 150 µl, most preferably between about 50 µl and about 100 µl of the volatile delivery enhancing compound is sorbed on the sorption element.

The sorption element advantageously acts as a reservoir for the volatile delivery enhancing compound.

The second compartment of the aerosol-generating article comprises a nicotine source. The nicotine source may comprise one or more of nicotine, nicotine base, a nicotine salt, such as nicotine-HCl, nicotine-bitartrate, or nicotine-ditartrate, or a nicotine derivative.

The nicotine source may comprise natural nicotine or synthetic nicotine.

The nicotine source may comprise pure nicotine, a solution of nicotine in an aqueous or non-aqueous solvent or a liquid tobacco extract.

The nicotine source may further comprise an electrolyte forming compound. The electrolyte forming compound may be selected from the group consisting of alkali metal hydroxides, alkali metal oxides, alkali metal salts, alkaline earth metal oxides, alkaline earth metal hydroxides and combinations thereof.

For example, the nicotine source may comprise an electrolyte forming compound selected from the group consisting of potassium hydroxide, sodium hydroxide, lithium oxide, barium oxide, potassium chloride, sodium chloride, sodium carbonate, sodium citrate, ammonium sulfate and combinations thereof

In certain embodiments, the nicotine source may comprise an aqueous solution of nicotine, nicotine base, a nicotine salt or a nicotine derivative and an electrolyte forming compound.

Alternatively or in addition, the nicotine source may further comprise other components including, but not limited to, natural flavours, artificial flavours and antioxidants.

The nicotine source may comprise a sorption element and nicotine sorbed on the sorption element.

The aerosol-generating article is preferably substantially cylindrical in shape.

The aerosol-generating article may have a transverse cross-section of any suitable

shape.

Preferably, the aerosol-generating article is of substantially circular transverse cross-section or of substantially elliptical transverse cross-section. More preferably, the aerosol-generating article is of substantially circular transverse cross-section.

The aerosol-generating article may simulate the shape and dimensions of a tobacco smoking article, such as a cigarette, a cigar, a cigarillo or a pipe, or a cigarette pack. In a preferred embodiment, the aerosol-generating article simulates the shape and dimensions of a cigarette.

For the avoidance of doubt, features described above in relation to one embodiment of the invention may also be applicable to other embodiment of the invention. In particular, features described above in relation to aerosol-generating devices according to the invention may also relate, where appropriate to aerosol-generating systems according to the invention, and vice versa.

The invention will now be further described with reference to the accompanying drawings in which:

Figure 1 shows a schematic longitudinal cross-section of an aerosol-generating system according to a first embodiment of the invention;

Figure 2 shows the temperature of an aerosol-generating device according to the first embodiment of the invention shown in Figure 1 as a function of time during operation; and

Figure 3 shows a comparison of the temperature of the aerosol-generating device of Figure 2 and an aerosol-generating device according to a second embodiment of the invention as a function of time during operation;

Figure 1 schematically shows an aerosol-generating system according to a first embodiment of the invention comprising an aerosol-generating article 2 and an aerosol-generating device 4.

The aerosol-generating article 2 has an elongate cylindrical shape and comprises a housing comprising a first compartment 6 comprising a volatile delivery enhancing compound source, a second compartment 8 comprising a nicotine source, and a third compartment 10. As shown in Figure 1, the first compartment 6, the second compartment 8, and the third compartment 10 are arranged in series and in coaxial alignment within the aerosol-generating article 2. The first compartment 6 is located at the distal or upstream end of the aerosol-generating article 2. The second compartment 8 is located immediately downstream of and abuts the first compartment 6. The third compartment 10 is located downstream of the second compartment 8 at the proximal or downstream end of the aerosol-generating article 2. Instead of or in addition to the third compartment 10, the aerosol-generating article 2 may comprise a mouthpiece at the proximal or downstream end thereof.

The upstream and downstream ends of the first compartment 6 and the second compartment 8 of the aerosol-generating article 2 are sealed by frangible barriers (not shown).

The aerosol-generating device 4 comprises a housing 12 comprising an elongate cylindrical cavity in which the aerosol-generating article 2 is received, a heat exchanger 14, a first solid-liquid phase-change material 16 and a second solid-liquid phase-change material 18.

The aerosol-generating device 4 further comprises a piercing member 20 positioned centrally within the cavity of the aerosol-generating device 4 and extending along the major axis of the cavity.

As shown in Figure 1, the length of the cavity is less than the length of the aerosol-generating article 2 so that the proximal or downstream end of the aerosol-generating article 2 protrudes from the cavity.

In the aerosol-generating system according to the first embodiment of the invention the first solid-liquid phase-change material 16 is positioned about the perimeter of the cavity and extends partially along the length of the cavity and fully around the circumference of the cavity. The second solid-liquid phase-change material 18 is positioned upstream of the first solid-liquid phase-change material 16 at the distal or upstream end of the cavity.

The heat exchanger 14 comprises a matrix of thermally conductive fins located at the distal or upstream end of the aerosol-generating device 4 and a hollow thermally conductive tube in thermal contact with the matrix of thermally conductive fins. As shown in Figure 1, the hollow thermally conductive tube surrounds the first solid-liquid phase-change material 16 and the second solid-liquid phase-change material 18.

In use, as the aerosol-generating article 2 is inserted into the cavity of the aerosol-generating device 4 the piercing member 20 of the aerosol-generating device 4 is inserted into the aerosol-generating article 2 and pierces the frangible barriers (not shown) at the upstream and downstream ends of the first compartment 6 and second compartment 8 of the aerosol-generating article 2. This allows a user to draw air into the housing of the aerosol-generating article 2 through the distal or upstream end thereof, downstream through the first compartment 6, the second compartment 8 and the third compartment 10 and out of the housing through the proximal or downstream end thereof.

Once the aerosol-generating article 2 is inserted into the cavity of the aerosol-generating device 4, the matrix of thermally conductive fins of the heat exchanger 14 are heated using a blue flame or torch lighter. Thermal energy is transferred from the matrix of thermally conductive fins to the first solid-liquid phase-change material 16 via the hollow conductive tube of the heat exchanger 14. The thermal energy is absorbed by the first solid-liquid phase-change material 16 causing the temperature of the first solid-liquid phase-change material 16 to increase. When the temperature reaches the melting temperature of the first solid-liquid phase-

change material 16, the first solid-liquid phase-change material 16 stores thermal energy as it changes phase from a solid to a liquid.

Once liquid, the temperature of the first solid-liquid phase-change material 16 will continue to increase upon further heating of the matrix of thermally conductive fins of the heat exchanger 14 by the blue flame or torch lighter. However, when the temperature of the first solid-liquid phase-change material 16 reaches the melting temperature of the second solid-liquid phase-change material 18, the second solid-liquid phase-change material 18 stores thermal energy as it changes phase from a solid to a liquid. This buffers the amount of thermal energy transferred to the first solid-liquid phase-change material 16 and so prevents overheating of the first solid-liquid phase-change material 16.

Heating of the matrix of thermally conductive fins of the heat exchanger 14 by the blue flame or torch lighter is discontinued before the second solid-liquid phase-change material 18 completes the phase change from a solid to a liquid. Once heating of the matrix of thermally conductive fins of the heat exchanger 14 by the blue flame or torch lighter is discontinued, the temperature of the first solid-liquid phase-change material 16 decreases. Upon reaching its melting temperature, the first solid-liquid phase-change material 16 releases the stored thermal energy as it changes phase from a solid to a liquid. The stored thermal energy released by the first solid-liquid phase-change material 16 as it solidifies heats the first compartment 6 and the second compartment 8 of the aerosol-generating article 2 received in the cavity of the aerosol-generating device 4 over an extended time period.

As the user draws air through the aerosol-generating article 2, volatile delivery enhancing compound vapour is released from the volatile delivery enhancing compound source in the first compartment 6 into the air stream drawn through the aerosol-generating article 2 and nicotine vapour is released from the nicotine source in the second compartment 8 into the air stream drawn through the aerosol-generating article 2. The volatile delivery enhancing compound vapour reacts with the nicotine vapour in the gas phase in the second compartment 8 and the third compartment 10 to form an aerosol, which is delivered to the user through the proximal or downstream end of the aerosol-generating article 2.

The heat exchanger 14 of an aerosol-generating device 4 according to the first embodiment of the invention shown in Figure 1 in which the first solid-liquid phase-change material 16 is sodium acetate trihydrate and the second solid-liquid phase-change material 18 is hexatriacontane is heated for 10 seconds using a blue flame or torch lighter as described above. The temperature of the aerosol-generating device 4 is measured as a function of time using a thermocouple positioned between the aerosol-generating device 4 and an aerosol-generating article 2 received in the cavity of the aerosol-generating device 4 at a position half way along the length of the first compartment 6 of the aerosol-generating article 2. The measurement is repeated six times. The results are shown in Figure 2.

As shown in Figure 2, the temperature profiles obtained for the six measurements are extremely similar. This demonstrates the reproducibility of the temperature profile of the aerosol-generating device according to the invention in use.

In each case, upon heating of the heat exchanger 14 by the blue flame or torch lighter the temperature of the aerosol-generating device 4 increases from room temperature to approximately 70 degrees Celsius in about 8 seconds. During this time, the sodium acetate trihydrate (the first solid-liquid phase-change material 16) changes phase from a solid to a liquid, at a temperature of approximately 57 degrees Celsius. Once heating of the heat exchanger 14 by the blue flame or torch lighter is discontinued, the temperature of the sodium acetate trihydrate starts to decrease. After approximately 150 seconds, the decrease in temperature of the sodium acetate trihydrate is sufficient for the sodium acetate trihydrate to change phase from a liquid to a solid. As the sodium acetate trihydrate changes phase from a liquid to a solid it releases thermal energy over a period of approximately 100 seconds to 150 seconds. The temperature of the aerosol-generating device therefore remains above 40 degrees Celsius for a total of more than 300 seconds.

The heat exchanger 14 of an aerosol-generating device 4 according to the first embodiment of the invention shown in Figure 1 in which the first solid-liquid phase-change material 16 is sodium acetate trihydrate and the second solid-liquid phase-change material 18 is hexatriacontane is heated for 8 seconds using a blue flame or torch lighter as described above. The temperature of the aerosol-generating device 4 is measured as a function of time using a thermocouple positioned between the aerosol-generating device 4 and an aerosol-generating article 2 received in the cavity of the aerosol-generating device 4 at positions at the (i) upstream end of the first compartment 6 of the aerosol-generating article 2, (ii) downstream end of the first compartment 6 of the aerosol-generating article 2 and (iii) downstream end of the second compartment 8 of the aerosol-generating article 2. For comparison, the heat exchanger 14 of an aerosol-generating device 4 according to a second embodiment of the invention of identical construction but in which the hexatriacontane (second solid-liquid phase-change material 18) is omitted is heated for 8 seconds using a blue flame or torch lighter as described above and the temperature of the aerosol-generating device 4 is measured as a function of time using a thermocouple positioned between the aerosol-generating device 4 and an aerosol-generating article 2 received in the cavity of the aerosol-generating device 4 at positions at the (i) upstream end of the first compartment 6 of the aerosol-generating article 2, (ii) downstream end of the first compartment 6 of the aerosol-generating article 2 and (iii) downstream end of the second compartment 8 of the aerosol-generating article 2. The results are shown in Figure 3.

As shown in Figure 3, the maximum temperature of the aerosol-generating device 4 according to the first embodiment of the invention at the (i) upstream end of the first compartment 6 of the aerosol-generating article 2, (ii) downstream end of the first compartment

6 of the aerosol-generating article 2 and (iii) downstream end of the second compartment 8 of the aerosol-generating article 2 is reduced compared to the aerosol-generating device 4 according to the second embodiment of the invention. In particular, the inclusion of hexatriacontane (second solid-liquid phase-change material 18) in the aerosol-generating device 4 according to the first embodiment of the invention, reduces the maximum temperature of the aerosol-generating device 4 according to the first embodiment of the invention at the (i) upstream end of the sodium acetate trihydrate (first solid-liquid phase change material 16) to below the decomposition temperature of sodium acetate trihydrate.

The invention has been exemplified above by reference to an aerosol-generating system comprising an aerosol-generating article comprising a first compartment and a second compartment arranged in series within the aerosol-generating article. However, it will be appreciated that aerosol-generating systems according to the invention may comprise aerosol-generating articles comprising a first compartment and a second compartment arranged in parallel within the aerosol-generating article.

The invention has also been exemplified above by reference to an aerosol-generating device comprising a heat exchanger configured to heat the first solid-liquid phase-change material to a temperature above the melting point of the first solid-liquid phase-change material. However, it will be appreciated that aerosol-generating devices according to the invention may comprise other types of heating means. In particular, it will be appreciated that aerosol-generating devices according to the invention may comprise an electric heater comprising one or more electrically resistive heating elements configured to heat the first solid-liquid phase-change material to a temperature above the melting point of the first solid-liquid phase-change material.

**CLAIMS:**

1. An aerosol-generating device for use in an aerosol-generating system, the aerosol-generating device comprising:

a cavity configured to receive an aerosol-generating article;

a first solid-liquid phase-change material positioned about a perimeter of the cavity;

heating means configured to heat the first solid-liquid phase-change material to a temperature above the melting point of the first solid-liquid phase-change material; and

a second solid-liquid phase-change material,

wherein the melting point of the second solid-liquid phase-change material is higher than the melting point of the first solid-liquid phase-change material.

2. An aerosol-generating device according to claim 1, wherein the first solid-liquid phase-change material has a melting point of between 30 degrees Celsius and 70 degrees Celsius.

3. An aerosol-generating device according to claim 1 or 2, wherein the first solid-liquid phase-change material is sodium acetate trihydrate.

4. An aerosol-generating device according to claim 1, 2 or 3, wherein the melting point of the second solid-liquid phase-change material is between 15 degrees Celsius and 25 degrees Celsius higher than the melting point of the first solid-liquid phase-change material.

5. An aerosol-generating device according to any one of claims 1 to 4, wherein the second solid-liquid phase-change material has a melting point of between 70 degrees Celsius and 90 degrees Celsius.

6. An aerosol-generating device according to any one of claims 1 to 5, wherein the second solid-liquid phase-change material is hexatriacontane.

7. An aerosol-generating device according to any one of claims 1 to 6, wherein the heating means comprises a heat exchanger.

8. An aerosol-generating device according to any one of claims 1 to 6, wherein the heating means comprises an electric heater.

9. An aerosol-generating system comprising an aerosol-generating device according to any one of claims 1 to 8 and an aerosol-generating article.

10. An aerosol-generating system comprising an aerosol-generating device according to any one of claims 1 to 8 and an aerosol-generating article, wherein the aerosol-generating article comprises:

a first compartment comprising a volatile delivery enhancing compound source; and

a second compartment comprising a nicotine source.

11. An aerosol-generating system according to claim 10, wherein the volatile delivery enhancing compound comprises an acid.

12. An aerosol-generating system according to claim 11, wherein the acid is selected from the group consisting of 3-methyl-2-oxovaleric acid, pyruvic acid, 2-oxovaleric acid, 4-methyl-2-oxovaleric acid, 3-methyl-2-oxobutanoic acid, 2-oxooctanoic acid and combinations thereof.

13. An aerosol-generating system according to claim 12, wherein the acid is pyruvic acid.

14. An aerosol-generating system according to any one of claims 10 to 13, wherein one or both of the first compartment and the second compartment of the aerosol-generating article is sealed by one or more frangible seals.

15. An aerosol-generating system according to any one of claims 10 to 14, wherein the aerosol-generating device further comprises:

a piercing member positioned within the cavity for piercing the first compartment and the second compartment of the aerosol-generating article.

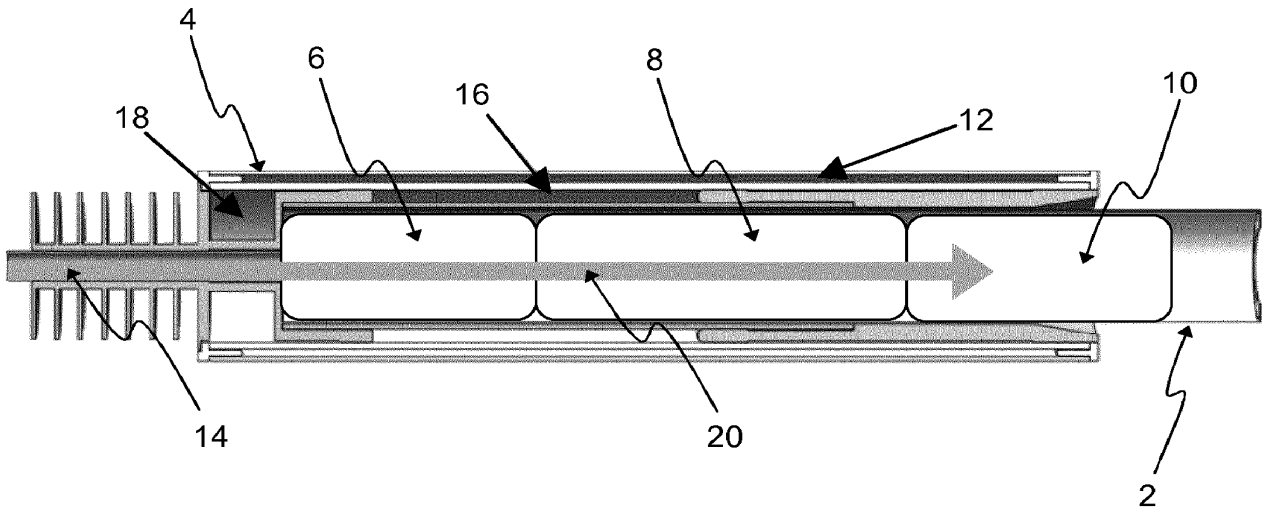



Figure 1

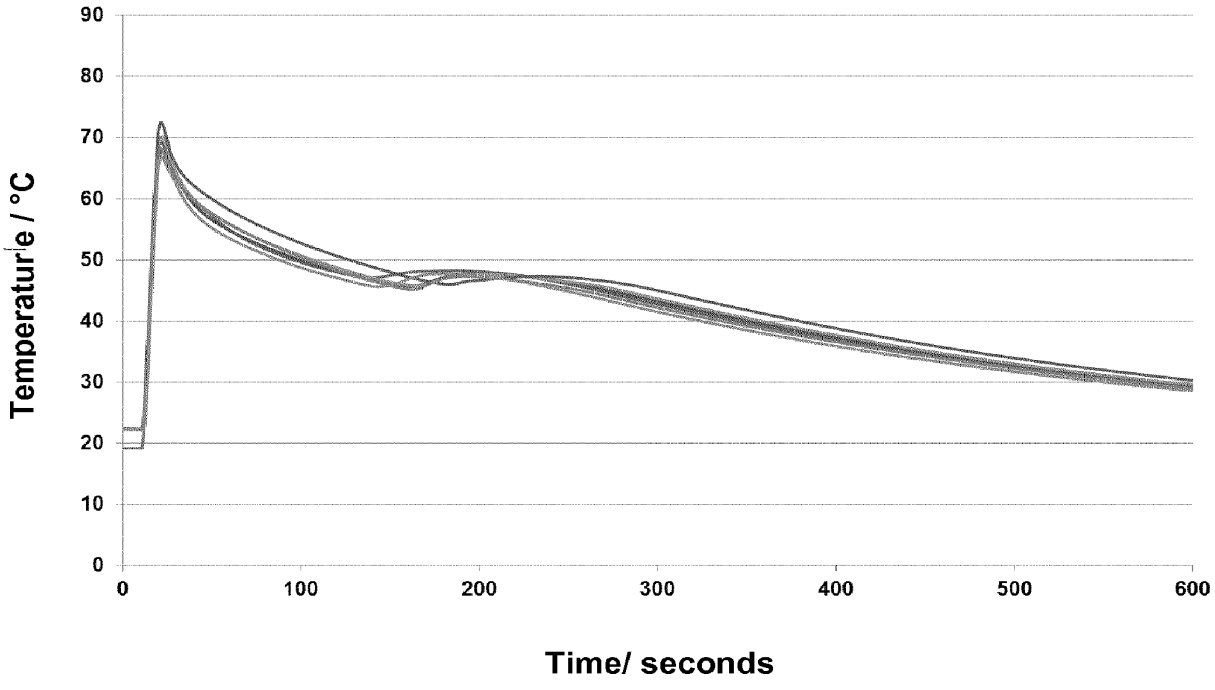



Figure 2

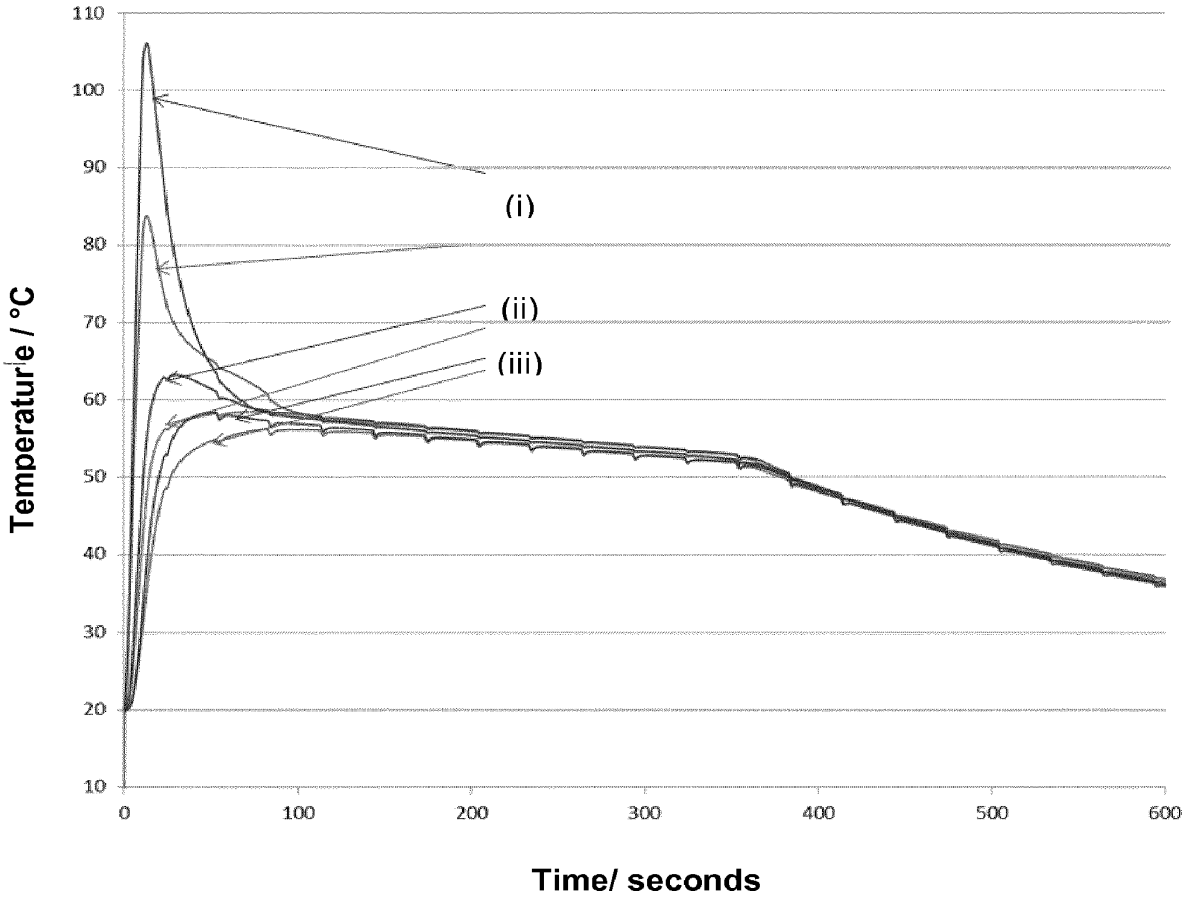

110
100
90
80
70
60
50
40
30
20
10
0
100
200
300
400
500
600
(i)
(ii)
(iii)
Temperature / °C
Time/ seconds

**Figure 3**

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/077890

A. CLASSIFICATION OF SUBJECT MATTER
INV. A24F47/00
ADD.

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)
A24F

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 April 2014 | 23/04/2014 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Kock, Søren |

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International application No
PCT/EP2013/077890

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(74) Agent: **REDDIE & GROSE LLP**; 16 Theobalds Road, London WC1X 8PL (GB).

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(54) **Title**: AEROSOL-GENERATING SYSTEM HAVING A PIERCING ELEMENT

Figure 1(a)

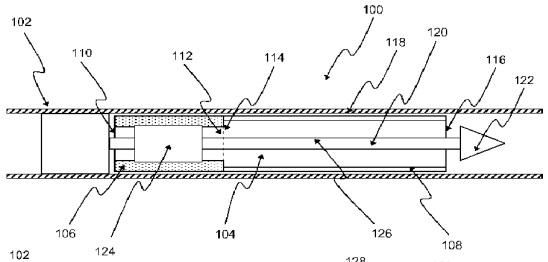
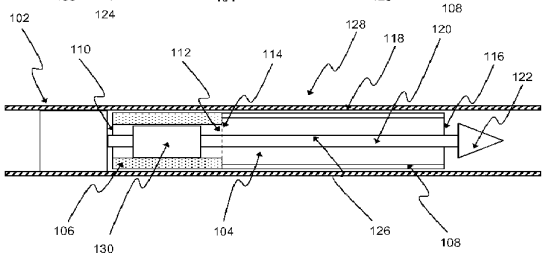



Figure 1(b)




(57) **Abstract**: The present invention relates to an aerosol-generating system (100) comprising: an aerosol-generating device (102) in cooperation with an aerosol-generating article (104). The article (104) comprising: a first sealed compartment (106) comprising a tubular porous element and a delivery enhancing compound sorbed on the tubular porous element; and a second compartment (108) comprising a volatile liquid. The device comprising: an outer housing (1 18) adapted to receive the article (104); an elongate piercing member (120) for piercing the first compartment (106) and the second compartment (108) of the article (104). The elongate piercing member (120) comprises: a piercing portion (122) adjacent a distal end of the elongate piercing member; and a shaft portion (126); and an obstructing portion (124) adjacent a proximal end of the elongate piercing member. The piercing portion (122) has a maximum diameter greater than the diameter of the shaft portion (126), and the obstructing portion (124) has an outer diameter such that it fits within the tubular porous element of the article (104) when the article (104) is received in the device (102). The invention also relates to a corresponding aerosol-generating device (102) and aerosol-generating article (104).

WO 2014/140087 A1

# AEROSOL-GENERATING SYSTEM HAVING A PIERCING ELEMENT

The present invention relates to an aerosol-generating system for delivering an aerosol to a user comprising an aerosol-generating device and an aerosol-generating article, and in particular to a smoking device for delivering aerosolised nicotine salt particles to a user. The invention further relates to an aerosol-generating device for receiving an aerosol-generating article.

WO 2008/121610 A1 discloses devices and methods for delivering nicotine to a subject in which a delivery enhancing compound is reacted with nicotine in the gas phase to form an aerosol of nicotine salt particles. In order to retain the delivery enhancing compound, a sorption element on which the delivery enhancing compound is sorbed can be provided. The volatile delivery enhancing compound can be stored without degradation by oxidation, hydrolysis or other unwanted reactions by sealing the compartment in which the delivery enhancing compound is located.

However, to obtain a more complete reaction of the nicotine with the delivery enhancing compound aerosol, the mixing of the reactants in the gas phase needs to be addressed.

Thus, it would be desirable to provide such an aerosol-generating system which enables sufficient mixing of the volatile delivery enhancing compound and the nicotine or other medicament during use of the aerosol-generating system.

It would be also desirable to provide an aerosol-generating system for delivering nicotine or other medicament to a user of the type disclosed in WO 2008/121610 A1 in which the retention of one or both of the volatile delivery enhancing compound and the nicotine or other medicament during storage is improved. It would also be desirable to provide an aerosol-generating system for delivering nicotine or other medicament to a user of the type disclosed in WO 2008/121610 A1 in which the stability of one or both of the volatile delivery enhancing compound and the nicotine or other medicament during storage is maintained.

According to a first aspect of the present invention, there is provided an aerosol-generating system comprising an aerosol-generating device in cooperation with an aerosol-generating article. The aerosol-generating article comprises a sealed first compartment comprising a tubular porous element and a delivery enhancing compound sorbed on the tubular porous element; and a second compartment comprising a volatile liquid. The aerosol-generating device comprises: an outer housing adapted to receive the aerosol-generating article; and an elongate piercing member for piercing the first compartment and the second compartment of the aerosol-generating article. The elongate piercing member comprises: a piercing portion adjacent a distal end of the elongate piercing member; a shaft portion; and an

obstructing portion adjacent a proximal end of the elongate piercing member. The piercing portion has a maximum diameter greater than the diameter of the shaft portion, and the obstructing portion has an outer diameter such that it fits within the tubular porous element of the article when the aerosol-generating article is received in the device.

This may improve the mixing of the delivery enhancing compound and the volatile liquid by controlling the air flow through the aerosl-generating system.

As used herein, the term "aerosol-generating device" refers to an aerosol-generating device that interacts with an aerosol-generating article to generate an aerosol that is directly inhalable into a user's lungs thorough the user's mouth.

As used herein, by "sorbed" it is meant that the delivery enhancing compound is adsorbed on the surface of the tubular porous element, or absorbed in the tubular porous element, or both adsorbed on and absorbed in the tubular porous element.

The aerosol-generating system may further comprise at least one air inlet upstream of the first compartment of the aerosol-generating article and at least one air outlet downstream of the second compartment of the aerosol-generating article, the at least one air inlet and the at least one air outlet being arranged when the aerosol-generating article is received in the aerosol-generating device to define an air flow pathway extending from the at least one air inlet to the at least one air outlet via the tubular porous element of the first compartment of the aerosol-generating article around the obstructing portion of the elongate piercing member of the aerosol-generating device, and via the second compartment of the aerosol-generating article around the shaft portion of the elongate piercing member of the aerosol-generating device. The second compartment may be downstream of the first compartment so that in use an air stream drawn through the aerosol-generating article passes through the first compartment and then passes through the second compartment.

In an alternative embodiment, the second compartment preferably comprises a tubular porous element, and the second compartment may be upstream of the first compartment so that in use an air stream drawn through the aerosol-generating article passes through the second compartment and then passes through the first compartment. In this alternative embodiment, the second compartment comprises a tubular porous element having the volatile liquid sorbed on the tubular porous element. The obstructing portion fits within the tubular porous element of the second compartment.

In this alternative embodiment, the aerosol-generating system may further comprise at least one air inlet upstream of the second compartment of the aerosol-generating article and at least one air outlet downstream of the first compartment of the aerosol-generating article, the at least one air inlet and the at least one air outlet being arranged when the aerosol-generating

article is received in the aerosol-generating device to define an air flow pathway extending from the at least one air inlet to the at least one air outlet via the tubular porous element of the second compartment of the aerosol-generating article around the obstructing portion of the elongate piercing member of the aerosol-generating device, and via the first compartment of the aerosol-generating article around the shaft portion of the elongate piercing member of the aerosol-generating device.

As used herein, the terms 'upstream', 'downstream' and 'distal' and 'proximal' are used to describe the relative positions of components, or portions of components, of aerosol-generating articles, aerosol-generating devices and aerosol-generating systems according to the invention in relation to the direction of air drawn through the aerosol-generating articles, aerosol-generating devices and aerosol-generating systems during use thereof. It will be understood that the terms 'distal' and 'proximal', when used to describe the relative positions of components of the elongate piercing member, are used such that the piercing portion is at the distal, 'free', end and the obstructing portion is at the proximal, 'fixed', end which is connected to the device.

As used herein, the term "longitudinal" is used to describe the direction between the downstream or proximal end and the opposed upstream or distal end of the aerosol-generating article or aerosol-generating device and the term "transverse" is used to describe the direction perpendicular to the longitudinal direction.

The upstream and downstream ends of the aerosol-generating article are defined with respect to the airflow when a user draws on the proximal or mouth end of the aerosol-generating article. Air is drawn into the aerosol-generating article at the distal or upstream end, passes downstream through the aerosol-generating articles and exits the aerosol-generating article at the proximal or downstream end.

As used herein, the term "air inlet" is used to describe one or more apertures through which air may be drawn into the aerosol-generating system.

As used herein, the term "air outlet" is used to describe one or more aperture through which air may be drawn out of the aerosol-generating system.

In such embodiments, the first compartment and the second compartment are arranged in series from air inlet to air outlet within the aerosol-generating system. That is, the first compartment is downstream of the air inlet, the second compartment is downstream of the first compartment and the air outlet is downstream of the second compartment. In use, a stream of air is drawn into the aerosol-generating system through the air inlet, downstream through the first compartment and the second compartment and out of the aerosol-generating system through the air outlet.

In an alternative embodiment, the second compartment and the first compartment are arranged in series from air inlet to air outlet within the aerosol-generating system. That is, the second compartment is downstream of the air inlet, the first compartment is downstream of the second compartment and the air outlet is downstream of the first compartment. In use, a stream of air is drawn into the aerosol-generating system through the air inlet, downstream through the second compartment and the first compartment and out of the aerosol-generating system through the air outlet.

As used herein, by "series" it is meant that the first compartment and the second compartment are arranged within the aerosol-generating article so that in use an air stream drawn through the aerosol-generating article passes through one of the first compartment and the second compartment and then passes through the other of the first compartment and the second compartment. Delivery enhancing compound vapour is released from the delivery enhancing compound in the first compartment into the air stream drawn through the aerosol-generating article and volatile liquid vapour is released from the second compartment into the air stream drawn through the aerosol-generating article. The delivery enhancing compound vapour reacts with the volatile liquid vapour in the gas phase to form an aerosol, which is delivered to a user.

The piercing member is preferably positioned within the outer housing along the central longitudinal axis of the aerosol-generating device.

The obstructing portion preferably has a diameter relative to the internal diameter of the tubular porous element such that the bulk air flow through the aerosol-generating system flows through the tubular porous element. In this way, the delivery enhancing compound may be entrained in the air more effectively. To effect this air flow, where the obstructing portion has a diameter less than the internal diameter of the tubular porous element, the resistance to draw of the channel bounded by the obstructing portion and the inner surface of the tubular porous element is greater than the resistance to draw of the tubular porous element. The diameter of the obstructing portion may be between about 90% and about 100% of the internal diameter of the tubular porous element.

In a preferred embodiment, the obstructing portion has a diameter such that it forms an interference fit within the tubular porous element. As used herein, the term 'interference fit' is used to refer to a fit which substantially prevents air flow between the components having an 'interference fit'. The diameter of the obstructing portion may be between about 100% and about 150% of the internal diameter of the tubular porous element, preferably between about 110% and about 140%. In a preferred embodiment, the diameter of the obstructing portion is about 133% of the internal diameter of the tubular porous element.

The internal diameter of the tubular porous element is preferably between about 2 mm and about 5 mm, more preferably between about 2.5 mm and about 3.5 mm. In a preferred embodiment, the internal diameter of the tubular porous element is about 3 mm.

The diameter of the obstructing portion is preferably between about 1.5 mm and about 7.5 mm, more preferably between about 3 mm and about 5 mm. In a preferred embodiment, the diameter of the obstructing portion is about 4 mm.

The maximum diameter of the piercing portion is preferably equal to or less than the diameter of the obstructing portion. More preferably, the maximum diameter of the piercing portion is between about 75% and about 100% of the diameter of the obstructing portion, and yet more preferably is between about 90% and about 100% of the obstructing portion.

The maximum diameter of the piercing portion is preferably between about 105% and about 125% of the diameter of the shaft portion. More preferably, the maximum diameter of the piercing portion is between about 110% and about 120% of the diameter of the shaft portion. In a preferred embodiment, the maximum diameter of the piercing portion is about 120% of the diameter of the shaft portion.

The obstructing portion preferably has a longitudinal length of between about 25% and about 75% of the longitudinal length of the tubular porous element. More preferably the obstructing portion has a longitudinal length of between about 40% and about 60% of the longitudinal length of the tubular porous element, and in one embodiment the obstructing portion has a longitudinal length of about 50% of the longitudinal length of the tubular porous element.

The obstructing portion is preferably arranged to be positioned centrally, along the longitudinal axis of the device, within the tubular porous element when the aerosol-generating article is received inserted in the device.

The tubular porous element preferably has a longitudinal length of between about 7.5 mm and about 15 mm, more preferably of between about 9 mm and about 11 mm, and in the preferred embodiment the tubular porous element has a longitudinal length of about 10 mm.

The obstructing portion preferably has a longitudinal length of between about 1.5 mm and about 9.5 mm, more preferably between about 3 mm and about 7 mm, and in the preferred embodiment the obstructing portion has a longitudinal length of about 5 mm.

In a preferred embodiment the tubular porous element is a hollow cylinder. The hollow cylinder is preferably a right circular hollow cylinder.

The piercing portion preferably has a maximum diameter of between about 75% and about 100% of the internal diameter of the hollow cylinder.

In a preferred embodiment the piercing portion is conical. However, it should be understood that the piercing portion may be of any shape suitable for piercing the compartments of the aerosol-generating article. Where the piercing portion is conical, the maximum diameter of the piercing portion corresponds to the diameter of the base circle of the cone.

The maximum diameter of the piercing portion is preferably between about 1.5 mm and about 5 mm, more preferably between about 1.75 mm and about 3.5 mm. In a preferred embodiment, the piercing portion has a maximum diameter of about 3 mm.

The second compartment is preferably a hollow cylinder, and the piercing portion preferably has a maximum diameter of between about 50% and about 75% of the internal diameter of the second compartment.

The second compartment preferably has an internal diameter of between about 4 mm and about 8 mm, more preferably between about 5 mm and about 7 mm. In a preferred embodiment the second compartment has an internal diameter of about 6.5 mm.

The second compartment preferably has a longitudinal length of between about 20 mm and about 50 mm, more preferably between about 30 mm and about 40 mm. In a preferred embodiment the second compartment has a longitudinal length of about 35 mm.

The longitudinal length of the elongate piercing member is preferably greater than the total longitudinal length of the first compartment and the second compartment. Providing a piercing member having such a length enables the first compartment and the second compartment of the aerosol-generating article to be pierced using only the elongate piercing member.

The shaft of the piercing member preferably has a diameter of between about 1 mm and about 3 mm, more preferably between about 1.5 mm and about 2.5 mm. In a preferred embodiment the shaft has a diameter of about 2 mm. The shaft of the piercing member is provided with a smaller diameter than the maximum diameter of the piercing portion so that, in use, air can flow around the shaft and through the holes formed in the first and second compartments by the piercing portion.

The second compartment is preferably sealed.

Preferably a first end of the first compartment is sealed by a frangible barrier, an interface between a second end of the first compartment and a first end of the second compartment is sealed by at least one frangible barrier, and a second end of the second compartment is sealed by a frangible barrier. In a preferred embodiment, each end of the first compartment and each end of the second compartment is sealed by a frangible barrier.

Preferably, each of the first compartment and the second compartment comprises a frangible barrier at each end. The frangible barrier is configured such that the barrier can be

pierced by the piercing member when the aerosol-generating article is inserted into the aerosol-generating device by the user.

Preferably, each frangible barrier is made from metal film, and more preferably from aluminium film.

Preferably, the first compartment and the second compartment of the aerosol-generating article abut one another. Alternatively, the first compartment and the second compartment may be spaced apart.

The volume of the first compartment and the second compartment may be the same or different. In a preferred embodiment, the volume of the second compartment is greater than the volume of the first compartment.

The aerosol-generating article preferably further comprises at least one further element. The aerosol-generating article may further comprise one, two, three, four, five or more further elements. The further element may be any of: a filter element; a third compartment; an aerosol forming chamber; and a hollow tube. In a preferred embodiment the further element comprises a mouthpiece. The mouthpiece may be sealed at the proximal end of the aerosol-generating article.

The mouthpiece may comprise any suitable material or combination of materials. Examples of suitable materials include thermoplastics that are suitable for food or pharmaceutical applications, for example polypropylene, polyetheretherketone (PEEK) and polyethylene.

In a preferred embodiment the outer housing of the aerosol-generating device comprises a cavity configured to receive the aerosol-generating article. Preferably, the cavity has a longitudinal length greater than the longitudinal length of the elongate piercing member. In this way, the piercing portion of the piercing member is not exposed, or accessible by the user.

Preferably, the cavity of the aerosol-generating device is substantially cylindrical. The cavity of the aerosol-generating device may have a transverse cross-section of any suitable shape. For example, the cavity may be of substantially circular, elliptical, triangular, square, rhomboidal, trapezoidal, pentagonal, hexagonal or octagonal transverse cross-section.

Preferably, the cavity of the aerosol-generating device has a transverse cross-section of substantially the same shape as the transverse cross-section of the aerosol-generating article to be received in the cavity.

The aerosol-generating system may further comprise a power supply, at least one heater, and control circuitry. The control circuitry is preferably configured to control the supply of power to the at least one heater such that the delivery enhancing compound and the volatile liquid are sufficiently volatilised to enable the generation of an aerosol.

The overall dimensions of the aerosol-generating system may be similar to a conventional smoking article such as a cigarette, a cigar a cigarillo or any other such smoking article.

In use, the user inserts the aerosol-generating article into the outer housing of the aerosol-generating device. As the user inserts the aerosol-generating article, the piercing member pierces a first end of the first compartment, passes through the hollow central portion of the tubular porous element, and then pierces a second end of the first compartment. The piercing member then pierces a first end of the second compartment (where included), passes through the second compartment and then pierces a second end of the second compartment (where included), and the obstructing portion fits within the tubular porous element so as to define the air flow pathway described herein. The user then draws on the proximal end of the aerosol-generating article causing air to flow along the air flow pathway, entraining delivery enhancing compound vapour from the delivery enhancing compound sorbed on the porous tubular element of the first compartment and volatile liquid vapour from the volatile liquid in the second compartment. An aerosol is generated by the delivery enhancing compound vapour reacting with the volatile liquid vapour in the gas phase. The generation of the aerosol is described in further detail below.

In the alternative embodiment, where the second compartment comprises a tubular porous element, and the second compartment is upstream of the first compartment, the aerosol-generating system functions as follows. In use, the user inserts the aerosol-generating article into the outer housing of the aerosol-generating device. As the user inserts the aerosol-generating article, the piercing member pierces a first end of the second compartment, passes through the tubular porous element, and then pierces a second end of the second compartment. The piercing member then pierces a s first end of the first compartment, passes through the first compartment and then pierces a second end of the first compartment. The obstructing portion fits within the tubular porous element of the second compartment so as to define the air flow pathway described herein with reference to the alternative embodiment. The user then draws on the proximal end of the aerosol-generating article causing air to flow along the air flow pathway, entraining volatile liquid vapour from the volatile liquid on the tubular porous element in the second compartment, and entraining delivery enhancing compound vapour from the delivery enhancing compound sorbed on the porous tbular element of the first compartment. An aerosol is generated by the delivery enhancing compound vapour reacting with the volatile liquid vapour in the gas phase.

According to a further aspect of the present invention, there is provided an aerosol-generating device for an aerosol-generating system as described herein. The aerosol-generating device comprises: an outer housing adapted to receive an aerosol-generating article,