11	Non Patent Literature	Stevens_1995_Use_of_Glucagon_to_Treat_Neonatal.pdf	2095868 594ca9f894ea68517f510f4f9db35ff1df2505be	no	3
Warnings:					
Information:					
12	Non Patent Literature	Swabrick_2002_Encyclopedia_of_Pharmaceutical_Technology_.pdf	281910 550bdc1b2868a61207bd6589fbfd7ca5d09ba76e	no	2
Warnings:					
Information:					
13	Non Patent Literature	Tsuchido_1987_Lysis_of_Bacillus_subtilis_Cells_by_Glycerol.pdf	3166784 a357d422b05fce16bfaf80f6b166989ea2d1d39f	no	4
Warnings:					
Information:					
14	Non Patent Literature	Turker_2004_Nasal_route_and_drug_.pdf	875630 1be06a1417a09125decec785bd82ae5abbbd052c	no	6
Warnings:					
Information:					
15	Non Patent Literature	Turton_1996_A_role_for_glucagon_like_.pdf	1073961 8deb1d2bc5e294c8f7d5196507319b18c3a35564	no	4
Warnings:					
Information:					
16	Non Patent Literature	US13495942_OA_1Oct2013.pdf	546105 dede09f83a1dd271f69e618ed8f26b9d798323ad	no	10
Warnings:					
Information:					
17	Non Patent Literature	Vidal_2005_Making_sense_of_antisense_.pdf	1315281 0b941198eca4158c56abcece7b1943c46cebb8e4	no	7
Warnings:					
Information:					
18	Non Patent Literature	Watanabe_2000_Antibacterial_Carbohydrate_Monoesters.pdf	2614493 1dafe1b4450d02d4b7e581a012e6e526591c1174	no	4
Warnings:					
Information:					
19	Non Patent Literature	Weber_1984_Metabolism_of_orally_.pdf	1325054 891474d8dd14f3351acd4b067c3dc9ebb9e1f408	no	8
Warnings:					
Information:					

20	Non Patent Literature	Webpage_for_Anatrace_products_of_Affymetrix_.pdf	251292 65cc6b535506c2b217edf91061df4ced74e1bda2	no	2
Warnings:					
Information:					
21	Non Patent Literature	Yamamoto_1989_The_Ocular_Route_for_Systemic_Insulin_Delivery.pdf	5620625 8c5158d55c3044989bf2f400bf69e873904644de	no	7
Warnings:					
Information:					
22	Non Patent Literature	Yu_Xinrui_2001_Triptan_Medicament_and_.pdf	973047 2b529955d48494acc7547d8790ec7f368be29953	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	40253876	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/413,439	03/27/2009	Steve Cartt	35401-716.201	9049

21971 7590 06/19/2014

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/19/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 12/413,439	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/21/2012*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *20-24,27-36,38 and 40-53* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *20-24,27-36,38 and 40-53* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *1pg(11/16/2012), 3pgs(4/15/2013), 9pgs(10/29/2013)*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/21/2012 has been entered.

Applicants' arguments, filed 5/21/2012, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 20-24, 27-36, 38 and 40-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehat (Intranasal midazolam for childhood seizures, The Lancet, vol.352, August 22, 1998 – See IDS dated 10/29/2013) in view of Sonne (U.S. 6,193,985- See IDS dated 9/16/2009) and Meezan (U.S. 2006/0046962).

Lehat teaches diazepam is widely used to treat acute seizures in adults and children and that intranasal administration of benzodiazepine compounds has been demonstrated as an effective way to manage acute childhood seizures (Abstract).

Lehat does not teach suitable excipients for the formulation.

Sonne teaches tocopherol compositions for the delivery of biologically active agents which are only sparingly soluble in water (col. 1, lines 7-13), such as diazepam (col. 1, lines 7-14). One particular nasal formulation contains 5g of diazepam, 44 g Tenox GT2 (70% tocopherol), 5 g Vitamin E TPGS, 1.45 g Pluronic and 0.1g benzalkonium chloride (example 1 at col. 7, lines 32-45). In preparing the formulation, the ingredients are heated slowly until a homogeneous phase is achieved (Sonne also teaches that co-solvent such as ethanol, benzyl alcohol, sesame oil or propylene glycol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity

(col. 6, lines 47-53). When ethanol is used in the formulations, it may be used in an amount of about 11% by weight of the formulation (See example 3 at col.8, lines 28-43). When sesame oil is used, it may be used in an amount of about 44% (example18, col12, lines 37-51) or about 60% (example 16 at col.12, lines 10-17). α-tocopherol may be used in amounts of 20 to 99.9% (col.5, lines 56-61). The active ingredient should be present in an amount of 0.001% to 40% (col.5, lines 55-61). Diazepam may be present at about 5% by weight (example 11 at col. 11, lines 1-13). Preservative as well as odor masking compounds may be included in the (col.7, lines 4-12). The composition may be in the form of a spray formulation (col. 6, lines 28-35). In general, administration to the nose can be difficult because of the limited volume which is acceptable for the nose, which is about 100µL (col.7, lines 25-30). Sonne teaches that the “compositions of the invention may be used directly as a solution of bioactive agents in the tocopherol solvent” (col.3, lines 60-61) and that the "[v]iscosity can be reduced by the addition of co-solvents such as ethanol (col.3, lines 65-66). Sonne teaches that “transmucosal delivery is preferred" (col.3, line 54) and "[n]asal...administrations are particularly preferred" (col.3, lines 58-59). The compositions of the invention may contain from 1-99.99% tocopherol (col.5, lines 55-57). Sonne also teaches that a co-solvent such as ethanol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, ethanol may be present in an amount of about 11% by weight of the formulation (See e.g. example 3 at col.8, lines 28-43). Thus, one of ordinary skill in the art would have found it obvious to

nasally administer a composition that contains only tocopherol or tocotrienol, an alcohol and optionally one or more alkyl glycosides.

Sonne does not teach the addition of a alkyl glycoside in an amount from 0.01% to 1%.

Meezan teaches that alkyl glycosidase is an absorption enhancer for drug administration (¶150). Specifically, Meezan demonstrates that the addition of 0.25% of alkyl glycoside can increase drug absorption from about 3% bioavailabilty to about 90% bioavailability when the drug is administered via a nasal spray. Meezan further teaches that the active ingredient for the nasal spray may be in the form of nanoparticles (¶63).

Meezan does not teach using a benzodiazapine active ingredient.

It would have been obvious to one of ordinary skill in the art treating seizures by oral administration of benzodiazepines as taught by Lehat to administer the drug in a benzodiazepine nasal formulation such as that taught by Sonne. In doing so, it would have been obvious adminsiter the formulation as nanoparticles comprising alkyl glycoside in order to increase absorption, and thus the bioavailability, of the active ingredient as taught by Meezan.

Applicants present the following arguments against the rejection.

Applicants argue that because the instant claims are to a solution which excludes water and oil.

Examiner disagrees. A solution can be one phase of a composition which comprises multiple phases such as the emulsion compositions exemplified by Sonne.

The instant claims recite a method of treating…comprising…administering… a pharmaceutical solution… consisting of... 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols… one or more alcohols or glycols, … and one or more alkyl glycosides. Thus, while the solution is limited by the phrase "consisting of", the use of the term "comprising" permits additional steps in the method. Such additional steps could include, for example, administration of an oil or water phase. Thus, the instant claims do not exclude the presence of water and oil as Applicants have alleged.

Applicants argue that Sonne is silent with regard to treating a person having a seizure disorder, and thus one of ordinary skill in the art would not be motivated to use the composition of Sonne to treat a person having a seizure disorder.

Examiner disagrees. The rejection is not based on one reference alone, but a combination of references. Here, Lehat is relied upon for supplying the motivation to administer a benzodiazepine to a patient having a seizure disorder.

Applicants argue that one of ordinary skill in the art would have no motivation to combine Sonne with Meezan. Since Sonne already teaches the inclusion of viatmin E, a penetration enhancer, a skilled artisan practicing the method of Sonne would have no reason to look anywhere else for penetration enhancers.

Examiner disagrees. While Sonne teaches that penetration enhancers may be included in the formulation, Sonne does not specifically state that they improve

absorption. Meezan teaches that the inclusion of an alkyl glycoside can drastically improve absorption. Thus, one of ordinary skill in the art making the formulation of Sonne would find it obvious to include an alkyl glycoside in order to improve the absorption as taught by Meezan.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	1	of	9	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US- 2002-0110524 Al	8/15/2002	Cowan, S. M. L. et al.	
	2.	US- 2002-0141971 Al	10/3/2002	William H. Frey, II	
	3.	US- 2003-0017203 Al	6/23/2003	Crotts et al.	
	4.	US- 2003-0040497 Al	2/27/2003	Teng et al.	
	5.	US- 2003-0087820 Al	5/1/2003	Young et al.	
	6.	US- 2003-0100755 Al	5/29/2003	Sham et al.	
	7.	US- 2003-0118547 Al	6/1/2303	Vandenberg, G. W.	
	8.	US- 2003-0118594 Al	6/26/2003	Nag et al.	
	9.	US- 2003-0158206 Al	8/21/2003	Billotte et al.	
	10.	US- 2003-0170206 Al	9/11/2003	Rasmussen et al.	
	11.	US- 2004-0115135 Al	6/17/2004	Quay	
	12.	US- 2004-0126358 Al	7/1/2004	Warne et al.	
	13.	US- 2004-0147473 Al	7/29/2004	Warriell, Jr.	
	14.	US- 2004-0258663 Al	12/23/2004	Quay & El-Shafy	
	15.	US-2004-141923 A1	07/22/2004	Dugger et al.	
	16.	US- 2005-0130260 Al	6/16/2005	Linden et. al.	
	17.	US- 2005-0234101 Al	10/20/2005	Stenkamp et al.	
	18.	US- 2006-0045869 A1	03/02/2006	Meezan et al.	
	19.	US- 2006-0046969 Al	3/2/2006	Maggio, E. T.	
	20.	US- 2006-0106227 Al	5/18/2006	Reddy et al.	
	21.	US- 2006-0147386 Al	07-06-2006	Wermling, D. P.	
	22.	US- 2007-0059254 Al	3/15/2007	Nikhilesh N. Singh	
	23.	US- 2007-0098805 Al	5/3/2007	Gary G. Liversidge	
	24.	US- 2007-0298010 Al	12/27/2007	Maggio, E. T.	
	25.	US- 2008-0268032 Al	10/30/2008	Edward T. Maggio	
	26.	US- 2009-0258865 Al	10/15/2009	Cartt et al.	
	27.	US- 2010-0203119 Al	8/12/2010	Leane et al.	

Examiner Signature	/Adam Milligan/	Date Considered	06/11/2014

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	28.	US- 2010-0209485 Al	8/19/2010	Edward T. Maggio	
	29.	US- 3,547,828	12/15/1970	Mansfield et al.	
	30.	US- 3,849,341	11/19/1974	Lambeiti, V.	
	31.	US- 4,397,951	8/9/1983	Taki et al.	
	32.	US- 4,748,158	5/31/1988	Biermann ***et*** al.	
	33.	US- 4,868,289	9/1/1989	Magnusson et al.	
	34.	US- 4,921,838	5/1/1990	Catsimpoolas et al.	
	35.	US- 5,182,258	1/1/1993	Chiou	
	36.	US- 5,192,528	3/3/1993	Radhakrishnan et al.	
	37.	US- 5,236,707	8/17/1993	William E. Stewart, II	
	38.	US- 5,268,461	12/7/1993	Shoji et al.	
	39.	US- 5,308,531	5/3/1994	Urfer et al.	
	40.	US- 5,317,010	5/31/1994	Pang et al.	
	41.	US- 5,369,095	11/29/1994	Kee et al.	
	42.	US- 5,550,220	8/27/1996	Meyer et al.	
	43.	US- 5,639,733	6/17/1997	Koike et al.	
	44.	US- 5,661,130	8/26/1997	Meezan et al.	
	45.	US- 5,738,845	4/14/1998	Imakawa	
	46.	US- 5,789,375	8/4/1998	Mukae et al.	
	47.	US- 5,795,896	8/18/1998	Löfroth et al.	
	48.	US- 5,814,607	9/29/1998	John S. Patton	
	49.	US- 5,817,634	10/1/1998	Meezan et al.	
	50.	US- 5,955,425	9/21/1999	Morley et al.	
	51.	US- 6,004,574	12/21/1999	Backstrom et al.	
	52.	US- 6,254,854	7/3/2001	Edwards, D. A. et al.	
	53.	US- 6,316,410	11/13/2001	Barbier et al.	
	54.	US- 6,395,300	5/28/2002	Straub et al.	
	55.	US- 6,482,834	9/20/2001	Spada, A. P. et al.	

Examiner Signature	/Adam Milligan/	Date Considered	06/11/2014

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U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	63.	EP-1417972 A1	5/12/2004	ELI LILLY & COMPANY		
	64.	JP1-151528 (English Abstract and Claims)	6/14/1989	TAIHO YAKUHN KOGYO KK		X
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	70.	WO-2003-055464	07/10/2003	BESINS INTERNATIONAL BELGIQUE ET AL.		

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	4	of	9	Attorney Docket Number	35401-716.201

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Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	139.	Webpage for Anatrace products of Affymetrix, http://www.affymetrix.com/estore/browse/level_three_category_and_products.jsp?category=35843&categoryldClicked=35843&expand=true&parent=35900, accessed online on 13 December 2012	
	140.	Yamamoto et al., "The Ocular Route for Systemic Insulin Delivery in the Albino Rabbit", The Journal of Pharmacology and Experimental Therapeutics, April 1989, pp. 249-255, Vol. 249; No. 1	
	141.	Yu Xinrui et al., "Triptan Medicament and Migraine", World Pharmacy (Synthetic Drug and Biochemical Drug Formulation Fascicule), 22(2):91-92 (2001)	X

Examiner Signature	/Adam Milligan/	Date Considered	06/11/2014

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	March 27, 2009
				First Named Inventor	CARTT, Steve et al.
				Art Unit	1612
				Examiner Name	MILLIGAN, ADAM C.
Sheet	1	of	1	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2008/0279784 A1	11/13/2008	Cartt et al.	
	2.	US-2009/0130216 A1	05/21/2009	Cartt et al.	
	3.	US-2009/0258865 A1	10/15/2009	Cartt et al.	
	4.	US-2009/0304801 A1	12/10/2009	Liversidge et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	5.	WO-2005/117830 A1	12/15/2005	Camurus, AB		
	6.	WO-2006/075123 A1	7/20/2006	Camurus, AB		
	7.	WO-2007/043057 A1	4/19/2007	Touitou et al.		
	8.	WO-2007/144081 A2	12/21/2007	LTS Lohmann Therapie-System A.G.		

NON PATENT LITERATURE DOCUMENTS

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	9.	PCT Application No. US09/038696 ISR dated September 28, 2009.	
	10.	PCT Application No. US12/42311 ISR dated August 31, 2012.	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12413439	CARTT ET AL.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Palm Inventor Search	3/11/2011	AM
EAST Search - see attached search history	3/11/2011	AM
NPL Search - caplus (benzodiazepine and alcohol or glycol and tocopherol or tocatrienol)	3/11/2011	AM
Updated EAST and STN Search	11/12/2011	AM
Updated EAST and STN Search	6/11/2014	AM
CPC Search	6/11/2014	AM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam Milligan
Sheet	1	of	3	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

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	1.	US-2001-0042932	11/22/2001	Mathiowitz et al.	
	2.	US-2002-0127278	09/12/2012	Kipp	
	3.	US-2002-0168402	11/14/2002	Kipp	
	4.	US-2003-0031719	02/13/2003	Kipp	
	5.	US-2006-0198896	09/07/2006	Liversidge et al.	
	6.	US-2008-0200418	08/21/2008	Maggio	
	7.	US-2008-0248123	10/09/2008	Swanson et al.	
	8.	US-2008-0299079	12/04/2008	Meezan et al.	
	9.	US-2009-0163447	06/25/2009	Maggio	
	10.	US-2009-0297619	12/03/2009	Swanson et al.	
	11.	US-2010-0068209	03/18/2010	Maggio	
	12.	US-2011-0172211	07/14/2011	Back et al.	
	13.	US-2011-0257096	10/20/2011	Maggio	
	14.	US-2012-0196941	08/02/2012	Maggio	
	15.	US-2013-0065886	03/14/2013	Cartt	
	16.	US-4,973,465	11/27/1990	Baurain et al.	
	17.	US-5,457,100	10/10/1995	Daniel	
	18.	US-5,661,130	08/26/1997	Meezan et al.	
	19.	US-5,861,510	01/19/1999	Piscipio et al.	
	20.	US-5,863,949	01/26/1999	Robinson et al.	
	21.	US-6,143,211	11/07/2000	Mathiowitz et al.	
	22.	US-6,193,985	02/27/2001	Sonne	
	23.	US-6,235,224	05/22/2001	Mathiowitz et al.	
	24.	US-6,428,814	08/06/2002	Bosch et al.	
	25.	US-6,610,271	08/26/2003	Wermeling	
	26.	US-6,616,914	09/09/2003	Ward et al.	
	27.	US-6,627,211	09/30/2003	Choi et al.	

Examiner Signature	/Adam Milligan/	Date Considered	06/11/2014

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				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam Milligan
Sheet	2	of	3	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-6,908,626	06/21/2005	Cooper et al.	
	29.	US-7,132,112	11/07/2006	Choi et al.	
	30.	US-7,434,579	10/14/2008	Young et al.	

U.S. PROVISIONAL PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Filing Date MM-DD-YYYY	Name of Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	31.	U.S. Prov. Appl. No. 60/148,464	08/12/1999	Noe	

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	32.	EP-00780386	6/25/1997	Hoffman-La Roche AG		
	33.	EP-0818442	1/14/1998	Pfizer Inc.		
	34.	EP-0945485	9/29/1999	Morton Int'l., Inc.		
	35.	EP-1004578	5/31/2000	Pfizer Products Inc.		
	36.	EP-606046	7/13/1994	CIBA-GEIGY AG		
	37.	EP-931788	7/28/1999	Pfizer Limited		
	38.	JP 2003-505403 (w/ Corresponding English equivalent WO-0106987)	2/12/2003	SK Corpororation (US)		X
	39.	JP 2005-508939 (w/ Corresponding English equivalent WO-03030872)	4/7/2005	Cooper, Eugene R.		X
	40.	JP 2007-510722 (w/ Corresponding English equivalent WO-2005-044234)	4/26/2007	Elan Pharma International Ltd.		X
	41.	WO-1990-05719	5/31/1990	British Bio-		
Examiner Signature	/Adam Milligan/			Date Considered	06/11/2014	

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				Technology Ltd.		
	42.	WO-1996-27583	9/12/1996	Pfizer Inc.		
	43.	WO-1996-33172	10/24/1996	Pfizer Inc.		
	44.	WO-1998-03516	1/29/1998	Pfizer Inc.		
	45.	WO-1998-07697	2/26/1998	Pfizer Inc.		
	46.	WO-1998-30566	7/16/1998	Pfizer Inc.		
	47.	WO-1998-33768	8/6/1998	Pfizer Products Inc.		
	48.	WO-1998-34915	8/13/1998	Pfizer Inc.		
	49.	WO-1998-34918	8/13/1998	Pfizer Inc.		
	50.	WO-1999-007675	2/18/1999	Pfizer Products Inc.		
	51.	WO-1999-29667	6/19/1999	Pfizer Limited		
	52.	WO-1999-52889	10/21/1999	Pfizer Inc.		
	53.	WO-1999-52910	10/21/1999	Pfizer Products Inc.		
	54.	WO-2000-74681	12/14/2000	Pfizer Limited		
	55.	WO-2005-089768	9/29/2005	Univ. of Kentucky Research Found.		
	56.	WO-2006-055603	5/26/2006	Elan Pharma International Ltd.		
	57.	WO-2006-088894	8/24/2006	Elan Pharma International Ltd.		

NON PATENT LITERATURE DOCUMENTS

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Examiner Signature	/Adam Milligan/	Date Considered	06/11/2014

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Attorney Docket No.: 35401-716.201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent Application of: Applicant: Steve Cartt Serial No.: 12/413,439 Filed: 03/27/2009 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Confirmation No.: 9049 Group Art Unit: 1612 Examiner: Milligan, Adam C. Customer Number: 21971 Certificate of Electronic Filing I hereby certify that the attached Response to Office Action and all marked attachments are being deposited by Electronic Filing by EFS – Web patent filing system on November 19, 2014. By: /Linda Anders/

FILED ELECTRONICALLY ON: NOVEMBER 19, 2014

Dear Madam:

RESPONSE TO NON-FINAL OFFICE ACTION DATED JUNE 19, 2014

In response to the Office Action mailed June 19, 2014, Applicants hereby file an amendment to the claims, remarks, a petition for a two (2) month extension of time, and the requisite extension fee. Applicants submit that the response is timely filed. In the event you consider any additional fees to be required for further examination, please charge them to Deposit Account No. 23-2415, referencing Docket No. 35401-716.201.

Amendments to the claims begin on page **2** of this paper.

Remarks begin on page **7** of this paper.

CLAIMS

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn claim in this or any other appropriate patent application.

1-19. (Canceled).

20. (Currently Amended) A method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising:

administering to one or more nasal mucosal membranes of [[a]] the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

21. (Original) The method of claim 20, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

22. (Original) The method of claim 21, wherein said patient is a human.

23. (Original) The method of claim 20, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam,

midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Original) The method of claim 23, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Canceled)

26. (Canceled)

27. (Original) The method of claim 20, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

28. (Original) The method of claim 20, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

29. (Original) The method of claim 20, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Previously Presented) The method of claim 20, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Previously Presented) The method of claim 30, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Previously Presented) The method of claim 31, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w).

34. (Previously Presented) The method claim 33, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w).

35. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

36. (Previously Presented) The method of claim 35, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

37. (Canceled)

38. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution is a pharmaceutically-acceptable spray formulation.

39. (Canceled).

40. (Previously Presented) The method of claim 38, wherein said pharmaceutical solution is a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

41. (Previously Presented) The method of claim 40, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.

42. (Previously Presented) The method of claim 40, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

43. (Previously Presented) The method of claim 42, wherein the administration of the pharmaceutical-solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.

44. (Previously Presented) The method of claim 43, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

45. (Previously Presented) The method of claim 43, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition.

46. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution contains at least about 0.01% (w/w) of an alkyl glycoside.

47. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

48. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution consists of diazepam, vitamin E, ethanol and optionally an alkyl glycoside.

49. (Previously Presented) The method of claim 48, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

50. (Previously Presented) The method of claim 49, wherein the alkyl glycoside is dodecyl maltoside.

51. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution consists of 1-20 mg diazepam, 45 % (w/w) to 85 % (w/w) vitamin E, 15% (w/w) to 55 % (w/w) of a combination of ethanol and benzyl alcohol, and 0.01 % (w/v) to 1 % (w/v) of alkyl glycoside.

52. (Previously Presented) The method of claim 51, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

53. (Previously Presented) The method of claim 52, wherein the alkyl glycoside is dodecyl maltoside.

REMARKS

Responsive to the Non-Final Rejection mailed June 19, 2014, Applicants request reconsideration of the outstanding rejections in view of the foregoing amendment and the following remarks.

The Amendment to the Claims

Upon entry of the foregoing amendment, Claim 20 has been amended to recite a method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and 0.01 % (w/v) to 1 % (w/v) of one or more alkyl glycosides. As this amendment is not believed to change the scope of the claims, Applicants submit that it does not constitute new matter. In any case, support for the claim amendment is found throughout the original specification, including paragraphs [064], [065], [075], [076] and [080]-[0125]. Thus, the status of the claims is:

Claims 1-19, 25, 26, 37 and 39 are canceled, without prejudice; and

Claims 20-24, 27-36, 38 and 40-53 are pending and under consideration.

Response to the § 103(a) Obviousness Rejection

Claims 20-24, 27-36, 38 and 40-53 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Lahet et al. (Lancet, vol. 352, August 22, 1998), Sonne (U.S. 6,193,985) and Meezan (US 2006/0046962). Applicants traverse this rejection.

Claim 20, from which each of the remaining pending claims depend, reads:

> A method of treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, comprising: administering to one or more nasal mucosal membranes of the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and 0.01 % (w/v) to 1 % (w/v) of one or more alkyl glycosides.

As can be seen in Claim 20, the claimed method comprises treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder. The method comprises administering a nasal solution. The recited nasal solution consists of each of: a benzodiazepine drug; one or more tocopherols or tocotrienols; one or more alcohols or glycols; and one or more alkylglycosides, each in specific proportions. The solution excludes anything else, including water and oil. M.P.E.P. 2111.03. ("The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim.").

Applicants previously observed that, while Sonne teaches emulsions and solutions, all the emulsions taught therein include water and oil, and all the disclosed solutions require oil. In contrast, the instant claims require solutions, and thus specifically exclude Sonne's emulsions. The instant claims also recite specific ingredients, while excluding others through the recitation of "consisting of" language. In particular, both water and oil are excluded from the instant claims, as they are not one of the recited ingredients.

The Office Action appears not to take notice of this difference between the prior art and the claimed methods, focusing instead on remediating the failure of Sonne to teach treatment of seizures. In particular, Lehat is relied upon for its teaching of nasal administration of midazolam for childhood seizures. As apparently recognized by the Office, Lehat, by itself, is insufficient to render obvious the claimed method. Office Action, p. 3 ("Lehat does not teach suitable excipients for the formulation."). Yet, Lehat addresses only one shortcoming of the

combination of Sonne and Meezan. Neither Sonne nor Meezan teach or suggest administration of a solution that contains only the ingredients recited in the instant claims.

Sonne teaches specific benzodiazepine formulations in Examples 1-3, 7-11, 17-19 and 22-23. Of these, Examples 1-3, 7-11, 17, 19 and 22-23 each describe an oil-in-water emulsion of the benzodiazepine. Such emulsions are specifically excluded from the instant claims, which recite solutions (not emulsions) and exclude any ingredients (such as water and oil) not included within the group of benzodiazepine drugs, tocopherols or tocotrienols, alcohols or glycols, and optionally alkyglycosides. Thus, none of these Examples provides sufficient motivation or teaching for one of ordinary skill in the art to modify the teaching of Lehat to practice the claimed methods.

Of the remaining examples, Example 18 is a solution of alprazolam in α-tocopherol and sesame oil for oral administration. Sonne certainly does not suggest nasal administration of this solution. (Nor does Lehat, which teaches that Midazolam is water soluble, thus suggesting, if anything, water-containing solutions of Midazolam.) And even if Sonne did teach nasal administration, Sonne still fails to teach or suggest exclusion of sesame oil. As each of the benzodiazepine compositions taught by Sonne contains oil (which is excluded from the instant claims) in some form or another (oil solution or emulsion), Sonne fails to provide the teaching or motivation for one of ordinary skill in the art to modify the teaching of Lehat to practice the claimed methods.

The Office Action fails to recognize these deficiencies of Sonne's disclosure of excipients. Rather, it focuses attention on "one particular nasal formulation," which contains 1.45 g Pluronic. Office Action, p. 4. Pluronic is a polymeric emulsifier, which is both excluded from, and logically related to, the nasal solutions recited in the instant claims. The recited nasal solutions, in contrast to Sonne's emulsions, do not include an emulsifier. So, the Sonne formulation is excluded from the instant claims. And, as the instant claims exclude a water phase, which would require an emulsifier like Pluronic, Sonne fails to provide motivation to modify those formulations to arrive at the formulations recited in the instant claims, because all of Sonne's solutions require water and oil. Further, as all of Sonne's solutions require oil,

Sonne fails to provide motivation to prepare the claimed nasal solutions, which do not require oil.

While Meezan teaches alkylglycosides, Meezan fails to provide the motivation or teaching to prepare the formulations recited in the instant claims, which are missing from Sonne and Lehat. Thus, contrary to what is implied in the Office Action, Sonne fails to provide sufficient teaching of the formulations recited in the instant claims. And none of the cited references provides the necessary motivation to modify the Sonne formulations to arrive at the formulations recited in the instant claims.

For at least the reasons given above, Applicants submit that the pending claims are not obvious within the meaning of § 103(a) in view of the teaching of Lehat, Sonne and Meezan. Withdrawal of the § 103(a) rejection is respectfully requested.

CONCLUSION

Applicants timely submit these remarks in response to the Office Communication dated June 19, 2014. In the event that fees are due in connection with the filing of this response, please charge the necessary fees to Deposit Account No. 23-2415 referencing Docket No. 35401-716.201. Applicants encourage the Examiner to contact the undersigned attorney, should there be any remaining issues that may be addressed by a telephonic interview.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: November 19, 2014

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Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Linda Anders
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**300**

Electronic Acknowledgement Receipt

EFS ID:	20742314
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Linda Anders
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Attorney Docket Number:	35401-716.201
Receipt Date:	19-NOV-2014
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Time Stamp:	15:07:55
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RAM confirmation Number	1281
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-201-response2.pdf	156591 4c805f15a5084e7fb97ee223e9c6147acb6d670c	yes	10

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	10

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30445 86d5da86ab9fa1e1408deeeba123d06f74c88266	no	2

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/413,439	Filing Date 03/27/2009	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/19/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 29	Minus	** 62	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
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				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	1	of	2	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 6,165,484	12/26/2000	Raad, et al.	
	2.	US 6,316,029	11/13/2001	Jain, et al.	
	3.	US 6,461,591	10/08/2002	Keller, et al.	
	4.	US 7,008,920	03/07/2006	Kimura, et al.	
	5.	US 8,895,546	11/25/2014	Cartt, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	6.	WO 2006-025882	03/09/2006	The UAB Research Foundation		

NON PATENT LITERATURE DOCUMENTS

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	7.	CA 2,723,470 Office action dated June 7, 2012	
	8.	Fix, "Oral controlled release technology for peptides: status and future prospects", Pharmaceutical Research 1996 Dec;13(12):1760-1764.	
	9.	Hussain et al, "Absorption enhancers in pulmonary protein delivery." J Control Release. 2004 Jan 8;94(1):15-24.	
	10.	Kissel et al., "Tolerability and absorption enhancement of intranasally administered octreotide by sodium taurodihydrofusidate in healthy subjects." Pharm Res. 1992 Jan;9(1):52-57.	
	11.	Kite et al., "Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro." J Clin Microbiol. 2004 Jul;42(7):3073-3076.	

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				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	2	of	2	Attorney Docket Number	35401-716.201

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	12.	Liu et al., "Interaction between chitosan and alkyl P-D-glucopyranoside and its effect on their antimicrobial activity", Carbohydrate Polymers. 2004; 56: 243-250.	
	13.	PCT/US08/62961 International Preliminary Report on Patentability dated 11/10/2009	
	14.	PCT/US09/38696 International Preliminary Report on Patentability dated 9/28/2010	
	15.	U.S. Serial No. 12/116,842 Office action mailed May 25, 2011	
	16.	U.S. Serial No. 12/116,842 Office action mailed April 2, 2013	
	17.	U.S. Serial No. 12/116,842 Office action mailed November 15, 2011	
	18.	U.S. Serial No. 12/116,842 Office action mailed December 17, 2013	
	19.	U.S. Serial No. 12/266,529 Office action mailed July 10, 2012	
	20.	U.S. Serial No. 12/266,529 Office action mailed November 16, 2011	
	21.	U.S. Serial No. 12/413,439 Office action mailed March 18, 2011	
	22.	U.S. Serial No. 12/413,439 Office action mailed November 21, 2011	
	23.	U.S. Serial No. 12/413,439 Office action mailed June 19, 2014	

Examiner Signature		Date Considered	

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(54) Title: ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

(57) Abstract: A composition including a surfactant and at least one alkyl glycoside and/or saccharide alkyl ester and a drug. The surfactant composition(s) when admixed with a drug is non-toxic and non-irritating, while stabilizing and increasing the bioavailability of the drug. The invention also provides compositions that enhance absorption of drugs via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route of a patient, including but not limited to insulin, glucagon and exendin-4.

WO 2006/025882 A2

ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Application Serial No. 60/649,958 filed February 3, 2005, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/637,284 filed December 17, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/632,038 filed November 30, 2004, now pending; the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/609,890 filed September 14, 2004, now pending; and the benefit under 35 USC § 119(e) of U.S. Application Serial No. 60/604,296 filed August 25, 2004, now pending. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The invention relates generally to non-irritating, non-toxic compositions providing enhanced bioavailability and more specifically to alkyl glycoside or saccharide alkyl ester compositions for delivery of therapeutic agents to a subject.

BACKGROUND INFORMATION

[0003] Therapeutic agents are often combined with various surfactants. Yet, surfactants are frequently irritating to the skin and other tissues, including mucosal membranes such as those found in the nose, mouth, eye, vagina, rectum, esophagus, intestinal tract, and the like. Many surfactants also cause proteins to denature, thus destroying their biological activity. Another serious limitation to the development and use of such agents is the ability to deliver them safely, non-invasively, efficiently and stably to the site of action. Therefore, an ideal enhancing surfactant will stabilize the therapeutic agent, be non-toxic and non-irritable to the skin or mucosal surfaces, and enhance the passage or absorption of the therapeutic agent through various membrane barriers without damaging the structural integrity and biological function of the membrane and increase bioavailability of the agent.

SUMMARY OF THE INVENTION

[0004] The present invention is based, in part, on the development of a therapeutic composition containing a drug enhancing agent useful for increasing the absorption and bioavailability of the drug, while at the same time avoiding various adverse toxic effects of drug. In particular, the drug enhancing agents of the invention contain a non-toxic surfactant consisting of at least an alkyl glycoside and/or saccharide alkyl ester. One advantage of the therapeutic compositions of the invention is that they permit administration and delivery of the therapeutic agents with high bioavailabilities at concentrations of enhancing agents that are dramatically below their so-called "no observable adverse effect levels" (their NOAEL's) . Accordingly, the present invention provides compositions, including alkyl glycosides and/or saccharide alkyl esters and a therapeutic agent (e.g. small molecule organic drug molecules, low molecular weight peptides such as Exenatide, GLP-1 and the like , proteins, and non-peptide therapeutic polymers such as low molecular weight heparin and inhibitory RNA), methods of administering and using the compositions e.g. via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or cerebral spinal fluid (CSF) delivery route, and methods of ameliorating a disease state in a subject by administration of such compositions

[0005] In one aspect, the present invention relates to a surfactant composition having at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed, mixed or blended with a therapeutic agent, a drug, or biologically active compound, the surfactant stabilizes the biological activity and increases the bioavailability of the drug.

[0006] Accordingly, in one aspect, the invention provides a therapeutic composition having at least one biologically active compound and at least one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester or sucrose ester and wherein the therapeutic composition stabilizes the biologically active compound for at least about 6 months, or more, and from about 4°C to about 25°C.

[0007] The invention also provides a method of administering a therapeutic composition having a surfactant including at least one alkyl glycoside and/or saccharide alkyl ester admixed, mixed, or blended with at least one therapeutic agent, or a drug, or biologically active compound, and administered or delivered to a subject, wherein the

alkyl has from about 10 to 24, 10 to 20, 10 to 16, or 10 to 14 carbon atoms, wherein the surfactant increases the stability and bioavailability of the therapeutic agent.

[0008] In yet another aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by, administering the compound via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route when admixed, mixed or blended with an absorption increasing amount of a suitable surfactant, wherein the surfactant is a nontoxic and nonionic hydrophobic alkyl joined by a linkage to a hydrophilic saccharide. Such low molecular weight compounds include but are not limited to, nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

[0009] The present invention also provides a method of treating diabetes including administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell), a blood glucose reducing amount of a therapeutic composition, for example, an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of incretin mimetic agent or insulin and lowering the level of blood glucose and treating diabetes in the subject.

[0010] The present invention also provides a method of treating congestive heart failure in a subject including administering to the subject in need thereof via the oral, ocular, nasal, nasolacrimal, or inhalation delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

[0011] In another aspect, the invention provides a method of treating obesity or diabetes associated with obesity in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or CSF delivery route, a therapeutically effective amount of a composition comprising a PYY peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic,

nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

[0012] In another aspect, the invention provides a method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject by administering via the oral, ocular, nasal, nasolacrimal, inhalation or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the compound is not insulin, calcitonin, or glucagon when the route of administration is oral, ocular, nasal, or nasolacrimal.

[0013] The present invention also provides a method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject by administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kilo Daltons (kD), with the proviso that the subject does not have diabetes when delivery is via the oral, ocular, nasal or nasolacrimal routes.

[0014] In one aspect of the invention, there is provided a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of Exenatide (exendin-4) in a pharmaceutically acceptable carrier.

[0015] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of GLP-1 in a pharmaceutically acceptable carrier.

[0016] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of nicotine in a pharmaceutically acceptable carrier.

[0017] In one aspect, the invention provides a pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of interferon in a pharmaceutically acceptable carrier.

[0018] In one aspect, the invention provides pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of PYY in a pharmaceutically acceptable carrier.

[0019] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier.

[0020] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of a peptide having a molecular weight of about 1-75 kD in a pharmaceutically acceptable carrier, with the proviso that the peptide is not insulin, calcitonin, and glucagon.

[0021] In one aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount erythropoietin in a pharmaceutically acceptable carrier.

[0022] In one aspect, the invention provides a method of increasing absorption of a compound into the CSF of a subject having administered intranasally the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide.

[0023] In yet another aspect, the invention provides a pharmaceutical composition having a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group

joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent selected from:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

[0024] In one aspect, the invention provides a method of increasing absorption of a low molecular weight compound into the circulatory system of a subject by administering, via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral

cavity (sublingual or Buccal cell) or CSF delivery route (a) the compound; (b) an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide; and (c) a mucosal delivery-enhancing agent.

[0025] In one aspect, the invention provides a method of controlling caloric intake by administering a composition having a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

[0026] In another aspect, the invention provides a method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

[0027] Still, in another aspect, the invention provides a controlled release dosage composition comprising:

(a) a core comprising:

(i) at least one therapeutic agent or drug;

(ii) at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is impermeable, permeable, semi-permeable or porous and becomes more permeable upon sustained contact with contents of the gastrointestinal tract.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1 is a graph showing the intranasal percent bioavailability compared to intravenous injection and the subject-to-subject coefficients of variation for MIACALCIN® (salmon calcitonin) with and without alkyl glycoside.

[0029] Figure 2 is a graph showing the effect of intranasal administration of insulin/0.25%TDM (filled circles) and intranasal administration of insulin alone (open circles) in reducing blood glucose levels.

[0030] Figure 3 is a graph showing the effect of intranasal (closed triangles) and intraperitoneal (IP) injection (closed circles) administration of exendin-4/0.25%TDM and

IP injection of saline alone, minus TDM (open circles) in reducing blood glucose levels following oral administration of glucose (i.e., in a so-called "glucose tolerance test").

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention may be understood more readily by reference to the following detailed description of specific embodiments and the Examples included therein.

[0032] The present invention is based on the discovery that therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside and/or at least one saccharide alkyl ester are stable, non-toxic, non-irritating, anti-bacterial compositions that increase bioavailability of the drug and have no observable adverse effects when administered to a subject.

[0033] A "therapeutic composition" can consist of an admixture with an organic or inorganic carrier or excipient, and can be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, or other form suitable for use. The carriers, in addition to those disclosed above, can include glucose, lactose, mannose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition, auxiliary stabilizing, thickening or coloring agents can be used, for example a stabilizing dry agent such as triulose.

[0034] A "drug" is any therapeutic compound, or molecule, or therapeutic agent, or biologically active compound, including but not limited to nucleic acids, small molecules, proteins, polypeptides or peptides, etc. The term "nucleic acids" also denotes DNA, cDNA, RNA, siRNA, RNAi, etc. which encode translated and untranslated regions or inhibits translated or untranslated regions of structural genes encoding a peptide or protein of the invention. For example, a nucleic acid of the invention can include 5' and 3' untranslated regulatory nucleotide sequences as well as translated sequences associated with the structural gene, e.g. GLP-1.

[0035] A peptide of the invention may be any medically or diagnostically useful peptide or protein of small to medium size (i.e. up to about 15 kD, 30 kD, 40 kD, 50 kD, 60 kD, 70 kD, 80 kD, 90 kD, 100 kD, for example). The mechanisms of improved polypeptide absorption are described in U.S. Patent No. 5,661,130 which is hereby incorporated by reference in its entirety. Invention compositions can be mixed with all such peptides, although the degree to which the peptide benefits are improved may vary according to the molecular weight and the physical and chemical properties of the peptide, and the particular surfactant used. Examples of polypeptides include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone (GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), prolactin, insulin, insulin like growth factor-I (IGF-I) somatomedin-C (SM-C), calcitonin, leptin and the leptin derived short peptide OB-3, melatonin, GLP-1 or Glucagon-like peptide-1,, GiP, neuropeptide pituitary adenylate cyclase, GM-1 ganglioside, nerve growth factor (NGF), nafarelin, D-tryp6)-LHRH, FGF, VEGF antagonists, leuprolide, interferon (e.g., α,β, γ) low molecular weight heparin, PYY, LHRH antagonists, Keratinocyte Growth Factor (KGF) , Glial-Derived Neurotrophic Factor (GDNF), ghrelin, and ghrelin antagonists. Further, in some aspects, the peptide or protein is selected from a growth factor, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, or a polypeptide involved in the blood coagulation cascade.

[0036] Other drugs or therapeutic compounds, molecules and/or agents include compounds or molecules of the central nervous system affecting neurotransmitters or neural ion channels (i.e. antidepressants (bupropion)), selective serotonin 2c receptor agonists, anti-seizure agents (topiramate, zonisamide), some dopamine antagonists, and cannabinoid-1 receptor antagonists (rimonabant)); leptin/insulin/central nervous system pathway agents (i.e. leptin analogues, leptin transport and/or leptin receptor promoters, ciliary neurotrophic factor (Axokine), neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin, cocaine and amphetamine regulated transcript

promoters, alpha-melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor-gamma receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin); gastrointestinal-neural pathway agents (i.e. agents that increase glucagon-like peptide-1 activity (extendin-4, liraglutide, dipeptidyl peptidase IV inhibitors), protein YY3-36, ghrelin, ghrelin antagonists, amylin analogues (pramlintide)); and compounds or molecules that may increase resting metabolic rate "selective" beta-3 stimulators/agonist, melanin concentrating hormone antagonists, phytostanol analogues, functional oils, P57, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11B-hydroxysteroid dehydrogenase type 1 activity, corticotropin-releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, and gastrointestinal lipase inhibitors (ATL962).

[0037] The therapeutic composition of the invention includes a drug and a drug absorption enhancing agent, for example, a surfactant. The term "surfactant" is any surface active agent that modifies interfacial tension of water. Typically, surfactants have one lipophilic and one hydrophilic group in the molecule. Broadly, the group includes soaps, detergents, emulsifiers, dispersing and wetting agents, and several groups of antiseptics. More specifically, surfactants include stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and glycerin monostearate; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

[0038] Preferably, the surfactant of the invention consists of at least one suitable alkyl glycoside. As used herein, "alkyl glycoside" refers to any sugar joined by a linkage to any hydrophobic alkyl, as is known in the art. Any "suitable" alkyl glycoside means one that fulfills the limiting characteristics of the invention, i.e., that the alkyl glycoside be nontoxic and nonionic, and that it increases the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route. Suitable compounds can be determined using the methods set forth herein.

[0039] Alkyl glycosides of the invention can be synthesized by known procedures, i.e., chemically, as described, e.g., in Rosevear et al., *Biochemistry* 19:4108-4115 (1980) or Koeltzow and Urfer, *J. Am. Oil Chem. Soc.*, 61:1651-1655 (1984), U.S. Pat. No. 3,219,656 and U.S. Pat. No. 3,839,318 or enzymatically, as described, e.g., in Li et al., *J. Biol. Chem.*, 266:10723-10726 (1991) or Gopalan et al., *J. Biol. Chem.* 267:9629-9638 (1992).

[0040] Alkyl glycosides of the present invention can include, but are not limited to: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl-, pentadecyl-,hexadecyl-, heptadecyl-, and octadecyl- α- or β-D-maltoside, -glucoside or -sucroside (synthesized according to Koeltzow and Urfer; Anatrace Inc., Maumee, Ohio; Calbiochem, San Diego, Calif.; Fluka Chemie, Switzerland); alkyl thiomaltosides, such as heptyl, octyl, dodecyl-, tridecyl-, and tetradecyl-β-D-thiomaltoside (synthesized according to Defaye, J. and Pederson, C., "Hydrogen Fluoride, Solvent and Reagent for Carbohydrate Conversion Technology" in Carbohydrates as Organic Raw Materials, 247-265 (F. W. Lichtenthaler, ed.) VCH Publishers, New York (1991); Ferenci, T., J. Bacteriol, 144:7-11 (1980)); alkyl thioglucosides, such as heptyl- or octyl 1-thio α- or β-D-glucopyranoside (Anatrace, Inc., Maumee, Ohio; see Saito, S. and Tsuchiya, T. Chem. Pharm. Bull. 33:503-508 (1985)); alkyl thiosucroses (synthesized according to, for example, Binder, T. P. and Robyt, J. F., Carbohydr. Res. 140:9-20 (1985)); alkyl maltotriosides (synthesized according to Koeltzow and Urfer); long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers; (synthesized according to Austrian Patent 382,381 (1987); Chem. Abstr., 108:114719 (1988) and Gruber and Greber pp. 95-116); derivatives of palatinose and isomaltamine linked by amide linkage to an alkyl chain (synthesized according to Kunz, M., "Sucrose-based Hydrophilic Building Blocks as Intermediates for the Synthesis of Surfactants and Polymers" in Carbohydrates as Organic Raw Materials, 127-153); derivatives of isomaltamine linked by urea to an alkyl chain (synthesized according to Kunz); long chain aliphatic carbonic acid ureides of sucrose β-amino-alkyl ethers (synthesized according to Gruber and Greber, pp. 95-116); and long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers (synthesized according to Austrian Patent 382,381 (1987), Chem. Abstr., 108:114719 (1988) and Gruber and Greber, pp. 95-116).

[0041] Surfactants of the invention consisting of an alkyl glycoside and/or a sucrose ester have characteristic hydrophile-lipophile balance (HLB) numbers, which can be calculated or determined empirically (Schick, M. J. Nonionic Surfactants, p. 607 (New York: Marcel Dekker, Inc. (1967)). The HLB number is a direct reflection of the hydrophilic character of the surfactant, i.e., the larger the HLB number, the more hydrophilic the compound. HLB numbers can be calculated by the formula: (20 times MW hydrophilic component)/(MW hydrophobic component+MW hydrophilic component), where MW=molecular weight (Rosen, M. J., Surfactants and Interfacial Phenomena, pp. 242-245, John Wiley, New York (1978)). The HLB number is a direct expression of the hydrophilic character of the surfactant, i.e., the larger the HLB number, the more hydrophilic the compound. A preferred surfactant has an HLB number of from about 10 to 20 and an even more preferred range of from about 11 to 15.

[0042] As described above, the hydrophobic alkyl can thus be chosen of any desired size, depending on the hydrophobicity desired and the hydrophilicity of the saccharide moiety. For example, one preferred range of alkyl chains is from about 9 to about 24 carbon atoms. An even more preferred range is from about 9 to about 16 or about 14 carbon atoms. Similarly, some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 13, 14, 16, 18, 20, 22, or 24 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside, etc. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

[0043] The surfactants of the invention can also include a saccharide. As use herein, a "saccharide" is inclusive of monosaccharides, oligosaccharides or polysaccharides in straight chain or ring forms, or a combination thereof to form a saccharide chain. Oligosaccharides are saccharides having two or more monosaccharide residues. The saccharide can be chosen, for example, from any currently commercially available saccharide species or can be synthesized. Some examples of the many possible saccharides to use include glucose, maltose, maltotriose, maltotetraose, sucrose and trehalose. Preferable saccharides include maltose, sucrose and glucose.

[0044] The surfactants of the invention can likewise consist of a sucrose ester. As used herein, "sucrose esters" are sucrose esters of fatty acids and is a complex of sucrose

and fatty acid. Sucrose esters can take many forms because of the eight hydroxyl groups in sucrose available for reaction and the many fatty acid groups, from acetate on up to larger, more bulky fatty acids that can be reacted with sucrose. This flexibility means that many products and functionalities can be tailored, based on the fatty acid moiety used. Sucrose esters have food and non-food uses, especially as surfactants and emulsifiers, with growing applications in pharmaceuticals, cosmetics, detergents and food additives. They are biodegradable, non-toxic and mild to the skin.

[0045] The surfactants of the invention have a hydrophobic alkyl group linked to a hydrophobic saccharide. The linkage between the hydrophobic alkyl group and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (Horton), amide (Carbohydrates as Organic Raw Materials, F. W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988); Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in Carbohydrates as Organic Raw Materials, pp. 95-116) or ester linkage (Sugar Esters: Preparation and Application, J. C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)). Further, preferred glycosides can include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of about 9-16 carbon atoms, e.g., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. Again, these compositions are amphipathic and nontoxic, because they degrade to an alcohol and an oligosaccharide.

[0046] The above examples are illustrative of the types of glycosides to be used in the methods claimed herein, but the list is not exhaustive. Derivatives of the above compounds which fit the criteria of the claims should also be considered when choosing a glycoside. All of the compounds can be screened for efficacy following the methods taught herein and in the examples.

[0047] The compositions of the present invention can be administered in a format selected from the group consisting of a tablet, a capsule, a suppository, a drop, a spray, an aerosol and a sustained release or delayed burst format. The spray and the aerosol can be achieved through use of an appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J.

Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss. The prolonged drug contact is non-toxic to the skin and mucosal surfaces.

[0048] The surfactant compositions of the invention are stable. For example, Baudys et al. in U.S. Patent No. 5,726,154 show that calcitonin in an aqueous liquid composition comprising SDS (sodium dodecyl sulfate, a surfactant) and an organic acid is stable for at least 6 months. Similarly, the surfactant compositions of the present invention have improved stabilizing characteristics when admixed with a drug. No organic acid is required in these formulations. For example, the composition of the invention maintains the stability of proteins and peptide therapeutics for about 6 months, or more, when maintained at about 4°C to 25°C.

[0049] The stability of the surfactant compositions are, in part, due to their high no observable adverse effect level (NOAEL). The Environmental Protection Agency (EPA) defines the no observable adverse effect level (NOAEL) as the exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Hence, the term, "no observable adverse effect level" (or NOAEL) is the greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions.

[0050] The Food and Agriculture Organization (FAO) of the United Nations of the World Health Organization (WHO) has shown that some alkyl glycosides have very high NOAELs, allowing for increased consumption of these alkyl glycosides without any adverse effect. This report can be found on the world wide web at inchem.org/documents/jecfa/jecmono/v10je11.htm. For example, the NOAEL for sucrose dodecanoate, a sucrose ester used in food products, is about 20-30 grams/kilogram/day, e.g. a 70 kilogram person (about 154 lbs.) can consume about 1400 - 2100 grams (or about 3 to 4.6 pounds) of sucrose dodecanoate per day without any observable adverse effect. Typically, an acceptable daily intake for humans is about 1% of the NOAEL, which translates to about 14–21 grams, or 14 million micrograms to 21 million micrograms, per day, indefinitely. Definitions of NOAELs and other related

definitions can be found on the world wide web at epa.gov/OCEPAterms. Thus, although some effects may be produced with alkyl glycoside levels anticipated in the present invention, the levels are not considered adverse, or precursors to adverse effects.

[0051] Accordingly, a subject treated with surfactant compositions of the invention having at least one alkyl glycoside, e.g. tetradecylmaltoside (TDM; or Intravail A), at a concentration of about 0.125% by weight of alkyl glycoside two times per day, or three times per day, or more depending on the treatment regimen consumes about 200 to 300 micrograms per day total of TDM. So, the effective dose of the TDM is at least 1000X fold lower than (i.e., 1/1000) of the NOAEL, and falls far below 1% of the NOAEL, which is the acceptable daily intake; or in this case about 1/50,000 of the acceptable daily intake.. Stated another way, alkyl glycosides of the present invention have a high NOAEL, such that the amount or concentration of alkyl glycosides used in the present invention do not cause an adverse effect and can be safely consumed without any adverse effect.

[0052] The surfactant compositions of the invention are also stable because they are physiologically non-toxic and non-irritants. The term, "nontoxic" means that the alkyl glycoside molecule has a sufficiently low toxicity to be suitable for human administration and consumption. Preferred alkyl glycosides are non-irritating to the tissues to which they are applied. Any alkyl glycoside used should be of minimal or no toxicity to the cell, such that it does not cause damage to the cell. Yet, toxicity for any given alkyl glycoside may vary with the concentration of alkyl glycoside used. It is also beneficial if the alkyl glycoside chosen is metabolized or eliminated by the body and if this metabolism or elimination is done in a manner that will not be harmfully toxic. The term, "non-irritant" means that the agent does not cause inflammation following immediate, prolonged or repeated contact with the skin surface or mucous membranes.

[0053] Moreover, one embodiment of the surfactant compositions, in particular, the sucrose esters, serve as anti-bacterial agents. An agent is an "anti-bacterial" agent or substance if the agent or its equivalent destroy bacteria, or suppress bacterial growth or reproduction. The anti-bacterial activity of sucrose esters and their fatty acids have been reported. Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al. (2000) describe that galactose and fructose laureates are particularly effective carbohydrate monoesters. Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213. Hence, the present invention is not limited to the sucrose ester described herein, but encompasses other carbohydrate esters, including galactose and fructose esters, that suppress bacterial growth and reproduction.

[0054] The surfactant compositions of the invention are typically present at a level of from about 0.01% to 20% by weight. More preferred levels of incorporation are from about 0.01% to 5% by weight, from about 0.01% to 2% by weight, from about 0.01% to 1%, most preferably from about 0.01% to 0.125% by weight. The surfactant is preferably formulated to be compatible with other components present in the composition. In liquid, or gel, or capsule, or injectable, or spray compositions the surfactant is most preferably formulated such that it promotes, or at least does not degrade, the stability of any protein or enzyme in these compositions. Further, the invention optimizes the concentration by keeping the concentration of absorption enhancer as low as possible, while still maintaining the desired effect.

[0055] The compositions of the invention when administered to the subject, yield enhanced mucosal delivery of the biologically active compound(s), or drug, with a peak concentration (or Cmax) of the compound(s) in a tissue, or fluid, or in a blood plasma of the subject that is about 15%, 20%, or 50% or greater as compared to a Cmax of the compound(s) in a tissue (e.g. CNS), or fluid, or blood plasma following intramuscular injection of an equivalent concentration of the compound(s) to the subject.

[0056] The measure of how much of the drug or compound(s) reaches the bloodstream in a set period of time, e.g. 24 hours can also be calculated by plotting drug blood concentration at various times during a 24-hour or longer period and then measuring the area under the curve (AUC) between 0 and 24 hours. Similarly, a measure of drug efficacy can also be determined from a time to maximal concentration (tmax) of the biologically active compound(s) in a tissue (e.g. CNS) or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours. The therapeutic compositions of the invention increase the speed of onset of drug action (i.e., reduce Tmax) by a factor of about 1.5-fold to 2-fold.

[0057] Also, the therapeutic compositions or formulations of the invention can be administered or delivered to a subject in need systemically or locally. Suitable routes may, for example, include oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), transmucosal administration, vaginal, rectal, parenteral delivery, including intramuscular, subcutaneous, intravenous, intraperitoneal, or CSF delivery. Moreover, the mode of delivery e.g. liquid, gel, tablet, spray, etc. will also depend on the method of delivery to the subject.

[0058] Additionally, the therapeutic compositions of the invention can consist of a pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" is an aqueous or non-aqueous agent, for example alcoholic or oleaginous, or a mixture thereof, and can contain a surfactant, emollient, lubricant, stabilizer, dye, perfume, preservative, acid or base for adjustment of pH, a solvent, emulsifier, gelling agent, moisturizer, stabilizer, wetting agent, time release agent, humectant, or other component commonly included in a particular form of pharmaceutical composition. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, and oils such as olive oil or injectable organic esters. A pharmaceutically acceptable carrier can contain physiologically acceptable compounds that act, for example, to stabilize or to increase the absorption of the specific inhibitor, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. A pharmaceutically acceptable carrier can also be selected from substances such as distilled water, benzyl alcohol, lactose, starches, talc, magnesium stearate, polyvinylpyrrolidone, alginic acid, colloidal silica, titanium dioxide, and flavoring agents.

[0059] Additionally, to decrease susceptibility of alkyl saccharides or saccharide alkyl esters to hydrolytic cleavage of the drug, various oxygen atoms within the drugs can be substituted for by sulfur (Defaye, J. and Gelas, *J. in Studies in Natural Product Chemistry* (Atta-ur-Rahman, ed.) Vol. 8, pp. 315-357, Elsevier, Amsterdam, 1991). For example, the heteroatom of the sugar ring can be either oxygen or sulfur, or the linkage between monosaccharides in an oligosaccharide can be oxygen or sulfur (Horton, D. and Wander, J. D., "Thio Sugars and Derivatives," The Carbohydrates: Chemistry and Biochemistry,

2d. Ed. Vol. IB, (W. Reyman and D. Horton eds.), pp. 799-842, (Academic Press, New York), (1972)). Oligosaccharides can have either α (alpha) or β (beta) anomeric configuration (see Pacsu, E., et al. in Methods in Carbohydrate Chemistry (R. L. Whistler, et al., eds.) Vol. 2, pp. 376-385, Academic Press, New York 1963).

[0060] A composition of the invention can be prepared in tablet form by mixing a therapeutic agent or drug and one alky glycoside and/or saccharide alkyl ester according to the invention, and an appropriate pharmaceutical carrier or excipient, for example mannitol, corn starch, polyvinylpyrrolidone or the like, granulating the mixture and finally compressing it in the presence of a pharmaceutical carrrier such as corn starch, magnesium stearate or the like. If necessary, the formulation thus prepared may include a sugar-coating or enteric coating or covered in such a way that the active principle is released gradually, for example, in the appropriate pH medium.

[0061] The term "enteric coating," is a polymer encasing, surrounding, or forming a layer, or membrane around the therapeutic composition or core. Also, the enteric coating can contain a drug which is compatible or incompatible with the coating. One tablet composition may include an enteric coating polymer with a compatible drug which dissolves or releases the drug at higher pH levels (e.g., pH greater than 4.0, greater than 4.5, greater than 5.0 or higher) and not at low pH levels (e.g., pH 4 or less); or the reverse.

[0062] In a preferred embodiment, the dose dependent release form of the invention is a tablet comprising:

(a) a core comprising:

(i) a therapeutic agent or drug;

(ii) a surfactant comprising at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is an impermeable, permeable, semi-permeable or porous coating and becomes more permeable or porous upon contacting an aqueous environment of a defined pH.

[0063] The term "membrane" is synonymous with "coating," or equivalents thereof. The terms are used to identify a region of a medicament, for example, a tablet, that is impermeable, permeable, semi-permeable or porous to an aqueous solution(s) or bodily

fluid(s), and/or to the therapeutic agent(s) or drug(s) encapsulated therein. If the membrane is permeable, semi-permeable or porous to the drug, the drug can be released through the openings or pores of the membrane in solution or *in vivo*. The porous membrane can be manufactured mechanically (e.g., drilling microscopic holes or pores in the membrane layer using a laser), or it can be imparted due to the physiochemical properties of the coating polymer(s). Membrane or coating polymers of the invention are well known in the art, and include cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in U.S. Pat. Nos. 3 ,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference.

[0064] Further, the enteric coating according to the invention can include a plasticizer, and a sufficient amount of sodium hydroxide (NaOH) to effect or adjust the pH of the suspension in solution or *in vivo*. Examples of plasticizers include triethyl citrate, triacetin, tributyl sebecate, or polyethylene glycol. Other alkalizing agents, including potassium hydroxide, calcium carbonate, sodium carboxymethylcellulose, magnesium oxide, and magnesium hydroxide can also be used to effect or adjust the pH of the suspension in solution or *in vivo*.

[0065] Accordingly, in one embodiment, an enteric coating can be designed to release a certain percentage of a drug or drugs in certain mediums with a certain pH or pH range. For example, the therapeutic composition of the invention may include at least one enteric coating encasing or protecting at least one drug which is chemically unstable in an acidic environment (e.g., the stomach). The enteric coating protects the drug from the acidic environment (e.g., pH < 3), while releasing the drug in locations which are less acidic, for example, regions of the small and large intestine where the pH is 3, or 4, or 5, or greater. A medicament of this nature will travel from one region of the gastrointestinal tract to the other, for example, it takes about 2 to about 4 hours for a drug to move from the stomach to the small intestine (duodenum, jejunum and ileum). During this passage or transit, the pH changes from about 3 (e.g., stomach) to 4, or 5, or to about a pH of 6 or 7 or greater. Thus, the enteric coating allows the core containing the drug to remain substantially

intact, and prevents premature drug release or the acid from penetrating and de-stabilizing the drug.

[0066] Examples of suitable enteric polymers include but are not limited to cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof. One skilled in the art will appreciate that other hydrophilic, hydrophobic and enteric coating polymers may be readily employed, singly or in any combination, as all or part of a coating according to the invention.

[0067] The therapeutic compositions of the invention in the form of a tablet can have a plurality of coatings, for example, a hydrophilic coating (e.g., hydroxypropylmethyl-cellulose), and/or a hydrophobic coating (e.g., alkylcelluloses), and/or an enteric coating. For example, the tablet core can be encases by a plurality of the same type of coating, or a plurality of different types of coating selected from a hydrophilic, hydrophobic or enteric coating. Hence, it is anticipated that a tablet can be designed having at least one, but can have more than one layer consisting of the same or different coatings dependent on the target tissue or purpose of the drug or drugs. For example the tablet core layer may have a first composition enclosed by a first coating layer (e.g. hydrophilic, hydrophobic, or enteri-coating), and a second same or different composition or drug having the same or

different dosage can be enclosed in second coating layer, etc. This layering of various coatings provides for a first, second, third, or more gradual or dose dependent release of the same or different drug containing composition.

[0068] In a preferred embodiment, a first dosage of a first composition of the invention is contained in a tablet core and with an enteric-coating such that the enteric-coating protects and prevents the composition contained therein from breaking down or being released into the stomach. In another example, the first loading dose of the therapeutic composition is included in the first layer and consists of from about 10% to about 40% of the total amount of the total composition included in the formulation or tablet. In a second loading dose, another percentage of the total dose of the composition is released. The invention contemplates as many time release doses as is necessary in a treatment regimen. Thus, in certain aspects, a single coating or plurality of coating layers is in an amount ranging from about 2% to 6% by weight, preferably about 2% to about 5%, even more preferably from about 2% to about 3% by weight of the coated unit dosage form.

[0069] Accordingly, the composition preparations of the invention make it possible for contents of a hard capsule or tablet to be selectively released at a desired site the more distal parts of the gastro-intestinal tract (e.g. small and large intestine) by selecting the a suitable pH-soluble polymer for a specific region. Mechanical expulsion of the composition preparations may also be achieved by inclusion of a water absorbing polymer that expands upon water absorption within a hard semi-permeable capsule thus expelling composition through an opening in the hard capsule.

[0070] Drugs particularly suited for dose dependent time release include but are not limited to insulin like growth factor-I (IGF-I), somatomedin-C (SM-C; diabetes, nerve function, renal function), insulin (diabetes), calcitonin (osteoporosis), leptin (obesity; infertility), leptin derived short peptide (OB-3), hGH (AIDs wasting, dwarfism), human parathyroid hormone (PTH) (osteoporosis), melatonin (sleep), GLP-1 or Glucagon-like peptide-1 (diabetes), GiP (diabetes), pituitary adenylate cyclase-activating polypeptide (PACAP) and islet function (diabetes), GM-1 ganglioside, (Alzheimers), nerve growth factor (NGF), (Alzheimers), nafarelin (endometriosis), Synarel® (nafarelin acetate nasal solution), (D-tryp6)-LHRH (fertility), FGF (duodenal ulcer, macular degeneration, burns,

wounds, spinal cord injuries, repair of bone and cartilage damage), VEGF antagonists (to block the receptor), VEGF (agonist) neonatal distress syndrome; ALS), leuprolide (prostate and breast cancer), interferon-alpha (chronic hepatitis C), low molecular weight heparin (blood clotting, deep vein thrombosis), PYY (obesity), LHRH antagonists (fertility), LH (luteinizing hormone), ghrelin antagonists (obesity), KGF (Parkinson's), GDNF (Parkinsons), G-CSF (erythropoiesis in cancer), Imitrex (migraine), Integrelin (anticoagulation), Natrecor® (congestive heart failure), human B-type natriuretic peptide (hBNP), SYNAREL® (Searl; nafarelin acetate nasal solution), Sandostatin (growth hormone replacement), Forteo (osteoporosis), DDAVP® Nasal Spray (desmopressin acetate), Cetrotide® (cetrorelix acetate for injection), Antagon™ (ganirelix acetate), Angiomax (bivalirudin; thrombin inhibitor), Accolate® (zafirlukast; injectable), Exendin-4 (Exanatide; diabetes), SYMLIN® (pramlintide acetate; synthetic amylin; diabetes), desmopressin, glucagon, ACTH (corticotrophin), C-peptide of insulin, GHRH and analogs (GnRHa), growth hormone releasing hormone, oxytocin, corticotropin releasing hormone (CRH), atrial natriuretic peptide (ANP), thyroxine releasing hormone (TRHrh), follicle stimulating hormone (FSH), prolactin, tobramycin ocular (corneal infections), Vasopressin, desmopresin, Fuzeon (Roche; HIV fusion inhibitor MW 4492), and Eptifibatide.

[0071] Further, it will be understood by one skilled in the art, that the specific dose level and frequency of dosage for any particular subject in need of treatment may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0072] It has been shown that alkyl glycosides, particularly alkylmaltosides and more specifically, dodecylmaltoside (DDM) and tetradecylmaltoside (TDM), stabilize insulin in solution and prevent aggregation of the peptide. Hovgaard et al., "Insulin Stabilization and GI absorption," *J. Control. Rel.*, 19 (1992) 458-463, *cited in* Hovgaard et al., "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132 (1996) 107-113 (hereinafter, "Hovgaard-1"). Further, Hovgaard-1 shows that even after 57 days, the DDM-insulin complex remained stable and possessed

nearly full biological activity. It is postulated that the stability of the complex is due to the length of the alkyl group (number of carbon atoms) and the higher ratio of DDM to insulin ratio the better (e.g. 4:1 and 16:1; see FIG. 1 in Hovgaard 1). However, according to Hovgaard-1, although the DDM-insulin complex was stable, the same stability was not shown for other maltosides. Yet, in a related study, Hovgaard et al.(1996) demonstrated that when DDM-insulin was orally administered to animals *in vivo*, bioavailability of the complex was weak (e.g. 0.5% - 1% bioavailability). Hovgaard et al., "Stabilization of insulin by alkylmaltoside. B. Oral absorption in vivo in rats," *Int. J. Pharmaceutics* 132 (1996) 115-121 (Hovgaard-2). Hence, an improved aspect of the invention is that the surfactant increases the bioavailability of a drug to the target tissues, organs, system etc., as well as increase drug stability.

[0073] Accordingly, one aspect of the invention is to provide therapeutic compositions having at least one drug and one surfactant, wherein the surfactant further consists of at least one alkyl glycoside and/or saccharide alkyl ester formulation which enhances the bioavailability of the drug. Determining the bioavailability of drug formulations is described herein. As used herein, "bioavailability" is the rate and extent to which the active substance, or moiety, which reaches the systemic circulation as an intact drug. The bioavailability of any drug will depend on how well is adsorbed and how much of it escapes being removed from the liver.

[0074] To determine absolute bioavailability, the tested drug and mode of administration is measured against an intravenous reference dose. The bioavailability of the intravenous dose is 100% by definition. For example, animals or volunteering humans are given an intravenous injections and corresponding oral doses of a drug. Urinary or plasma samples are taken over a period of time and levels of the drug over that period of time are determined.

[0075] The areas under the curve (AUC), of the plasma drug concentration versus time curves, are plotted for both the intravenous and the oral doses, and calculation of the bioavailability of both formulations is by simple proportion. For example, if the same intravenous and oral doses are given, and the oral AUC is 50% of the intravenous AUC, the bioavailability of the oral formulation is 50%. Note that the bioavailability of any drug is due to many factors including incomplete absorption, first pass clearance or a

combination of these (discussed more below). Further, the peak concentration (or C_{max}) of the plasma drug concentration is also measured to the peak concentration (C_{max}) of the plasma drug concentration following intramuscular (IM) injection of an equivalent concentration the drug. Moreover, the time to maximal concentration (or t_{max}) of the plasma drug is about 0.1 to 1.0 hours.

[0076] To determine the relative bioavailability of more than one formulation of a drug (e.g. an alkyl glycoside or saccharide alkyl ester drug formulation), bioavailability of the formulations are assessed against each other as one or both drugs could be subject to first pass clearance (discussed more below) and thus undetected. For example, a first oral formulation is assessed against a second oral formulation. The second formulation is used as a reference to assess the bioavailability of the first. This type of study provides a measure of the relative performance of two formulations in getting a drug absorbed.

[0077] Bioavailabilities of drugs are inconsistent and vary greatly from one drug to the next. For example, the bioavailability of MIACALCIN® (salmon calcitonin from Novartis) nasal spray, a prescription medication for the treatment of postmenopausal osteoporosis in women, has a mean bioavailability of about 3% (range is 0.3%-30.6%; see FIG. 1). The MIACALCIN® product information sheet can be found on the world wide web at miacalcin.com/info/howWorks/index.jsp and drugs.com/PDR/Miacalcin_Nasal_Spray.html. The data on MIACALCIN®, which was obtained by various investigators using different methods and human subjects, show great variability in the drug's bioavailability, e.g. in normal volunteers only ~3% of the nasally administered dose is bioavailable, as compared to the same dose administered by intramuscular injection (MIACALCIN® product insert). This represents two orders of a magnitude in variability and is undesirable to the consumer.

[0078] Poor bioavailability of a drug can also be observed in NASCOBAL® (Nastech), or cyanocobalamin, which is used for the treatment and maintenance of the hematologic status of patients who are in remission following intramuscular vitamin B_{12} therapies. The gel formulation was administered intranasally and the bioavailability of B_{12} was compared to intramuscular B_{12} injections. The peak concentrations of B_{12} (or the Tmax) was reached in 1-2 hours after intranasal administration, and relative to the

intramuscular injection, the bioavailability of B_{12} nasal gel was found to be about 8.9% (90% confidence intervals, 7.1% to 11.2%).

[0079] The alkyl glycosides or sucrose esters of the present invention include any compounds now known or later discovered. Drugs which are particularly well suited for admixture with the alkyl glycosides and/or saccharide alkyl esters of the invention are those that are difficult to administer by other methods, e.g. drugs that are degraded in the gastrointestinal (GI) tract or those that are not absorbed well from the GI tract, or drugs that can be self-administered via the ocular, nasal, nasolacrimal, inhalation, or CSF delivery route instead of traditional methods such as injection. Some specific examples include peptides, polypeptides, proteins, nucleic acids and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent. Other compounds include, for example, nicotine, interferon (e.g., alpha, beta, gamma), PYY, GLP-1, synthetic exendin-4 (Exenatide), parathyroid hormone, and human growth hormone or other low molecular weight peptides and proteins.

[0080] Alternatively, bioavailability of a drug can be determined by measuring the levels of the drug's first pass clearance by the liver. Alkyl glycosides and/or saccharide alkyl ester compositions of the invention administered intranasally or via oral cavity (sublingual or Buccal cell) do not enter the hepatic portal blood system, thereby avoiding first pass clearance by the liver. Avoiding first past clearance of these formulations by the liver is described herein. The term, "first pass liver clearance" is the extent to which the drug is removed by the liver during its first passage in the portal blood through the liver to the systemic circulation. This is also called first pass metabolism or first pass extraction.

[0081] The two major routes of drug elimination from the body are excretion by the kidneys whereby the drug is unchanged; and elimination by the liver, whereby the drug is metabolized. The balance between these two routes depends on the relative efficiency of the two processes. The present invention describes herein elimination by the liver or liver clearance. First pass liver clearance is described by Birkett et al (1990 and 1991), which

is incorporated by reference in its entirety. Birkett et al., *Aust Prescr,* 13(1990):88-9; and Birkett et al., *Austra Prescr* 14:14-16 (1991).

[0082] Blood carrying drug from the systemic circulation enter the liver via the portal vein, and the liver in turn extracts a certain percentage or ratio (i.e. 0.5 or 50%) of that drug. The remainder left over (i.e. 0.2 or 20%) re-enters the systemic circulation via the hepatic vein. This rate of clearance of the drug is called the hepatic extraction ratio. It is the fraction of the drug in the blood which is irreversibly removed (or extracted) during the first pass of the blood through the liver. If no drug is extracted, the hepatic extraction ratio is zero. Conversely, if the drug is highly extracted in the first pass through the liver, the hepatic extraction ratio may be as high as 100% or 1.0. In general, clearance of the drug by the liver depends then on the rate of delivery of that drug to the liver (or the hepatic blood flow), and on the efficiency of removal of that drug (or the extraction ratio).

[0083] Therefore, the net equation used to determine hepatic clearance is:

(hepatic clearance – blood flow) = (unbound fraction * intrinsic clearance) / blood flow + (unbound fraction * intrinsic clearance) **(1)**

[0084] The "unbound fraction" of drug is dependent on how tightly the drug is bound to proteins and cells in the blood. In general, it is only this unbound (or free) drug which is available for diffusion from the blood into the liver cell. In the absence of hepatic blood flow and protein binding, the "intrinsic clearance" is the ability of the liver to remove (or metabolize) that drug. In biochemical terms, it is a measure of liver enzyme activity for a particular drug substrate. Again, although intrinsic clearance can be high, drugs cannot be cleared more rapidly than that presented to the liver. In simple terms, there are two situations: where liver enzyme activity is very high or very low (i.e. high extraction ratio or low extraction ratio).

[0085] When liver enzyme activity is low, the equation simplifies to:

hepatic clearance = unbound fraction * intrinsic clearance **(2)**

[0086] Clearance then is independent of blood flow, but instead depends directly on the degree of protein binding in the blood and the activity of drug metabolizing enzymes towards that drug.

[0087] In contrast, when liver enzyme activity is high, the equation is:

hepatic clearance = liver blood flow (3)

[0088] In this scenario, because the enzymes are so active the liver removes most of the drug presented to it and the extraction ratio is high. Thus, the only factor determining the actual hepatic clearance is the rate of supply of drug to the liver (or hepatic blood flow)..

[0089] First pass liver clearance is important because even small changes in the extraction of drugs can cause large changes in bioavailability. For example, if the bioavailability of drug A by oral administration is 20% by the time it reaches the systemic circulation, and the same drug A by intravenous administration is 100%, absent no other complicating factors, the oral dose will therefore have to be 5 times the intravenous dose to achieve similar plasma concentrations.

[0090] Secondly, in some instances where liver enzyme activity is very high, drug formulations should be designed to have the drug pass directly through to the systemic circulation and avoid first pass liver clearance all together. For example, drugs administered intranasally, sublingual, buccal, rectal, vagina, etc. directly enter the systemic circulation and do not enter the hepatic portal blood circulation to be partially or fully extracted by the liver. Alternatively, where drugs cannot be administered by the above means, a tablet with at least one enteric-coating layer to prevent release of the drug in the stomach (i.e. highly acidic environment) is provided. Thus, an objective of the invention is to administer drugs using these alternative routes.

[0091] Additionally, first pass liver clearance is an important factor because many patients are on more than one drug regimen, and this may cause drug interactions which increase or decrease liver enzyme activity; thereby increasing or decreasing metabolism (increasing or decreasing the hepatic extraction ratio) of the drug of interest.

[0092] Hence, therapeutic compositions of the invention can be administered directly to the systemic circulatory system and avoid first pass liver clearance. .Avoiding first pass clearance assures that more of the drug will be available to the system. Stated another way, by avoiding first pass liver clearance, the bioavailability of the drug is increased.

[0093] The present invention also relates to methods of increasing absorption of a low molecular compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation, or the CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

[0094] The composition formulation is appropriately selected according to the administration route, such as oral administration (oral preparation), external administration (e.g., ointment), injection (preparations for injection), and mucosal administration (e.g., buccal and suppository) etc. For example, excipients (e.g., starch, lactose, crystalline cellulose, calcium lactate, magnesium aluminometasilicate and anhydrous silicate), disintegrators (e.g., carboxymethylcellulose and calcium carboxymethylcellulose), lubricants (e.g., magnesium stearate and talc), coating agents (e.g., hydroxyethylcellulose), and flavoring agents can be used for oral and mucosal formulations; whereas, solubilizers and auxiliary solubilizers capable of forming aqueous injections (e.g., distilled water for injection, physiological saline and propylene glycol), suspending agents (e.g., surfactant such as polysorbate 80), pH regulators (e.g., organic acid and metal salt thereof) and stabilizers are used for injections; and aqueous or oily solubilizers and auxiliary solubilizers (e.g., alcohols and fatty acid esters), tackifiers (e.g., carboxy vinyl polymer and polysaccharides) and emulsifiers (e.g., surfactant) are used for external agents. The drug and the alkyl glycoside can be admixed, mixed, or blended along with the above excipients, disintegrators, coating polymers, solubilizers, suspending agents, etc., prior to administration, or they can be administered sequentially, in either order. It is preferred that they be mixed prior to administration.

[0095] The term, "mucosal delivery-enhancing agent" includes agents which enhance the release or solubility (e.g., from a formulation delivery vehicle), diffusion rate, penetration capacity and timing, uptake, residence time, stability, effective half-life, peak or sustained concentration levels, clearance and other desired mucosal delivery characteristics (e.g., as measured at the site of delivery, or at a selected target site of activity such as the bloodstream or central nervous system) of a compound(s) (e.g., biologically active compound). Enhancement of mucosal delivery can occur by any of a variety of mechanisms, including, for example, by increasing the diffusion, transport, persistence or stability of the compound, increasing membrane fluidity, modulating the

availability or action of calcium and other ions that regulate intracellular or paracellular permeation, solubilizing mucosal membrane components (e.g., lipids), changing non-protein and protein sulfhydryl levels in mucosal tissues, increasing water flux across the mucosal surface, modulating epithelial junction physiology, reducing the viscosity of mucus overlying the mucosal epithelium, reducing mucociliary clearance rates, and other mechanisms.

[0096] Exemplary mucosal delivery enhancing agents include the following agents and any combinations thereof:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the compound for

enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

[0097] Additional mucosal delivery-enhancing agents include, for example, citric acid, sodium citrate, propylene glycol, glycerin, ascorbic acid (e.g., L-ascorbic acid), sodium metabisulfite, ethylenediaminetetraacetic acid (EDTA) disodium, benzalkonium chloride, sodium hydroxide, and mixtures thereof.

[0098] Therapeutic agents or drugs of the present invention can be peptides or proteins, medically or diagnostically useful, of small to medium size, e.g. up to about 15 kD, 30 kD, 50 kD, 75 kD, etc., or a protein having between about 1-300 amino acids or more. The methods of the invention also anticipate the use of small molecules, for example, an organic compound that has a molecular weight of less than 3 kD, or less than 1.5 kD.

[0099] The mechanisms of improved drug absorption according to the invention are generally applicable and should apply to all such peptides or protein, although the degree to which their absorption is improved may vary according to the molecular weight (MW) and the physico-chemical properties of the peptide or protein, and the particular enhancer used. Examples of peptides or protein include vasopressin, vasopressin polypeptide analogs, desmopressin, glucagon, corticotropin (ACTH), gonadotropin, calcitonin, C-peptide of insulin, parathyroid hormone (PTH), growth hormone (HG), human growth hormone (hGH), growth hormone releasing hormone (GHRH), oxytocin, corticotropin releasing hormone (CRH), somatostatin or somatostatin polypeptide analogs, gonadotropin agonist or gonadotrophin agonist polypeptide analogs, human atrial natriuretic peptide (ANP), human thyroxine releasing hormone (TRH), follicle stimulating hormone (FSH), and prolactin.

[0100] One preferred composition of the invention is the peptide drug is Exenatide (or exendin-4) and an alkyl glycoside. Exenatide is a synthetic version of exendin-4, and has been used in clinical trials by Amylin™ Pharmaceuticals. Exendin-4 is a low molecular weight peptide that is the first of a new class of therapeutic medications known as incretin mimetic agents or hormones. Incretin hormones are any of various gastrointestinal (GI)

hormones and factors that act as potent stimulators of insulin secretion, e.g. as gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), or Exenatide, or exendin-4, or equivalents thereof.

[0101] Exendin-4 is a naturally occurring 39-amino acid peptide isolated from salivary secretions of the Gila Monster Lizard. Eng et al., "Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas," *J. Biol. Chem.* 267(15):7402-7405(1992). Exenatide exhibits similar glucose lowering actions to glucagons like peptide, or GLP-1. Exenatide is being investigated for its potential to address important unmet medical needs of many people with type 2 diabetes. Clinical trials suggest that Exenatide treatment decreases blood glucose toward target levels and is associated with weight loss. The effects on glucose control observed with Exenatide treatment are likely due to several actions that are similar to those of the naturally occurring incretin hormone GLP-1 (see Example 7). These actions include stimulating the body's ability to produce insulin in response to elevated levels of blood glucose, inhibiting the release of glucagon following meals and slowing the rate at which nutrients are absorbed into the bloodstream. In animal studies Exenatide administration resulted in preservation and formation of new beta cells, the insulin-producing cells in the pancreas, which fail as type 2 diabetes progresses.

[0102] Use of Exenatide, incretin mimetic agents or equivalents thereof can be used to treat various forms of diabetes including but not limited to brittle diabetes, chemical diabetes or impaired glucose tolerance, gestational diabetes, diabetes insipidus, diabetes insipidus central, diabetes insipidus nephrogenic, diabetes insipidus pituitary, latent diabetes, lipatrophic diabetes, maturity-onset diabetes of youth (MODY), diabetes mellitus (DM), diabetes mellitus adult-onset (type 2 DM), diabetes mellitus insulin-dependent (IDDM, or type 1 DM), diabetes mellitus non-insulin dependent (NIDDM), diabetes mellitus juvenile or juvenile-onset, diabetes mellitus ketosis-prone, diabetes mellitus ketosis-resistant, diabetes mellitus malnutrition-related (MRDM), diabetes mellitus tropical or tropical pancreatic, diabetes mellitus, preclinical diabetes, or diabetes induced by various drugs e.g. thiazide diabetes, steroid diabetes, or various diabetes animal model including but not limited to alloxan diabetes and puncture diabetes.

[0103] In another aspect, therapeutic compositions of the invention are used to treat obesity. Obesity is a common problem in both adults and adolescents. For example, PYY3-36 (or AC162352) is a hormone that plays a critical role in decreasing appetites. The gut hormone fragment peptide PYY3–36 (PYY) reduces appetite and food intake when infused into subjects of normal weight. Similar to the adipocyte hormone, leptin, PYY reduces food intake by modulating appetite circuits in the hypothalamus. However, in obese patients there is a resistance to the action of leptin, thereby limiting leptin's therapeutic effectiveness. Still other studies show that PYY reduces food intake. Injection of PYY revealed that they eat on average 30% less than usual, resulting in weight loss. Hence, PYY 3-36 has potential as a treatment for obesity. Amylin™ Pharmaceuticals submitted an Investigational New Drug application for PYY 3-36 in 2003.

[0104] Compounds whose absorption can be increased by the method of this invention include any compounds now known or later discovered, in particular drugs, or therapeutic compounds, molecules or agents that are difficult to administer by other methods, for example, drugs that are degraded in the gastrointestinal (GI) tract or that are not absorbed well from the GI tract, or drugs that subjects could administer to themselves more readily via the ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route than by traditional self-administration methods such as injection. Some specific examples include peptides, polypeptides, proteins and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent. Other compounds include, for example, nicotine, interferon (e.g., alpha, beta, gamma), PYY, GLP-1, synthetic exendin-4 (Exenatide), parathyroid hormone (PTH), and human growth hormone or other low molecular weight peptides and proteins.

[0105] Further, the therapeutic compositions of the invention also contemplate non-peptide drugs or therapeutic agents. For example, in U.S. Pat. No. 5,552,534, non-peptide compounds are disclosed which mimic or inhibit the chemical and/or biological activity of a variety of peptides. Such compounds can be produced by appending to certain core species, such as the tetrahydropyranyl ring, chemical functional groups which cause the compounds to be at least partially cross-reactive with the peptide. As will be recognized,

compounds which mimic or inhibit peptides are to varying degrees cross-reactivity therewith. Other techniques for preparing peptidomimetics are disclosed in U.S. Pat. Nos. 5,550,251 and 5,288,707. The above U.S. patents are incorporated by reference in their entirety.

[0106] The method of the invention can also include the administration, along with the alkyl glycoside and a protein or peptide, a protease or peptidase inhibitor, such as aprotinin, bestatin, alpha$_1$ proteinase inhibitor, soybean trypsin inhibitor, recombinant secretory leucocyte protease inhibitor, captopril and other angiotensin converting enzyme (ACE) inhibitors and thiorphan, to aid the protein or peptide in reaching its site of activity in the body in an active state (i.e., with degradation minimal enough that the protein is still able to function properly). The protease or peptidase inhibitor can be mixed with the alkyl glycoside and drug and then administered, or it can be administered separately, either prior to or after administration of the glycoside or drug.

[0107] The invention also provides a method of lowering blood glucose level in a subject comprising administering a blood glucose-reducing amount of a composition comprising insulin and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of insulin and lowering the level of blood glucose. A "blood glucose-reducing amount" of such a composition is that amount capable of producing the effect of reducing blood glucose levels, as taught herein. Preferred is an amount that decreases blood glucose to normoglycemic or near normoglycemic range. Also preferred is an amount that causes a sustained reduction in blood glucose levels. Even more preferred is an amount sufficient to treat diabetes, including diabetes mellitus (DM) by lowering blood glucose level. Thus, the instant method can be used to treat diabetes mellitus. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

[0108] Also provided is a method of raising blood glucose level in a subject by administering a blood glucose-raising amount comprising glucagons and at least one alkyl glycoside and/or saccharide alkyl ester. When the composition includes insulin, it can be used to cause the known effect of insulin in the bloodstream, i.e., lower the blood glucose levels in a subject. Such administration can be used to treat diabetes mellitus, or related

diseases. A "blood glucose-raising amount" of glucagon in such a composition is that amount capable of producing the effect of raising blood glucose levels. A preferred amount is that which increases blood glucose to normoglycemic or near-normoglycemic range. Another preferable amount is that which causes a sustained rising of blood glucose levels. Even more preferred, is that amount which is sufficient to treat hypoglycemia by raising blood glucose level. Thus, this method can be used to treat hypoglycemia. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

[0109] Similarly, when this composition includes glucagon, it can be used to cause the known effect of glucagon in the bloodstream, i.e., to raise the blood glucose levels in a subject. Such administration can therefore be used to treat hypoglycemia, including hypoglycemic crisis.

[0110] The invention also provides methods for ameliorating neurological disorders which comprises administering a therapeutic agent to the cerebral spinal fluid (CSF). The term "neurological disorder" denotes any disorder which is present in the brain, spinal column, and related tissues, such as the meninges, which are responsive to an appropriate therapeutic agent. The surprising ability of therapeutic agents of the present invention to ameliorate the neurological disorder is due to the presentation of the therapeutic agent to persist in the cerebro-ventricular space. The ability of the method of the invention to allow the therapeutic agent to persist in the region of the neurological disorder provides a particularly effective means for treating those disorders.

[0111] It will be understood, however, that the specific dose level and frequency of dosage for any particular subject in need of treatment may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. Generally, however, dosage will approximate that which is typical for known methods of administration of the specific compound. For example, for intranasal administration of insulin, an approximate dosage would be about 0.5 unit/kg regular porcine insulin (Moses et al.). Dosage for compounds affecting blood glucose levels optimally would be that

required to achieve proper glucose levels, for example, to a normal range of about 5-6.7 mM. Additionally, an appropriate amount may be determined by one of ordinary skill in the art using only routine testing given the teachings herein (see Examples).

[0112] Furthermore, the compositions of the invention can be administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained release format. The spray and the aerosol can be achieved through use of the appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J. Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss.

[0113] The present invention is more particularly described in the following examples which are intended as illustrative only since numerous modifications and variations therein will be apparent to those skilled in the art. The following examples are intended to illustrate but not limit the invention.

EXAMPLE 1

ALKYL GLYCOSIDE AND/OR SUCROSE ESTER FORMULATIONS DO NOT CAUSE MUCOSA IRRITATION OR DISRUPTION

[0114] The nasal mucosa is highly vascularized and hence optimal for high drug permeation. Moreover, absorption of drug(s) through the nasal mucosa is available to the central nervous system (CNS). Although local application of drugs is desirable, a challenge for this method of administration is mucosal irritancy.

[0115] A formulation consisting of an alkyl glycoside (0.125% TDM) in a commercial over-the-counter (OTC) nasal saline was administered *in vivo* to human nasal epithelium over a period of over one month. The 0.125% TDM formulation is compared to the control, namely the same commercial (OTC) nasal saline, over the same period of time. Results show that during and after 33 days of daily TDM administration (i.e., the duration of the study), there is no observable irritation of the nasal mucosa (data not shown). Thus,

compositions of the invention are non-toxic and non-irritable providing repeated and long-term intranasal administration, which is beneficial for those patients with chronic and ongoing disease(s).

[0116] A similar test was performed using sucrose dodecanoate, a sucrose ester. Sucrose dodecanoate is administered *in vivo* to human nasal epithelium and during and after 47 days (i.e., the duration of the study), no observable irritation was detected (data not shown). Thus, these results show that alkyl glycosides and sucrose esters of the invention are non-toxic and do not cause mucosa irritation when administered daily over a long period of time.

EXAMPLE 2

ALKYL GLYCOSIDE AND/OR SUCROSE ESTER COMPOSITIONS STABILIZE DRUGS BY INCREASING DRUG BIOAVAILABILITY AND REDUCING DRUG BIOAVAILABILITY VARIANCE

[0117] Stability of the alkyl glycoside depends, in part, on the number of carbon atoms, or branching of the alkyl chain, with tetradecylmaltoside (TDM) having the greatest effect; but other highly branched alkyl chains including DDM also have stabilizing effects. In contrast to Hovgaard-1, which described the preference for a high alkyl glycoside to drug ratio, the instant invention shows that this ratio is much lower. For example, alkyl glycosides in the range of about 0.01% to about 6% by weight result in good stabilization of the drug; whereas Hovgaard-1 shows stabilization is only achieved at much higher ratios of alkyl glycosides to drug (10:1 and 16:1). Even more interesting, alkyl glycosides of the invention in the range of about 0.01% to about 6% have increased bioavailability (see FIG. 1). This is in sharp contrast to Hovgaard-2, which showed relatively low bioavailability (0.5-1%) at the high alkyl glycoside ratios (10:1 and 16:1).

[0118] Figure 1 is a graph comparing the bioavailability of the drug MIACALCIN® (salmon calcitonin from Novartis) with and without alkyl glycoside (TDM). MIACALCIN® is a nasal spray and administered directly onto the nasal epithelium or nasal mucosa. Figure 1 shows that MIACALCIN® minus alkyl glycoside has very low bioavailability levels in humans (MIACALCIN® product specification insert), as

compared to the MIACALCIN® with alkyl glycoside as administered to rats. More specifically, intranasal delivery of MIACALCIN® with 0.125% and 0.250% alkyl glycoside (TDM) resulted in about 43% to about 90% bioavailability, respectively. The bioavailability of intranasal administration of MIACALCIN® without alkyl glycoside is only about 3% in humans, and was undetectable in rats, suggesting that the rat is a stringent model for estimating intranasal drug absorption in humans. Thus, the alkyl glycoside of the invention enhances absorption and increases bioavailability of the drug.

[0119] Furthermore, besides increasing the bioavailability of the drug, the alkyl glycoside compositions of the invention effectively decrease the bioavailability variance of the drug. Figure 1 shows that administration of MIACALCIN® with alkyl glycoside (0.125% or 0.25%) intranasally has a bioavailability variance of +/- 8%, whereas the bioavailability variance without alkyl glycoside is 0.3% to 30%, or a two orders of magnitude change. The increase in bioavailability and the decrease in the bioavailability variance ensures patient-to-patient variability is also reduced. The results as shown in FIG. 1 are administered intranasally, however, similar results are expected for oral, buccal, vaginal, rectal, etc. delivery and at different alkyl glycoside concentrations.

[0120] Thus, contrary to the art, the alkyl glycoside compositions of the invention, in the range of about 0.01% to about 6% result in increased bioavailability and reduced bioavailability variance. This has not otherwise been reported.

EXAMPLE 3

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS INSULIN PRODUCES HYPOGLYCEMIC EFFECTS *IN VIVO*

[0121] Normal rats were anesthetized with a mixture of xylazine/ketamine to elevate their blood glucose levels. The elevated levels of D-glucose that occur in response to anesthesia provide an optimal system to measure the systemic hypoglycemic action of drug administration, e.g. insulin-containing eye drops. This animal model mimics the hyperglycemic state seen in diabetic animals and humans. In the experimental animal group, anesthetized rats are given eye drops containing insulin. Blood glucose levels from the experimental group are compared to anesthetized animals which received eye drops without insulin. The change in blood glucose levels and the differential systemic responses reflects the effect of insulin absorbed via the route of administration, e.g. ocular route.

[0122] Adult male Sprague-Dawley rats (250-350g) were fed *ad libitum*, and experiments were conducted between 10:00 a.m. and 3:00 p.m. Rats were anesthetized with a mixture of xylazine (7.5 mg/kg) and ketamine (50 mg/kg) given intraperitoneally (IP) and allowed to stabilize for 50-90 min before the administration of eye drops. Anesthesia of a normal rat with xylazine/ketamine produces an elevation in blood glucose values which provides an optimal state to determine the systemic hypoglycemic action of insulin-containing eye drops. Blood D-glucose values were measured by collecting a drop of blood from the tail vein at 5-10 min intervals throughout the experiment and applying the blood to glucometer strips (Chemstrip bG) according to directions provided with the instrument (Accu-Chek II, Boehringer Mannheim Diagnostics; Indianapolis, Ind.). Blood D-glucose values ranged from 200 to 400 mg/dl in anesthetized nondiabetic rats.

[0123] At time 0, after a 50-90 min stabilization period, rats were given 20 µl of eye drops composed of phosphate-buffered saline (PBS) with or without 0.2% regular porcine insulin and 0.125%-0.5% of the absorption enhancing alkyl glycoside (e.g. TDM) to be tested. Eye drops were instilled at time 0 using a plastic disposable pipette tip with the eyes held open, and the rat was kept in a horizontal position on a warming pad (37°C.) throughout the protocol. The rats were given additional anesthesia if they showed signs of awakening. Rats received in each eye 20 µl of 0.125-0.5% absorption enhancer in

phosphate buffered saline, pH 7.4 with (experimental) or without (control) 0.2% (50 U/ml) regular porcine insulin (Squibb-Novo, Inc.) for a total of 2 U per animal. Octyl-β-D-maltoside, decyl-β-D-maltoside, dodecyl-μ-D-maltoside, tridecyl-β-D-maltoside and tetradecyl-β-D-maltoside were obtained from Anatrace, Inc. (Maumee, Ohio). Hexylglucopyranoside, heptylglucopyranoside, nonylglucopyranoside, decylsucrose and dodecylsucrose were obtained from Calbiochem, Inc. (San Diego, Calif.); Saponin, BL-9 and Brij 78 were obtained from Sigma Chemical Co. (St. Louis, Mo.).

[0124] The D-glucose levels in the blood remained elevated when the animals received eye drops containing: 1) saline only; 2) 0.2% regular porcine insulin in saline only; or 3) absorption enhancer only. However, when rats received eye drops containing 0.2% regular porcine insulin and several alkylmaltoside or alkylsucrose compounds, a pronounced decrease in blood D-glucose values occurred and was maintained for up to two hours. Insulin administered ocularly with 0.5% dodecyl-β-D-maltoside (see Table I) or 0.5% decyl-β-D-maltoside (see Table III) results in a prompt and sustained fall in blood glucose levels which are maintained in the normoglycemic (80-120 mg/dl) or near-normoglycemic (120-160 mg/dl) range for the two hour duration of the experiment. Hence, at least two alkylmaltosides are effective in achieving sufficient absorption of insulin delivered via the ocular route to produce a prompt and sustained fall in blood glucose levels in experimentally hyperglycemic animals. The surfactant compositions of the invention are therefore useful to achieve systemic absorption of insulin and other peptides/proteins, e.g., glucagon and macromolecular drugs and heparin delivered via the ocular route in the form of eye drops.

[0125] Several other alkylmaltosides are also effective as absorption enhancers for ocular administration of insulin including 0.5% tridecylmaltoside (see Table III) and 0.125% (Table II) and 0.5% tetradecyl maltoside. These studies show that alkylmaltosides with the longer alkyl chains (or number of carbon atoms), e.g., dodecyl-, tridecyl- and tetradecyl-β-D-maltosides, are more effective. The increase in the number of carbon atoms also contributes to the greater hydrophobic/hydrophilic structural balance and absorption enhancing effect. The shorter alkyl chains (fewer carbon atoms) e.g., decylmaltoside, or no, e.g., octylmaltoside, produce less absorption enhancing activity. It is noted that the most effective alkylmaltosides produce effects comparable to or greater

than those seen with other absorption enhancers such as saponin, and with the added advantage that they can be metabolized to nontoxic products following systemic absorption.

[0126] The effects of the alkylmaltosides as absorption enhancers are dose-dependent, as can be seen by examining the effects of different concentrations ranging from 0.125-0.5% in producing a hypoglycemic effect when combined with insulin. Whereas, 0.5% and 0.375% dodecylmaltoside appear equally effective in achieving systemic absorption of insulin and reduction of blood glucose levels, 0.25% has a smaller and more transient effect and 0.125% is ineffective (Table I). Similarly, tridecylmaltoside also shows a dose-dependent effect in lowering blood glucose concentrations when combined with insulin, but the effect achieved with even 0.25% of the absorption enhance is sustained for the two hour time course of the experiment. Thus, dose-dependent effects of the alkylmaltosides suggest that they achieve enhancement of protein absorption via the ocular route in a graded fashion proportional to the concentration of the agent.

TABLE I

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	0.125%	0.25%	0.375%	0.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	144 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

[0127] The absorption enhancing effects of the alkyl saccharides were not confined to the alkylmaltosides alone since dodecylsucrose (0.125%, 0.25%, 0.375%) also shows a dose-dependent effect in producing ocular absorption of insulin and reduction in blood glucose levels. This effect is observed even at 0.125% alkyl saccharide (from 335 mg/dl.+-.26 mg/dl at time 0 min. to 150 mg/dl +-.44 mg/dl at time 120 min.). 0.5% decylsucrose was also effective in reducing blood glucose levels, but as shown for the alkylmaltosides, a reduction in the length of the alkyl chain, and hence the hydrophobic properties of the molecule, appears to reduce the potency of the alkylsucrose compounds. However, a significant and sustained reduction in blood glucose levels is achieved with 0.5% decylsucrose (from 313 mg/dl.+-.15 mg/dl at time 0 min. to 164 mg/dl+-.51 mg/dl at time 120 min.). The absorption enhancing abilities of alkyl saccharides with two distinct disaccharide moieties suggests that it is the physicochemical properties of the compounds which are crucial to their activity and that other alkyl saccharides, e.g., dodecyllactose, have the right balance of properties to be equally or more effective as absorption enhancers while retaining the metabolic and nontoxic properties of the alkylsaccharide enhancing agents. These alkyl saccharides are anticipated by the invention.

[0128] Studies with alkylglucosides were also conducted; 0.5% hexylglucoside and 0.5% heptylglucoside were ineffective at promoting insulin absorption from the eye, but 0.5% nonylglucoside effectively stimulated insulin absorption and reduced blood glucose levels (from 297 mg/dl to 150 mg/dl). This result once further supports that the alkyl chain length, as well as the carbohydrate moiety, play critical roles in effectively enhancing insulin absorption.

[0129] It should be noted that no damaging effects (i.e. non-irritants) to the ocular surface were observed with any of the alkylmaltoside or alkylsucrose agents employed in these studies. Furthermore, the prompt and sustained hypoglycemic effects produced by these agents in combination with insulin suggest that these absorption enhancers do not adversely affect the biological activity of the hormone, in keeping with their nondenaturing, mild surfactant properties.

[0130] Thus, therapeutic compositions on the invention consisting of at least an alkyl glycoside and a drug are stable and the alkyl glycosides enhance the absorption of the drug.

EXAMPLE 4

OCULAR AND INTRANASAL ADMINISTRATION OF TDM PLUS INSULIN PRODUCES HYPOGLYCEMIC EFFECTS *IN VIVO*

[0131] Since previous Examples showed that administration via eye drops of an absorption enhancer with drug e.g. insulin results in significant absorption of the drug via the nasolacrimal drainage system, therapeutically effective administration of insulin with alkylmaltosides, alkylsucrose and like agents by intranasal administration is tested herein.

[0132] Tetradecylmaltoside (TDM) in combination with insulin also produced a drop in blood D-glucose levels when administered in the form of a drop intranasally as well as via a drop by the ocular route. Eye drops containing 0.2% regular porcine insulin with 0.125% tetradecylmaltoside are administered to rats as previously described. The administration of the composition produces a prompt and prominent drop in blood glucose levels. The drop in blood glucose levels decrease even more by administration of a nose drop containing the same concentration of insulin with 0.5% tetradecylmaltoside

(Table II). Thus, intranasal delivery and administration of the alkyl saccharide with drug results in lowering of blood glucose levels.

TABLE II

Effect of Insulin Eye Drops, Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats

Time (min)	Blood Glucose (mg/dl)
-20	319
-10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops Added	
135	129
150	74
165	76
180	68

EXAMPLE 5

OCULAR ADMINISTRATION OF ALKYL SACCHARIDES PLUS INSULIN PRODUCES HYPERGLYCEMIC EFFECTS *IN VIVO*

[0133] Previous studies demonstrated that insulin absorption from the eye is stimulated by saponin, BL-9 and Brij-78. BL-9 and Brij-78 are ineffective at stimulating the absorption of glucagon from the eye, whereas saponin is effective. Glucagon absorption from the eye was measured in rats given eye drops containing various

surfactants plus glucagon (30 μg) (Eli Lilly, Indianapolis, Indiana) by monitoring an elevation in blood D-glucose levels. In these experiments, rats were anesthetized with sodium pentobarbital rather than xylazine/ketamin. This modification of the procedure resulted in basal blood glucose levels in the normoglycemic range and made it possible to readily monitor the hyperglycemic action of any glucagon absorbed from the eye.

[0134] Paired animals that receive eye drops containing the surfactant alone, or glucagon alone, were compared to animals receiving eye drops with the surfactant plus glucagon. When eyedrops containing 0.5% saponin plus glucagon are administered to rats, the level of D-glucose in blood rises significantly, but no such effect is observed with eye drops containing 0.5% BL-9 or 0.5% Brij-78 plus glucagon. Interestingly, when eye drops containing dodecylsucrose, decylmaltose or tridecylmaltose plus glucagon are administered to rats which were previously treated with eye drops containing these surfactant agents plus insulin, the glucagon is absorbed and blood D-glucose values increase significantly (Table III). This result confirms that ocular administration of certain alkylsaccharides can enhance the absorption of drugs, including glucagon and insulin. Moreover, it is now possible to treat for a hypoglycemic crisis using a formulation with at least an alkyl saccharide of the invention.

TABLE III

Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats

	Surfactant Agent		
	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
Time (min)	Blood Glucose Concentration (mg/dl)		
-20	266	249	255
-10	305	287	307
	Insulin Eye Drops Added		
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75
	Glucagon Eye Drops Added		
130	111	95	82
140	143	99	121
150	202	132	148
160	247	157	173
170	242	171	162
180	234	180	162
190	211	189	156

EXAMPLE 6

INTRANASAL ADMINISTRATION OF 0.25% TDM PLUS INSULIN DECREASES BLOOD GLUCOSE LEVELS *IN VIVO*

[0135] Intranasal administration of drugs or agents are possible in animal models e.g. mice and rats, although the nasal opening in is very small. In the experiments and results described herein, an anesthesia-induced hyperglycemia model was used (described in Examples above). Hyperglycemic animals were induced by an intraperitoneal (IP) injection containing xylazine-ketamine and blood glucose levels were monitored over a period of time. Immediately after the xylazine-ketamine injection, there was an increase

in the blood glucose levels as shown in FIG. 2 (closed dark circles), and blood glucose levels were about 450 mg/dl. The increase in blood glucose levels was attributed to the inhibition of pancreatic insulin secretion. Blood glucose levels peak to about 482 mg/dl by 30 minutes after the xylazine-ketamine injection (FIG. 2). Then, at approximately 33 minutes after the xylazine-ketamine injection, 6 μL of insulin (Humalog) in 0.25% tetradecylmaltoside (TDM; or Intravail A) was administered intranasally using a long thin micropipette tip, and blood glucose levels were monitored at about 15 minute intervals. After administration of the 0.25% TDM/insulin composition, there was a rapid decrease in blood glucose levels, reaching a low of about 80 mg/dl at about the 60 minute time point, or about 30 minutes after the insulin administration (FIG. 2). At about the 75 minute time point, blood glucose levels gradually returned to the baseline level in a normoglycemic mouse, or about 80-100 mg/dl.

[0136] The results above were compared with animals treated with insulin alone (same dosage), minus 0.25% TDM (FIG.2, open circles). The insulin only treatment showed blood glucose levels do not start to decline until at about the 120 minute time mark, or about 110 minutes after the insulin administration. Further, the blood glucose levels observed in animals treated with insulin alone never return to normoglycemic levels, as was observed in those animals receiving insulin plus 0.25%TDM (FIG. 2).

[0137] Thus, these results again demonstrate that compositions of the invention consisting of certain alkyl glycosides or alkyl saccharides plus a drug, e.g. insulin, effectively lower blood glucose levels, and that these effects are measurable shortly after administration of the drug.

EXAMPLE 7

INTRANASAL ADMINISTRATION OF 0.25% TDM (INTRAVAIL A) + EXENDIN-4 DECREASES BLOOD GLUCOSE LEVELS *IN VIVO*

[0138] The ob/ob mouse model was utilized for the studies described herein. Friedman, J. M. , *Nature* 404, 632-634 (2000). All animals received an intraperitoneal (IP) injection of a bolus of 2 g/kg glucose for purposes of determining glucose tolerance. At time 0 the experimental animals were given about 100 micrograms/kg of exendin-4/0.25% TDM (exendin-4 from American Peptide) either as 10 µl of nasal drops (FIG. 3; closed triangles), or by IP injection (FIG. 3; closed circles), or by and IP injection of saline alone (no drug, no TDM; FIG. 3; open circles). Control animals were previously performed and received no drugs. The results of this study are shown in FIG. 3.

[0139] Figure 3 shows that glucose tolerance of the animals were different since blood glucose levels vary at time 0 when the animals received the glucose bolus. Regardless, of the glucose tolerance level at time 0, immediately after injection of the glucose bolus, blood glucose levels increased in all three animals. The blood glucose level of the animal receiving the IP injection of saline alone does not decrease as rapidly as the experimental animals receiving the drug. Moreover, the animal receiving the IP injection of saline alone never reached a normoglycemic level (FIG.3, open circles). In contrast, the experimental animals, after administration of nasal drops of exendin-4/TDM, or IP injection of exendin-4/TDM, showed a rapid and immediate decrease in blood glucose levels.

[0140] Also exendin-4 administered about 15-30 minutes ahead of the glucose bolus (before time 0 in FIG. 3; data not shown) produced an even more pronounced lowering of blood glucose effect, because the absorption of the hormone takes a certain amount of time to be absorbed and to be active. Thus, exendin-4 (or Exenatide) which is currently in human clinical trials, when combined with alkyl glycosides of the invention, effectively treats a hyperglycemic condition by lowering the blood glucose levels of the hyperglycemic subject.

[0141] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference

into this application in order to more fully describe the state of the art to which this invention pertains.

Birkett et al., (1991) "Bioavailability and first pass clearance," *Austra Prescr* 14:14-16.

Birkett et al., (1990) "How drugs are cleared by the liver," *Austra Prescr* 3:88-89.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides: A spectroscopic evaluation," *Int. J. Pharmaceutics* 132:107-113.

Hovgaard et al., (1996) "Stabilization of insulin by alkylmaltosides. B. Oral absorption *in vivo* in rats," *Int. J. Pharmaceutics* 132:115-121.

Tetsuaki et al. (1997) "Lysis of *Bacillus subtilis* cells by glycerol and sucrose esters of fatty acids," *Applied and Environmental Microbiology,* 53(3):505-508.

Watanabe et al., (2000) "Antibacterial carbohydrate monoesters suppressing cell growth of *Streptococcus mutan* in the presence of sucrose," *Curr Microbiol* 41(3): 210-213.

[0142] Although the present process has been described with reference to specific details of certain embodiments thereof in the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

What is claimed is:

1. A surfactant composition comprising of at least one alkyl glycoside and/or at least one saccharide alkyl ester, and when admixed with a drug, the surfactant stabilizes the biological activity and increases the bioavailability, of the drug.

2. The composition of claim 1, wherein the drug is a peptide or a protein.

3. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level.

4. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 10 times higher than the daily intake amount of the surfactant.

5. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 100 times higher than the daily intake amount of the surfactant.

6. The composition of claim 1, wherein the surfactant has a high no observable adverse effect level at least 1000 times higher than the daily intake amount of the surfactant.

7. The composition of claim 1, wherein the surfactant is a physiological non-irritant.

8. The composition of claim 1, wherein the surfactant has from about 10 to 16 carbon atoms.

9. The composition of claim 1, wherein the surfactant and the drug are administered to subjects.

10. The composition of claim 1, wherein the surfactant and the drug are administered to humans.

11. The composition of claim 1, wherein the surfactant has anti-bacterial activity.

12. The composition of claim 1, wherein the surfactant and the drug do not enter the hepatic portal blood system.

13. The composition of claim 1, wherein the surfactant is stable for at least six months from about 4°C to 25°C.

14. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 20%.

15. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 5%.

16. The composition of claim 1, wherein the surfactant concentration is from about 0.01% to 2%.

17. A therapeutic composition comprising of at least one biologically active compound(s) and at least one surfactant, wherein the surfactant is further comprised of at least one alkyl glycoside and/or saccharide alkyl ester and wherein said composition stabilizes the biological activity of the drug, for at least about 6 months from about 4°C to 25°C.

18. The composition of claim 17, wherein the pH of the composition is less than 8.0.

19. The composition of claim 17, wherein the composition is stable for at least six months from about 4°C to 25°C.

20. The composition of claim 17, wherein the composition concentration is from about 0.01% to 20%.

21. The composition of claim 17, wherein the composition concentration is from about 0.01% to 5%.

22. The composition of claim 17, wherein the composition concentration is from about 0.01% to 2%.

23. A stable therapeutic composition according to claim 17, wherein the composition is formulated for mucosal administration to a subject.

24. A stable therapeutic composition according to claim 17, wherein the administration to the subject yields enhanced mucosal delivery of said biologically active compound(s) comprising:

a) a peak concentration (C_{max}) of said biologically active compound(s) in a CNS tissue or fluid or in a blood plasma of said subject that is about 15% or greater as compared to a peak concentration of the biologically active compounds in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject;

b) an area under concentration curve (AUC) of the biologically active compound(s) in the central nervous system (CNS) tissue or fluid or in the blood plasma of the subject that is 20% or greater compared to an AUC of biologically active compound(s) in CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to said subject; or

c) a time to maximal concentration (t_{max}) of the biologically active compound(s) in a central nervous system (CNS) tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

25. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS tissue or fluid or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

26. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields a peak concentration (C_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater as compared to a peak concentration of the biologically active compound(s) in the CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to the subject.

27. The therapeutic composition of claim 17, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active compound(s) in said CNS tissue or fluid or in a blood plasma of the subject that is 20% or greater compared to an AUC of said biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration or dose of said biologically active compound(s) to said subject.

28. The therapeutic composition of claim 17, wherein the composition following mucosal administration to the subject yields an area under concentration curve (AUC) of said biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject that is 50% or greater compared to an AUC of the biologically active compound(s) in said CNS or blood plasma following intramuscular injection of an equivalent concentration of the biologically active compound(s) to the subject.

29. The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.1 to 1.0 hours.

30. The pharmaceutical composition of claim 17, wherein the composition following mucosal administration to the subject yields a time to maximal plasma concentration (t_{max}) of the biologically active compound(s) in the CNS tissue or fluid or in the blood plasma of the subject between about 0.2 to 0.5 hours.

31. A method of administering a drug composition comprising of a surfactant having at least one alkyl glycoside and/or saccharide alkyl ester mixed with at least one drug and delivered to a subject, wherein the alkyl has from about 10 to 24 carbon atoms, and the surfactant increases the stability and bioavailability of the drug.

32. The method of claim 31, wherein the surfactant has a high no observable adverse effect level.

33. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 10 times higher than the daily intake amount of the surfactant.

34. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 100 times higher than the daily intake amount of the surfactant.

35. The method of claim 31, wherein the surfactant has a high no observable adverse effect level 1000 times higher than the daily intake amount of the surfactant.

36. The method of claim 31, wherein the surfactant reduces the bioavailability variance from patient to patient.

37. The method of claim 31, wherein the composition does not enter the hepatic portal blood system.

38. The method of claim 31, wherein the pH of the composition is less than 8.0.

39. The method of claim 31, wherein the composition is stable for at least six months from about 4°C to 25°C.

40. The method of claim 31, wherein the composition concentration is from about 0.01% to 20%.

41. The method of claim 31, wherein the composition concentration is from about 0.01% to 5%.

42. The method of claim 31, wherein the composition concentration is from about 0.01% to 2%.

43. The method of claim 31 wherein the composition is administered to the mucosal membranes or tissue of a subject.

44. The method of claim 1, wherein the composition is further comprised of an enteric coating.

45. The method of claim 1, wherein the alkyl glycoside is tetradecylmaltoside (TDM).

46. The method of claim 45, wherein the TDM has anti-bacterial activity.

47. A method of increasing absorption of a low molecular weight compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell), or CSF delivery route, the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, wherein the compound is selected from nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

48. The method of claim 47, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

49. The method of claim 47, wherein the alkyl has from 9 to 24 carbons.

50. The method of claim 49, wherein the alkyl has from 9 to 14 carbon atoms.

51. The method of claim 50, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

52. The method of claim 47, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

53. The method of claim 47, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

54. The method of claim 47, wherein the compound is a protein or a peptide.

55. The method of claim 54, and further comprising administering a protease or peptidase inhibitor.

56. The method of claim 47, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

57. The method of claim 47, wherein the composition is an intranasal spray.

58. The method of claim 47, wherein the administered dosage of the composition comprises a total volume of about 0.03 mL to about 0.3 mL per administered dose.

59. The method of claim 47, wherein the administered dosage of the composition comprises a total volume of about 0.1 mL per administered dose.

60. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 20 μg.

61. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per kg.

62. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 1% or greater than 1%.

63. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 0.5%.

64. The method of claim 47, wherein the composition is an intranasal spray.

65. The method of claim 47, wherein the composition comprises a total volume of about 0.03 mL to about 0.3 mL per administered dose.

66. The method of claim 47, wherein the composition comprises a total volume of about 0.1 mL per administered dose.

67. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per administered dose.

68. The method of claim 47, wherein the therapeutic effective amount of exendin-4 is from about 10 μg per kg.

69. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 1% or greater than 1%.

70. The method of claim 47, wherein the amount of Intravail alkyl glycoside is from about 0.01% to about 0.5%.

71. A method of claim 47, wherein the composition is administered within 60 minutes before a meal.

72. A method of claim 47, wherein the composition is in the form of a single or unit dose and comprising no preservatives.

73. A method of claim 47, wherein the compound further comprises a polymeric coating selected from a group consisting of a hydrophilic, hydrophobic or enteric coating.

74. A method of claim 47, wherein the coating is an enteric coating.

75. A method of claim 47, wherein the enteric coating is selected from selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate

copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof.

76. A method of treating diabetes comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a blood glucose reducing amount of a composition comprising an incretin mimetic agent or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby increasing the effectiveness of incretin mimetic agent or insulin and lowering the level of blood glucose and treating the diabetes in the subject.

77. The method of claim 76, wherein the subject has Type-2 diabetes.

78. The method of claim 76, wherein the subject is a human.

79. The method of claim 76, wherein the incretin mimetic is Exenatide.

80. A method of treating congestive heart failure in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a therapeutically effective amount of a composition comprising a GLP-1 peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

81. A method of treating obesity or diabetes associated with obesity in a subject comprising administering to a subject in need thereof via the oral, ocular, nasal, nasolacrimal, inhalation or pulmonary, or oral cavity (sublingual or Buccal cell) delivery route, a therapeutically effective amount of a composition comprising a PYY peptide or a functional equivalent thereof, and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, thereby treating the subject.

82. A method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject comprising administering via the oral, ocular, nasal, nasolacrimal, inhalation, pulmonary, oral cavity (sublingual, Buccal cell), or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the compound is not insulin, calcitonin, or glucagon.

83. The method of claim 82, wherein the compound has a molecular weight of less than about 15 kD.

84. The method of claim 82, wherein the compound is selected from vasopressin, a vasopressin polypeptide analog, desmopressin, glucagon, corticotropin, gonadotropin, C-peptide of insulin, parathyroid hormone, human growth hormone, growth hormone, growth hormone releasing hormone, oxytocin, corticotropin releasing hormone, somatostatin, a somatostatin polypeptide analog, gonadotropin agonist, a gonadotropin agonist polypeptide analog, atrial natriuretic peptide, thyroxine releasing hormone, follicle stimulating hormone, or prolactin.

85. The method of claim 82, wherein the compound is selected from a growth factor, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, or a polypeptide involved in the blood coagulation cascade.

86. A method of increasing absorption of a low molecular weight therapeutic compound into the circulatory system of a subject comprising administering via the oral,

ocular, nasal, nasolacrimal, inhalation or pulmonary, oral cavity (sublingual or Buccal cell) or CSF delivery route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide, wherein the compound is from about 1-30 kD, with the proviso that the subject does not have diabetes.

87. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of Exenatide in a pharmaceutically acceptable carrier.

88. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of GLP-1 in a pharmaceutically acceptable carrier.

89. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of nicotine in a pharmaceutically acceptable carrier.

90. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of interferon in a pharmaceutically acceptable carrier.

91. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of PYY in a pharmaceutically acceptable carrier.

92. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic

saccharide in combination with a therapeutically effective amount of parathyroid hormone in a pharmaceutically acceptable carrier.

93. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount of a peptide having a molecular weight of about 1-75 kD in a pharmaceutically acceptable carrier, with the proviso that the peptide is not insulin, calcitonin, and glucagon.

94. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a therapeutically effective amount erythropoietin in a pharmaceutically acceptable carrier.

95. A method as in claims 47-94 for ameliorating neurological disorder which comprises intranasal administration to the cerebrospinal fluid (CSF) of a subject with the disorder of a therapeutically effective amount of a therapeutic agent such that the therapeutic agent persists in the cerebro-ventricular space for a time sufficient to ameliorate the disorder.

96. A method for ameliorating neurological disorder which comprises intranasal administration to the cerebrospinal fluid (CSF) of a subject with the disorder of a therapeutically effective amount of a therapeutic agent as in claims 87-95 such that the therapeutic agent persists in the cerebro-ventricular space for a time sufficient to ameliorate the disorder.

97. A method of increasing absorption of a compound into the CSF of a subject comprising administering intranasally the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

98. The method of claim 97, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

99. The method of claim 97, wherein the alkyl has from 9 to 24 carbons.

100. The method of claim 97, wherein the alkyl has from 9 to 14 carbon atoms.

101. The method of claim 97, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

102. The method of claim 97, wherein the compound is a protein or a peptide.

103. The method of claim 102, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon.

104. The method of claim 97, and further comprising administering a protease or peptidase inhibitor.

105. The method of claim 97, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

106. A method of controlling caloric intake by administering a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of TDM alkyl saccharide.

107. A method of controlling blood glucose levels in a subject by administering to a subject a composition comprising a therapeutic effective amount of exendin-4, or related GLP-1 peptide, with an effective amount of Intravail alkyl saccharide.

108. A pharmaceutical composition comprising a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl group joined by a linkage to a hydrophilic saccharide in combination with a mucosal delivery-enhancing agent wherein the mucosal delivery-enhancing agent is selected from:

(a) an aggregation inhibitory agent;

(b) a charge-modifying agent;

(c) a pH control agent;

(d) a degradative enzyme inhibitory agent;

(e) a mucolytic or mucus clearing agent;

(f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from:

(i) a surfactant; (ii) a bile salt; (ii) a phospholipid additive, mixed micelle, liposome, or carrier; (iii) an alcohol; (iv) an enamine; (v) an NO donor compound; (vi) a long-chain amphipathic molecule; (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid; (x) a cyclodextrin or beta-cyclodextrin derivative; (xi) a medium-chain fatty acid; (xii) a chelating agent; (xiii) an amino acid or salt thereof; (xiv) an N-acetylamino acid or salt thereof; (xv) an enzyme degradative to a selected membrane component; (ix) an inhibitor of fatty acid synthesis; (x) an inhibitor of cholesterol synthesis; and (xi) any combination of the membrane penetration enhancing agents recited in (i) - (x);

(h) a modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, mucoadhesive, support or complex-forming species with which the compound is effectively combined, resulting in stabilization of the compound for enhanced nasal mucosal delivery, wherein the formulation of the compound with the intranasal delivery-enhancing agents provides for increased bioavailability of the compound in a blood plasma of a subject.

109. The pharmaceutical composition of claim 108, further comprising a plurality of intranasal delivery-enhancing agents.

110. The pharmaceutical composition of claim 108, wherein said mucosal delivery-enhancing agent(s) is/are selected from the group consisting of citric acid, sodium citrate,

propylene glycol, glycerin, L-ascorbic acid, sodium metabisulfite, EDTA disodium, benzalkonium chloride, sodium hydroxide and mixtures thereof.

111. The pharmaceutical composition of claim 108, wherein the alkyl has from 10 to 16 carbon atoms.

112. A method of increasing absorption of a low molecular weight compound into the circulatory system of a subject comprising administering, via the ocular, nasal, nasolacrimal, inhalation, or CSF delivery route (a) the compound; (b) an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide; and (c) a mucosal delivery-enhancing agent.

113. The method of claim 112, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

114. The method of claim 112, wherein the alkyl has from 9 to 24 carbons.

115. The method of claim 112, wherein the alkyl has from 9 to 14 carbon atoms.

116. The method of claim 112, wherein the alkyl has from 10 to 16 carbon atoms.

117. The method of claim 112, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

118. The method of claim 112, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

119. The method of claim 112, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

120. The method of claim 112, wherein the compound is a protein or a peptide.

121. The method of claim 112, wherein the method comprises a protease or peptidase inhibitor.

122. The method of claim 112, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

123. The method of claim 112, wherein the compound is selected from nicotine, interferon, PYY, GLP-1, synthetic exendin-4, parathyroid hormone, human growth hormone, or a small organic molecule.

124. A dosage dependent release composition comprising:

(a) a core comprising:

(i) at least one therapeutic agent or drug;

(ii) a surfactant comprising at least one alkyl glycoside and/or saccharide alkyl ester; and

(b) at least one membrane coating surrounding the core, wherein the coating is impermeable, permeable, semi-permeable or porous and becomes more permeable upon sustained contact with contents of the gastrointestinal tract.

125. The membrane coating of claim 124 further comprising an alkalizing agent and/or a plasticizer.

126. The composition of claim 124 wherein the core is in the form of a tablet, hard capsule or gel capsule.

127. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 7.

128. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 6.

129. The composition of claim 124, wherein release of the drug is in a pH between about 4 and 5.

130. The composition of claim 124, wherein the coating is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate malate, cellulose benzoate phthalate, cellulose propionate phthalate, methylcellulose phthalate, carboxymethylethylcellulose, ethylhydroxyethylcellulose phthalate, shellac, styrene-acrylic acid copolymer, methyl acrylate-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, butyl acrylate-styrene-acrylic acid copolymer, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methyl acrylate-methacrylic acid-octyl acrylate copolymer, vinyl acetate-maleic acid anhydride copolymer, styrene-maleic acid anhydride copolymer, styrene-maleic acid monoester copolymer, vinyl methyl ether-maleic acid anhydride copolymer, ethylene-maleic acid anhydride copolymer, vinyl butyl ether-maleic acid anhydride copolymer, acrylonitrile-methyl acrylate-maleic acid anhydride copolymer, butyl acrylate-styrene-maleic acid anhydride copolymer, polyvinyl alcohol phthalate, polyvinyl acetal phthalate, polyvinyl butylate phthalate and polyvinyl acetoacetal phthalate, or combinations thereof.

131. The composition of claim 124, wherein the drug is selected from a group consisting of insulin like growth factor-I (IGF-I), somatomedin-C (SM-C), insulin, calcitonin, leptin, leptin derived short peptide (OB-3), hGH, human parathyroid hormone (PTH), melatonin, GLP-1 or Glucagon-like peptide-1, GiP, pituitary adenylate cyclase-activating polypeptide (PACAP), GM-1 ganglioside, nerve growth factor (NGF), nafarelin, Synarel®, (D-tryp6)-LHRH, FGF, VEGF antagonists, VEGF agonist, leuprolide, interferon-alpha, low molecular weight heparin, PYY, LHRH antagonists, LH, ghrelin antagonists, KGF, GDNF, G-CSF, Imitrex, Integrelin, Natrecor®, human B-type natriuretic peptide (hBNP), SYNAREL®, Sandostatin, Forteo, DDAVP® Nasal Spray, Cetrotide®, Antagon™, Angiomax, Accolate®, Exendin-4, SYMLIN®, desmopressin, glucagon, ACTH, C-peptide of insulin, GHRH and analogs (GnRHa), growth hormone

releasing hormone, oxytocin, corticotropin releasing hormone (CRH), atrial natriuretic peptide (ANP), thyroxine releasing hormone (TRHrh), follicle stimulating hormone (FSH), prolactin, or tobramycin ocular.

132. The composition of claim 124, wherein the coating is a porous coating.

133. The composition of claim 124, further comprising a protease inhibitor.

134. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 24 carbon atoms.

135. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 20 carbon atoms.

136. The composition of claim 124, wherein the alkyl alkyl has from about 10 to 16 carbon atoms.

137. The composition of claim 124, wherein the alkyl group has from about 10 to 14 carbon atoms.

138. The composition of claim 124, wherein the alkyl glycoside is tetradecyl maltoside (TDM).

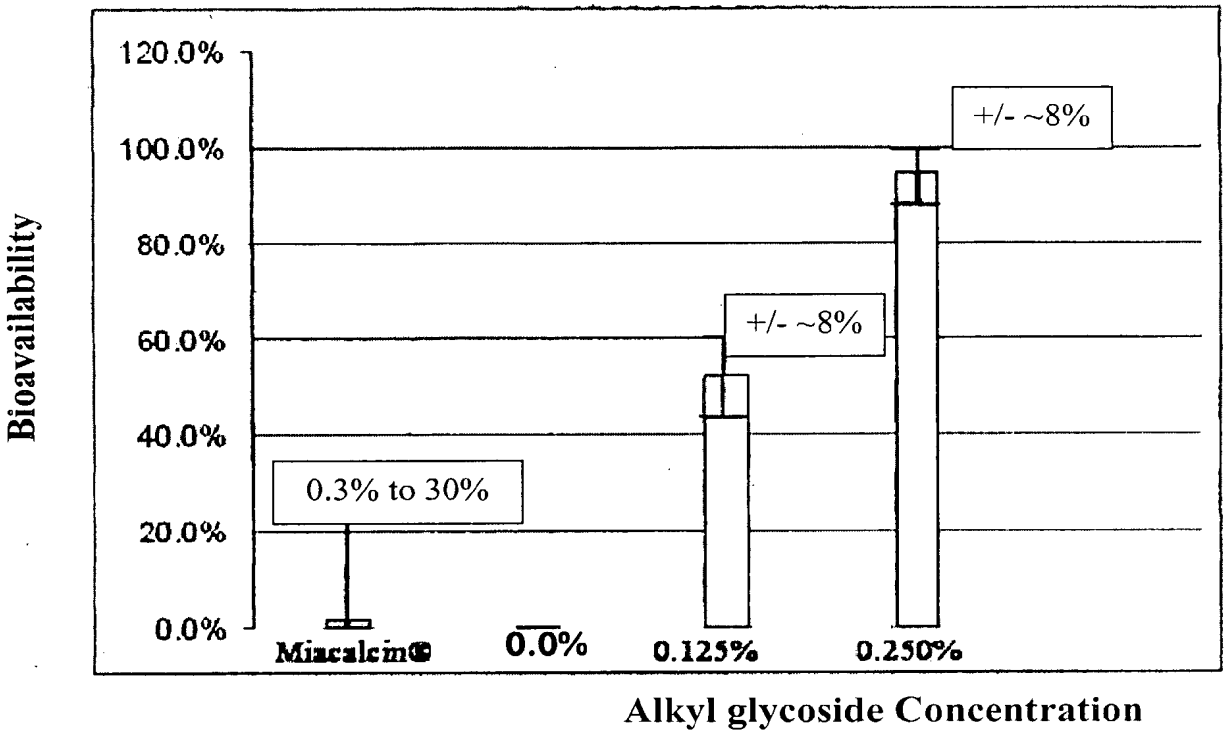

120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
Bioavailability
0.3% to 30%
+/- ~8%
+/- ~8%
Miacalcin®
0.0%
0.125%
0.250%
Alkyl glycoside Concentration

Figure 1

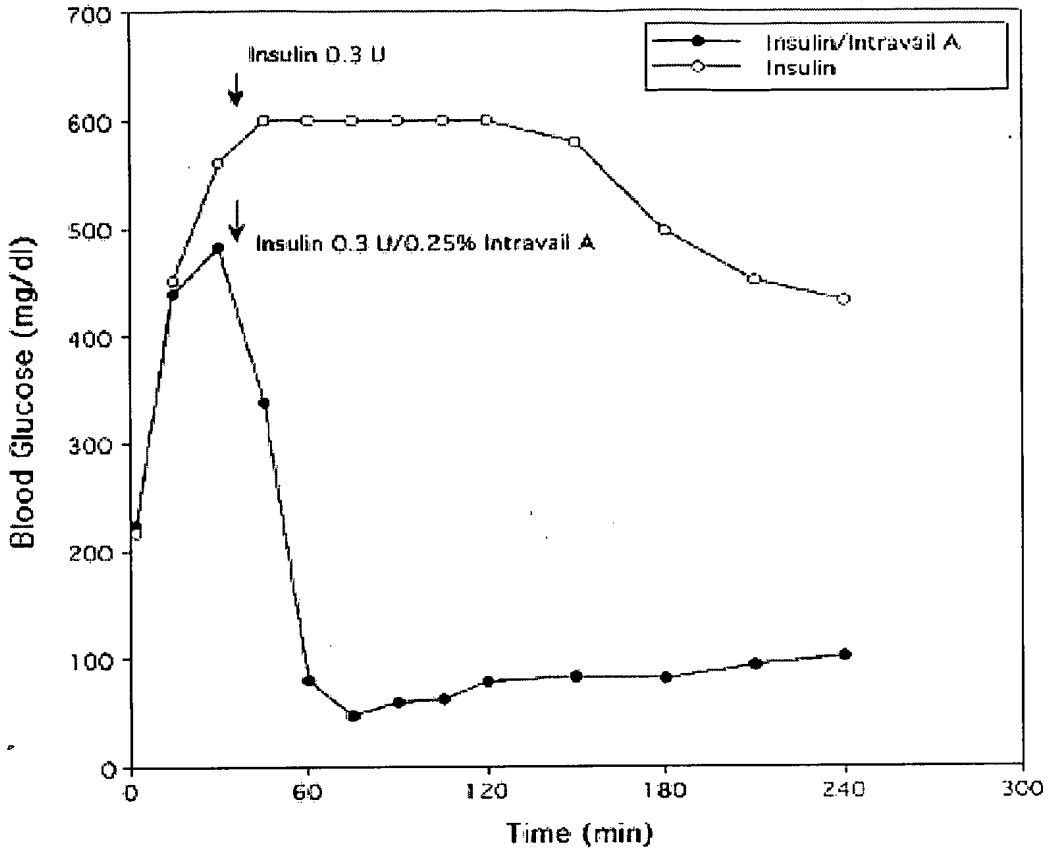

Insulin/Intravail A
Insulin
Insulin 0.3 U
Insulin 0.3 U/0.25% Intravail A
Blood Glucose (mg/dl)
Time (min)
0
100
200
300
400
500
600
700
0
60
120
180
240
300

Figure 2

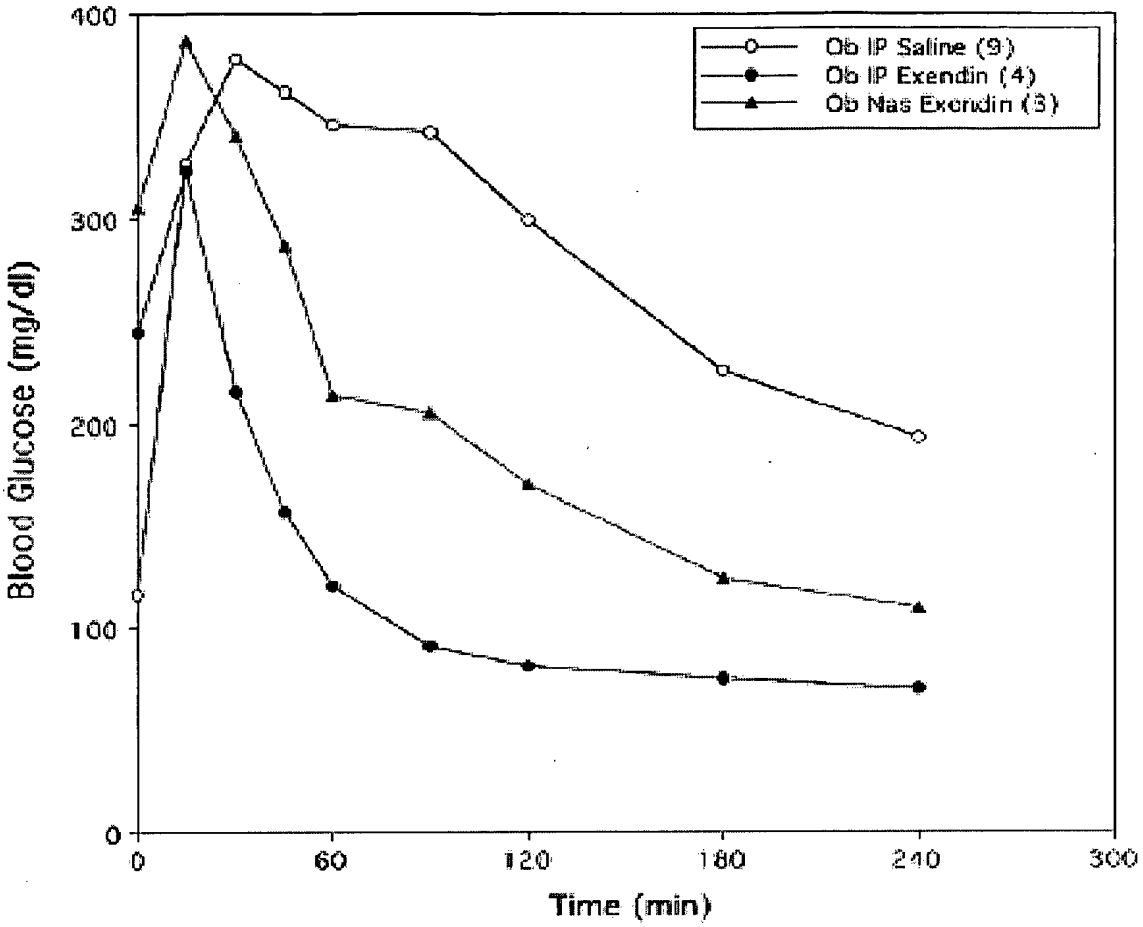

Ob IP Saline (9)
Ob IP Exendin (4)
Ob Nas Exendin (3)
Blood Glucose (mg/dl)
400
300
200
100
0
0
60
120
180
240
300
Time (min)

Figure 3

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 32103-714.601	**FOR FURTHER ACTION** See item 4 below	
International application No. PCT/US2008/062961	International filing date *(day/month/year)* 07 May 2008 (07.05.2008)	Priority date *(day/month/year)* 07 May 2007 (07.05.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant QUESTOR PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - ☐ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV — Lack of unity of invention
   - ☐ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☐ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 10 November 2009 (10.11.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MATTHEW V. GRUMBLING
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	04 AUG 2008
Applicant's or agent's file reference 32103-714.601	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/62961	07 May 2008 (07.05.2008)	07 May 2007 (07.05.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/55 (2008.04)
USPC - 514/220; 514/221

Applicant QUESTOR PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 July 2008 (25.07.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 3, 6, 10-13, 17-26, 46-60	YES
	Claims	1, 4, 5, 7-9, 14-16, 27-45, and 61-65	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1 - 65	NO
Industrial applicability (IA)	Claims	1 - 65	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 4, 5, 7-9, and 14-16 lack novelty under PCT Article 33(2) as being anticipated by US 2003/0181411 A1 to Bosch, et. al. (hereinafter 'Bosch').

As to claim 1, Bosch discloses a composition for nasal administration of a medicament (claim 6; para [0147]) comprising
-- a first population of particles having a first effective average particle size (claim 1; para [0070]-[0074]) and
-- a second population of particles having a second effective average particle size (claim 17; para [0070]-[0074]).
Bosch does not specifically disclose that the first effective average particle size is at least 1.5 times that of the second effective average particle size, but said limitation is inherently present in Bosch's disclosure. Bosch discloses that the first population of particles has an average size in the range of about 50 to about 500 nm (claim 1; para [0070]-[0074]) and the second population of particles has a average size in the range of about 2000 to about 10,000 nm (claim 17; para [0070]-[0074]), thereby disclosing the claimed limitation that the first effective average particle size is at least 1.5 times that of the second effective average particle size.

As to claim 4, Bosch further discloses a medicament where the particles in the medicament have an average size of greater than about 2,000 nm (claim 16; para [0043], [0070]).

As to claim 5, Bosch further discloses a medicament wherein the first population of particles is coated with at least one surface acting agent (claim 12, para [0073]).

As to claim 7, Bosch further discloses
-- the first population of particles has an average size in the range of about 50 to about 500 nm (claim 1; para [0070]-[0074]) and
-- the second population of particles has a average size in the range of about 2000 to about 10,000 nm (claim 17; para [0070]-[0074]).

As to claim 8, Bosch further discloses a pharmaceutical composition where the difference between the average particle size of the first and second populations is greater than about 100 nm (para [0116]-[0117]).

As to claim 9, Bosch further discloses a pharmaceutical composition, where the difference between the average particle size of the first and second particle populations is in a range greater than about 10% (para [0116]-[0117]).

As to claim 14, Bosch discloses:
-- a pharmaceutical particulate composition for nasal delivery of a medicament (claim 6; para [0147]) comprising
-- particulates having a multimodal particle size distribution (para [0072]).

As to claim 15, Bosch further discloses a composition where the particulates have a bimodal particle size distribution (claim 1, 17; para [0070]-[0074]).

As to claim 16, Bosch further discloses a composition where the particulates have a trimodal or higher order modal particle size distribution (para [0072]).

Claims 27-45 and 61-65 lack novelty under PCT Article 33(2) as being anticipated by US 2006/0198896 A1 to Liversidge, et. al. (hereinafter 'Liversidge').

As to claim 27, Liversidge discloses
-- an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles (claim 5), wherein:
-- the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 5); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 5).

As to claim 28, Liversidge further discloses a medicament with at least one benzodiazepine, specifically lorazepam (para [0001]).

As to claim 29, Liversidge further discloses an aerosol composition where the droplets of the aerosol have a mass median aerodynamic diameter of from about 2 mc.m to about 10 mc.m (claim 8).

********** SEE SUPPLEMENTAL SHEET TO CONTINUE **********

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 56 is objected to as lacking an antecedent basis for the "the non-aqueous dispersion or suspension." For the purpose of the search, claim 56 was construed as dependent from claim 46, not claim 53.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2):

As to claim 30, Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (para [0154]).

As to claim 31, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 32, Liversidge discloses
-- a method of administering a benzodiazepine drug to a patient (claim 13), comprising:
-- administering to the nose or nasal cavity an effective amount of an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles (claim 13), wherein
-- the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 17); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 16).

As to claim 33, Liversidge further discloses the use of clorazepam (claim 13).

As to claim 34, Liversidge further discloses a method where the nanoparticulate benzodiazepine drug particles have an effective average particle size of less than about 400 nm (claim 16).

As to claim 35, Liversidge further discloses a method where the droplets of the aerosol have a mass median aerodynamic diameter of from about 2 to about 10 mc.m (claim 20).

As to claim 36, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 37, Liversidge discloses a
-- pharmaceutical composition for nasal administration of benzodiazepine (para [0032]), comprising
-- benzodiazepine particles (claim 1) and
-- one or more surface active agents adsorbed to a surface thereof (claim 1).

As to claim 38, Liversidge further discloses the use of clorazepam (claim 1).

As to claim 39, Liversidge further discloses a pharmaceutical composition in the form of an aqueous suspension or dispersion (para [0033]).

As to claim 40, Liversidge further discloses a pharmaceutical composition in the form of a spray powder (para [0032]).

As to claim 41, Liversidge further discloses a pharmaceutical composition where the benzodiazepine particles have a average particle size less than approximately 50 nm to less than approximately 1000 nm (claim 4).

As to claim 42, Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (para [0154]).

As to claim 43, Liversidge discloses
-- a method of administering a benzodiazepine drug to a patient (claim 13), comprising
-- administering to the patient's nose or nasal cavity a pharmaceutical composition (para [0154]);
-- comprising particles of a benzodiazepine drug having a surface active agent adsorbed to a surface thereof (claim 13).

As to claim 44, Liversidge further discloses the use of clorazepam (claim 13).

As to claim 45, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 61, Liversidge discloses:
-- a nanoparticulate composition (claim 1) comprising:
-- (a) a benzodiazepine having an effective average particle size of less than about 2000 nm (claim 1)
-- wherein the benzodiazepine is selected from the group consisting of alprazolam (claim 1)
-- and (b) at least one surface stabilizer (claim 1).

As to claim 62, Liversidge further discloses the use of a surface stabilizer selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant (claim 2).

As to claim 63, Liversidge further discloses a composition wherein the surface stabilizer is hypromellose (claim 3).

••••••••••••••••••••••••••••••••••• SEE THE FOLLOWING SUPPLEMENTAL BOX TO CONTINUE •••

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2) and the preceding Supplemental Box:

As to claim 64, Liversidge further discloses the composition, as above, formulated as an injectable composition (claim 9).

As to claim 65, Liversidge discloses
-- a method of treating a subject in need (claim 13) comprising administering to the subject a nanoparticulate benzodiazepine composition comprising (claim 13);
-- a benzodiazepine having an effective average particle size of less than about 2000 nm (claim 13);
-- wherein the benzodiazepine is alprazolam (claim 13); and
-- at least one surface stabilizer (claim 13).

Claims 2-3, 6, 10-13, 17-26, and 46-60 lack an inventive step under PCT Article 33(3) as being obvious over Bosch, as above, in view of Liversidge.

As to claim 2, Bosch discloses the medicament of claim 1. Liversidge discloses at least one benzodiazepine (para [0001]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using at least one benzodiazepine in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]).

As to claim 3, Liversidge further discloses a medicament with at least one benzodiazepine, specifically lorazepam (para [0001]).

As to claim 6, Bosch further discloses a medicament wherein the composition comprises a third population of particles having a third average particle size distribution different from the first and second populations of particles (para [0072]). Liversidge discloses the use of benzodiazepines as nanoparticles in a medicament (para [0001]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using benzodiazepine in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of several average particle sizes in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a multi-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]).

As to claim 10, the combination of Bosch and Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (Bosch, para [0033], [0147]; Liversidge, para [0154]).

As to claim 11, Liversidge further discloses the use of the medicament for an anticonvulsant effect (para [0001], defined as 'treating status epilepticus').

As to claim 12, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a benzodiazepine plasma concentration maximum Cmax (para [0067]). While neither Liversidge nor Bosch specifically discloses the limitation of obtaining a Cmax twice; such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because the claimed combination is an obvious experimental procedure. A skilled artisan would be motivated to measure the Cmax more than once to attain reliable data.

As to claim 13, neither Liversidge nor Bosch specifically discloses the limitation of obtaining a Cmax twice; first from 1 to 30 minutes after administration of the composition, and second from 5 to 360 minutes after administration of the composition. However, such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because adding the step of measuring the Cmax twice in two discrete time intervals to the disclosures of Liversidge and Bosch is an obvious experimental procedure. A skilled artisan would be motivated to measure the Cmax more than once to attain reliable data. Furthermore, this claim limitation simply recites the definition of "normal experimentation," as applied to the Liversidge and Bosch disclosures.

As to claim 17, Bosch discloses the medicament of claim 14, as above. Liversidge further discloses at least one benzodiazepine (para [0001]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using at least one benzodiazepine in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]).

As to claim 18, Liversidge further discloses a medicament with at least one benzodiazepine, specifically lorazepam (para [0001]).

As to claim 19, Bosch further discloses a medicament where the particles in the medicament have an average size of greater than about 2,000 nm (claim 16; para [0043], [0070]).

As to claim 20, Bosch further discloses a bimodal particle size distribution that fall within the range of:
-- the first population of particles has an average size in the range of about 25 to about 4,000 nm (claim 1; para [0070]-[0074]) and
-- the second population of particles has a average size of about 500 to about 10,000 nm (claim 17; para [0070]-[0074]).

********** SEE THE FOLLOWING SUPPLEMENTAL BOX TO CONTINUE **********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2) and the preceding Supplemental Box:

As to claim 21, Bosch further discloses a bimodal particle size distribution that fall within the range of:
-- the first population of particles has an average size in the range of about 50 to about 2,000 nm (claim 1; para [0070]-[0074]) and
-- the second population of particles has a average size of about 1,000 to about 10,000 nm (claim 17; para [0070]-[0074]).

As to claim 22, the combination of Bosch and Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (Bosch, para [0033], [0147]; Liversidge, para [0154]).

As to claim 23, Liversidge further discloses the use of an effective amount of the composition is effectively used to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, or reduce or ameliorate the frequency of seizure (para [0001], defined as 'treating status epilepticus').

As to claim 24, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a first Cmax (para [0067]) occurring at a first Tmax after administration (para [0068], [0074]). While neither Liversidge nor Bosch specifically discloses the limitation of obtaining a Cmax and Tmax again at a later time; such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because the claimed combination is an obvious experimental procedure. A skilled artisan would be motivated to measure the Cmax and Tmax more than once to attain reliable data.

As to claim 25, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a benzodiazepine plasma concentration maximum Cmax (para [0067]). While neither Liversidge nor Bosch specifically discloses the limitation of obtaining a shoulder or Cshoulder; such a combination would be obvious to a skilled artisan practicing the Liversidge and Bosch disclosures through normal experimentation, because the claimed combination is an obvious statistical procedure. A skilled artisan would be motivated to measure the Cshoulder to attain reliable and useful data.

As to claim 26, Liversidge further teaches obtaining a benzodiazepine plasma concentration curve having a single plasma benzodiazepine concentration maximum Cmax (para [0067]).

As to claim 46, Bosch discloses the medicament of claim 1, as above. Liversidge discloses a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles (para [0036]). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles in the medicament taught by Bosch to formulate a medicament utilizing dry nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]). Further, the use of a non-aqueous dispersion is an obvious composition to use in an aerosol, and is also taught by Bosch (para [0187]).

As to claim 47, Liversidge further discloses the use of clorazepam (claim 1).

As to claim 48, Liversidge further discloses
-- droplets of nanoparticulate benzodiazepine particles (para [0036]), with
-- the droplets having a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 5); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 5).

As to claim 49, Liversidge further discloses a non-aqueous dispersion or suspension is adapted for nasal administration (para [0036], [0209]).

As to claim 50, Liversidge further discloses a dispersion or suspension further comprises at least one additional ingredient selected from the group consisting of active pharmaceutical ingredients and enhancers (para [0091]). Bosch also discloses the use of additional ingredient selected from the group consisting of active pharmaceutical ingredients (para [0037]).

As to claim 51, the combination of Bosch and Liversidge further discloses administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril (Bosch, para [0033], [0147]; Liversidge, para [0154]).

As to claim 52, Liversidge further discloses administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a composition as above (para [0209]).

As to claim 53, Bosch discloses the medicament of claim 1. Liversidge discloses an aqueous dispersion or suspension of nanoparticulate benzodiazepine particles (claim 5). It would have been obvious to a skilled artisan to combine the teachings of Bosch and Liversidge by using an aqueous dispersion or suspension of nanoparticulate benzodiazepine particles in the medicament taught by Bosch to formulate a medicament utilizing nanoparticles of more than one average particle size in the treatment of anxiety, insomnia, or seizure. The advantage of such a combination is the creation of a dual-release composition, where each population of particles exhibit a different rate of absorption, Cmax, and Tmax within the same medicament, as taught by Bosch (para [0070]-[0074]). Further, the use of an aqueous dispersion is an obvious composition to use in a spray, and is also taught by Bosch (para [0140]).

********** SEE THE FOLLOWING SUPPLEMENTAL BOX TO CONTINUE **********

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/62961

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
BOX V(2) and the preceding Supplemental Box:

As to claim 54, Liversidge further discloses the use of clorazepam (claim 1).

As to claim 55, Liversidge further discloses
-- an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles (claim 5), wherein:
-- the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 mc.m (claim 5); and
-- the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm (claim 5).

As to claim 56, Liversidge further discloses a non-aqueous dispersion or suspension adapted for nasal administration (para [0154]).

As to claim 57, Liversidge further discloses a dispersion or suspension further comprises at least one additional ingredient selected from the group consisting of active pharmaceutical ingredients and enhancers (para [0091]).

As to claim 58, Liversidge further discloses a method of using a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine as above, comprising administering an effective amount of the dispersion or suspension to the nose by administering a therapeutically effective amount of the composition to at least one nostril (para [0154]).

As to claim 59, Liversidge further discloses a method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a composition as above (para [0154]).

As to claim 60, Liversidge further discloses the use of lorazepam (para [0209]).

Claims 1-64 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 35401-716601	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2009/038696	International filing date *(day/month/year)* 27 March 2009 (27.03.2009)	Priority date *(day/month/year)* 28 March 2008 (28.03.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant HALE BIOPHARMA VENTURES, LLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 28 September 2010 (28.09.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Philippe Becamel e-mail: pt12.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
WILSON SONSINI GOODRICH & ROSATI

650 PAGE MILL ROAD PALO ALTO CA 94304 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)* **28 SEPTEMBER 2009 (28.09.2009)**

Applicant's or agent's file reference
35401-716601

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2009/038696	**27 MARCH 2009 (27.03.2009)**	28 MARCH 2008 (28.03.2008)

International Patent Classification (IPC) or both national classification and IPC

A61K 31/5513(2006.01)i, A61K 31/355(2006.01)i, A61K 9/16(2006.01)i, A61K 47/10(2006.01)i, A61P 25/22(2006.01)i

Applicant

HALE BIOPHARMA VENTURES, LLC et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302 -701, Republic of Korea Facsimile No. 82-42-472-7140	28 SEPTEMBER 2009 (28.09.2009)	KIM, YONG Telephone No.82-42-481-8164

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/038696

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material
   - ☐ a sequence listing
   - ☐ table(s) related to the sequence listing

   b. format of material
   - ☐ on paper
   - ☐ in electronic form

   c. time of filing/furnishing
   - ☐ contained in the international application as filed.
   - ☐ filed together with the international application in electronic form.
   - ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/038696

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 20-47

because:

☒ the said international application, or the said claims Nos. 20-45 relate to the following subject matter which does not require an international search *(specify)*:

The subject-matter of claims 20-45 does not require an opinion with respect to industrial applicability as it is substantially directed to method for treatment of the human body by therapy (Rules 43 bis.1(b), Rule 67.1(iv)).

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 46, 47 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 46 and 47 relate to a composition, and are indicated as referring to claims 20 and 21, respectively. However, the claims 20 and 21 relate to a method of treating a patient. Thus claims 46 and 47 are too unclear to make meaningful search possible.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 20-47

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Istructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2009/038696

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-19	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims	None	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 2007043057 A2 (19 April 2007)
D2: WO 2005117830 A1 (15 December 2005)

The present claims 1-19 relate to a pharmaceutical composition for nasal administration comprising (a) a benzodiazepine drug, (b) tocopherols or tocotriols (30-90% (w/w)), (c) alcohols or glycols (10-70% (w/w)) in a pharmaceutically-acceptable formulation for administration ~~to~~ through nasal mucosal membranes of patients.

D1 and D2 are considered to represent the most relevant state of the art. D1 discloses compositions for intranasal administration, which comprises diazepam, water, phospholipids and C2-C4 alcohols or glycols (12-30% (w/w)), tocopherol (0.001-5% (w/w)). D2 discloses a liquid depot formulation comprising a lipid, phospholipid and tocopherol.

1. Novelty and Inventive Step

Although D1 and D2 disclose the compositions for intranasal administration, the constituents and their ratio in the composition of the present claims are different from those of D1 or D2 in that the composition of D1 or D2 contains the phospholipids, and the ratio of tocopherol is 30-90% (w/w) in D1, whereas that of the present claims does not contain the phospholipids, and the ratio of tocopherol is 0.001-5% (w/w).

Moreover, the pharmaceutical composition (solution or suspension) of the present claims exhibits good stability, good pharmacokinetic profile and low toxicity.

Thus, the subject-matter of claims 1-19 is novel and inventive under Article 33(2) and 33(3) PCT.

2. Industrial Applicability

Claims 1-19 appear to be industrially applicable under Article 33(4) PCT.

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Rose Flanagan
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	20802127
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Rose Flanagan
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	25-NOV-2014
Filing Date:	27-MAR-2009
Time Stamp:	17:51:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$90
RAM confirmation Number	5231
Deposit Account	232415
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Neurelis_IDS_35401_716_201_Nov2014.pdf	187330 7cc30e073ed9503ed1faca8114b5110bdc00181f	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	6	
Warnings:					
Information:					
2	Foreign Reference	WO2006025882A2.pdf	3225121 7bae7d1475dd3735aba5ea14f1a39f599b2d80c2	no	70
Warnings:					
Information:					
3	Non Patent Literature	CA2723470_OA_07JUN2012.pdf	400068 8bd2c230796385bf8eb3e828724f76e8078b499c	no	3
Warnings:					
Information:					
4	Non Patent Literature	FIX-Oral-controlled-1760.pdf	584804 1bd94ffbd9cd445a7757b631ecc291dca53253ba	no	5
Warnings:					
Information:					
5	Non Patent Literature	HUSSAIN-Absorption-enhancers-15.pdf	941677 22c3a1ef69e2ba8aab912ca999eb5836fd04af0f	no	10
Warnings:					
Information:					
6	Non Patent Literature	KISSEL-Tolerability-52.pdf	866837 115caf77aedc7c3d63bb9231957d96405c96307c	no	6
Warnings:					
Information:					

7	Non Patent Literature	KITE-in-vivo-generated-biofilms-3073.pdf	392692 6353a3263a77f3401baf5b24c993fcce05218546	no	4
Warnings:					
Information:					
8	Non Patent Literature	LIU-Interaction-between-243.pdf	639619 c90738835bdc608889208d078451e459cd518d61	no	8
Warnings:					
Information:					
9	Non Patent Literature	PCTUS0862961_IPRP_10NOV2009.pdf	470387 bb41ba5cd9deb4426c99ae15c20880f62a17932f	no	9
Warnings:					
Information:					
10	Non Patent Literature	PCTUS0938696_IPRP_28SEP2010.pdf	220438 2b0580afbcb66a2017cc24a8043129228cf3babf	no	5
Warnings:					
Information:					
11	Non Patent Literature	US12116842_OA_25MAY2011.pdf	517557 12c9d30c1ca3bab3abeb3087db8558829b076fed	no	13
Warnings:					
Information:					
12	Non Patent Literature	US12116842_OA_02APR2013.pdf	625390 b15b0b533c6a0c604cdf07ecc0cdc1728526b1d6	no	17
Warnings:					
Information:					
13	Non Patent Literature	US12116842_OA_15NOV2011.pdf	626516 ef70b5070a30a6aa97cc31326cd9ae6877bb8852	no	15
Warnings:					
Information:					
14	Non Patent Literature	US12116842_OA_17DEC2013.pdf	499399 4d48768a56a295e16f9e11adc7e4d523f6f07880	no	12
Warnings:					
Information:					
15	Non Patent Literature	US12266529_OA_10JUL2012.pdf	672641 a3d74af8d19ca37ff4808fceafec507870f2e8f8	no	16
Warnings:					
Information:					

16	Non Patent Literature	US12266529_OA_16NOV2011.pdf	582557 1860737bfdc59251229a313f543c191552ceb398	no	15
Warnings:					
Information:					
17	Non Patent Literature	US12413439_OA_18MAR2011.pdf	299732 bb2d355f99f84bf7b2484d57c6176bc537d9939a	no	14
Warnings:					
Information:					
18	Non Patent Literature	US12413439_OA_21NOV2011.pdf	303247 5355ce4751949113c695ec02aa4aa21e1a01ac54	no	9
Warnings:					
Information:					
19	Non Patent Literature	US12413439_OA_19June2014.pdf	321754 b63186cf682af39596254cf6572fe2317686e380	no	8
Warnings:					
Information:					
20	Fee Worksheet (SB06)	fee-info.pdf	30515 fc11ceb9f4b6bd88464c080088c82bc3b98e6a7d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	12408281		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt *et al.*	Group Art Unit: 1612
Serial Number: 12/413,439	Examiner: Milligan, Adam C.
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: November 25, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☐ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☒ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☒ a fee of $90.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: November 25, 2014

By: /Matthew V. Grumbling/
Matthew V. Grumbling
Reg. No.: 44,427

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/413,439	03/27/2009	Steve Cartt	35401-716.201	9049

21971 7590 03/13/2015

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/13/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 12/413,439	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/19/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *20-24,27-36,38 and 40-53* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *20-24,27-36,38 and 40-53* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *2pgs(11/25/2014)*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Applicants' arguments, filed 11/19/2014, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20-24, 27-36, 38 and 40-53 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lehat (Intranasal midazolam for childhood seizures, The Lancet, vol.352, August 22, 1998 – See IDS dated 10/29/2013) in view of Sonne (U.S. 6,193,985- See IDS dated 9/16/2009) and Meezan (U.S. 2006/0046962).

Applicants argue that the instant claims exclude the emulsions of Sonne because both oil and water are excluded from the instant claims based on the use of “consisting of” language.

Examiner disagrees. Claim 20 recites a method of treating against seizures…comprising: administering to one or more nasal mucosal membranes of [[a]] the patient with a seizure disorder a pharmaceutical solution … consisting of 1 to 20 mg

of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1% (w/v) of one or more alkyl glycosides. Applicants are correct that “consisting of" language limits the scope of the term to specifically recited components; however, the instant claim uses “consisting of” only to define the term "pharmaceutical solution”. The open ended term “comprising” is used to define the recited method. Thus, the claim permits the application of components in addition to defined solution. Such an additional component may be an additional phase of an emulsion, as taught by Sonne. Because the instant claims do not exclude the additional phase (i.e. oil) of Sonne as Applicants have alleged, Applicants argument is not found persuasive. Accordingly, the rejection is maintained.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	1	of	2	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 6,165,484	12/26/2000	Raad, et al.	
	2.	US 6,316,029	11/13/2001	Jain, et al.	
	3.	US 6,461,591	10/08/2002	Keller, et al.	
	4.	US 7,008,920	03/07/2006	Kimura, et al.	
	5.	US 8,895,546	11/25/2014	Cartt, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	6.	WO 2006-025882	03/09/2006	The UAB Research Foundation		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	7.	CA 2,723,470 Office action dated June 7, 2012	
	8.	Fix, "Oral controlled release technology for peptides: status and future prospects", Pharmaceutical Research 1996 Dec;13(12):1760-1764.	
	9.	Hussain et al, "Absorption enhancers in pulmonary protein delivery." J Control Release. 2004 Jan 8;94(1):15-24.	
	10.	Kissel et al., "Tolerability and absorption enhancement of intranasally administered octreotide by sodium taurodihydrofusidate in healthy subjects." Pharm Res. 1992 Jan;9(1):52-57.	
	11.	Kite et al., "Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro." J Clin Microbiol. 2004 Jul;42(7):3073-3076.	

Examiner Signature	/Adam Milligan/	Date Considered	03/09/2015

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	2	of	2	Attorney Docket Number	35401-716.201

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	12.	Liu et al., "Interaction between chitosan and alkyl P-D-glucopyranoside and its effect on their antimicrobial activity", Carbohydrate Polymers. 2004; 56: 243-250.	
	13.	PCT/US08/62961 International Preliminary Report on Patentability dated 11/10/2009	
	14.	PCT/US09/38696 International Preliminary Report on Patentability dated 9/28/2010	
	15.	U.S. Serial No. 12/116,842 Office action mailed May 25, 2011	
	16.	U.S. Serial No. 12/116,842 Office action mailed April 2, 2013	
	17.	U.S. Serial No. 12/116,842 Office action mailed November 15, 2011	
	18.	U.S. Serial No. 12/116,842 Office action mailed December 17, 2013	
	19.	U.S. Serial No. 12/266,529 Office action mailed July 10, 2012	
	20.	U.S. Serial No. 12/266,529 Office action mailed November 16, 2011	
	21.	U.S. Serial No. 12/413,439 Office action mailed March 18, 2011	
	22.	U.S. Serial No. 12/413,439 Office action mailed November 21, 2011	
	23.	U.S. Serial No. 12/413,439 Office action mailed June 19, 2014	

Examiner Signature	/Adam Milligan/	Date Considered	03/09/2015

**EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons required to respond to a collection of information unless it contains a valid OMB control number.

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				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	1	of	1	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 2015-0065491	03/05/015	Cartt	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	2.	CA 2,723,470 Office Action dated February 19, 2015	
	3.	CN 201280039077.9 Office Action dated December 26,2014	X

Examiner Signature		Date Considered	

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Rose Flanagan
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	21797993
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Rose Flanagan
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	17-MAR-2015
Filing Date:	27-MAR-2009
Time Stamp:	17:44:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$90
RAM confirmation Number	4220
Deposit Account	232415
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Neurelis35401_716201_IDS_17 Mar2015.pdf	186701 c72ef324582878da14d0af68fcaa19ddf8d6 0db0	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	5	
	Information Disclosure Statement (IDS) Form (SB08)		6	6	
Warnings:					
Information:					
2	Non Patent Literature	CA2756690_OA_19FEB2015. pdf	344037 e83113dc801db90e0ec6b90bcaf630e5d9b e018c	no	5
Warnings:					
Information:					
3	Non Patent Literature	ChineseOA_26Dec2014_transla tion.pdf	178717 8efe832241aa7c30d382d09e36530d3f30b b2d34	no	4
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30766 148b71d4abb5ee8eb2c5bbafaf9b12eebf2 68242	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	740221		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt *et al.*	Group Art Unit: 1612
Serial Number: 12/413,439	Examiner: Milligan, Adam C.
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: March 17, 2015

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☐ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $90.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☒ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $90.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☒ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☒ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: March 16, 2015

By: /Matthew V. Grumbling/
Matthew V. Grumbling
Reg. No.: 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

STATEMENTS UNDER 37 C.F.R. § 1.97(E)

(Attachment to Information Disclosure Statement)

☒ *37 CFR §1.97(e)(1).* **THE UNDERSIGNED HEREBY STATES THAT** each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement:

☒ All references cited herein;

-- OR --

☐ The following subset of references: _____

--AND/OR--

☐ *37 CFR §1.97(e)(2).* **THE UNDERSIGNED HEREBY STATES THAT** no item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. §1.56(c) more than three months prior to the filing of this Information Disclosure Statement:

☐ All references cited herein;

-- OR --

☐ The following subset of references: _____

Respectfully submitted,

Dated: _____ By: _____

Matthew V. Grumbling
Reg. No.: 44,427

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 021971

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12413439	Filing Date	2009-03-27	Docket Number (if applicable)	35401-716.201	Art Unit	1612
First Named Inventor	Steve Cartt			Examiner Name	Adam C. Milligan		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 232415

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Matthew V. Grumbling/	Date (YYYY-MM-DD)	2015-09-11
Name	Matthew V. Grumbling	Registration Number	44427

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Attorney Docket No.: 35401-716.201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent Application of: Applicant: Steve Cartt Serial No.: 12/413,439 Filed: 03/27/2009 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Confirmation No.: 9049 Group Art Unit: 1612 Examiner: Milligan, Adam C. Customer Number: 21971 Certificate of Electronic Filing I hereby certify that the attached Response to Office Action and all marked attachments are being deposited by Electronic Filing by EFS – Web patent filing system on September 11, 2015. By: /Misty Elam/

FILED ELECTRONICALLY ON: SEPTEMBER 11, 2015

Dear Madam:

RESPONSE TO FINAL OFFICE ACTION DATED MARCH 13, 2015

In response to the Office Action mailed March 13, 2015, Applicants hereby file a three month extension of time, a Request for Continued Examination (RCE), amendments and remarks traversing the final rejection. Applicants submit that the response is timely filed. In the event you consider any additional fees to be required for further examination, please charge them to Deposit Account No. 23-2415, referencing Docket No. 35401-716.201.

Amendments to the claims begin on page **2** of this document.

Remarks begin on page **7** of this document.

A **Request for Continued Examination** is filed with this document.

An **Information Disclosure Statement** is filed with this document.

CLAIMS

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn claim in this or any other appropriate patent application.

1-19. (Canceled).

20. (Currently Amended) A method of intranasal administration of a benzodiazepine drug for treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, consisting of ~~comprising~~:

administering to one or more nasal mucosal membranes of the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

21. (Original) The method of claim 20, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

22. (Original) The method of claim 21, wherein said patient is a human.

23. (Original) The method of claim 20, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam,

midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Original) The method of claim 23, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Canceled)

26. (Canceled)

27. (Original) The method of claim 20, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ-tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

28. (Original) The method of claim 20, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

29. (Original) The method of claim 20, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Previously Presented) The method of claim 20, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Previously Presented) The method of claim 30, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Previously Presented) The method of claim 31, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w).

34. (Previously Presented) The method claim 33, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w).

35. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

36. (Previously Presented) The method of claim 35, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

37. (Canceled)

38. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution is a pharmaceutically-acceptable spray formulation.

39. (Canceled).

40. (Previously Presented) The method of claim 38, wherein said pharmaceutical solution is a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

41. (Previously Presented) The method of claim 40, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril.

42. (Previously Presented) The method of claim 40, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

43. (Previously Presented) The method of claim 42, wherein the administration of the pharmaceutical-solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.

44. (Previously Presented) The method of claim 43, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

45. (Previously Presented) The method of claim 43, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition.

46. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution contains at least about 0.01% (w/w) of an alkyl glycoside.

47. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

48. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution consists of diazepam, vitamin E, ethanol and optionally an alkyl glycoside.

49. (Previously Presented) The method of claim 48, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

50. (Previously Presented) The method of claim 49, wherein the alkyl glycoside is dodecyl maltoside.

51. (Previously Presented) The method of claim 20, wherein the pharmaceutical solution consists of 1-20 mg diazepam, 45 % (w/w) to 85 % (w/w) vitamin E, 15% (w/w) to 55 % (w/w) of a combination of ethanol and benzyl alcohol, and 0.01 % (w/v) to 1 % (w/v) of alkyl glycoside.

52. (Previously Presented) The method of claim 51, wherein the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof.

53. (Previously Presented) The method of claim 52, wherein the alkyl glycoside is dodecyl maltoside.

REMARKS

Responsive to the final rejection mailed March 13, 2015 ("Office Action"), Applicants request reconsideration of the outstanding rejections in view of the foregoing amendment and the following remarks.

Interview Summary

The undersigned would like to thank Primary Examiner Adam Milligan for the courtesy of a telephone interview on September 9, 2015. As discussed during the telephone interview, Applicants herein present amendments to the claims which they believe address the concerns raised in the final rejection and place the application in condition for allowance. In particular, the claims are now limited to a method of intranasal administration of a benzodiazepine drug for the recited indications; and the claims also contain a "consisting of" transition, which, as discussed in more detail herein, overcomes the view expressed in the Office Action that the "comprising" language permitted the presence of other phases.

The Pending Claims

Upon entry of the foregoing amendment, Claim 20 recites a method of intranasal administration of a benzodiazepine drug for treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, consisting of: administering to one or more nasal mucosal membranes of the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

The status of the claims is:

Claims 1-19, 25, 26, 37 and 39 are canceled, without prejudice; and

Claim 20 is amended herein. Claims 20-24, 27-36, 38 and 40-53 are pending and under consideration. As the amendment does not broaden the pending claims, no new matter has been added.

Response to the § 103(a) Obviousness Rejection

Claims 20-24, 27-36, 38 and 40-53 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Lahet et al. (Lancet, vol. 352, August 22, 1998), Sonne (U.S. 6,193,985) and Meezan (US 2006/0046962). Applicants traverse this rejection.

As best understood by Applicants, the position taken in the Office Action is that, while the recitation of "consisting of" with respect to the formulation excludes an emulsion formulation containing water and oil, the recitation of "comprising" with respect to the recited method would permit administration of components in addition to the defined solution, and that a hypothetical additional component could be an additional phase of an emulsion, as taught by Sonne.

While Applicants disagree that the combination of Lehat *et al.*, Sonne and Meezan renders obvious a method as recited in the previously-pending claims, in the interest of advancing prosecution, Applicants have amended the claims to recite "consisting of" rather than "comprising," as indicated in the listing of the claims. As the "consisting of" language in the claims is closed, the positive recitation of a "solution" in the claims clearly excludes inclusion of the other components, such as those necessary to form separate phases.

In order to present a viable *prima facie* case of obviousness under § 103, it is necessary that all the elements of the claims be present in the collection of art applied against the claims. Applicants submit that the combination of Lehat *et al.*, Sonne and Meezan fail to teach or suggest a method of intranasal administration of a benzodiazepine drug for one or more of the recited indications, consisting of: administering to one or more nasal mucosal membranes of the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of the recited components of the solution. As recitation of "consisting of" in the transitional phrase for the "administering" step closes the claim to other intranasal modes of

administration, by the reasoning of the Office Action, it necessarily excludes the other components of an emulsion taught by Sonne. Thus, the combination of Lahet *et al.*, Sonne and Meezan would not have suggested the subject matter of the instant claims to one of ordinary skill in the art at the time of the invention.

For at least the reasons given above, Applicants submit that the pending claims are not obvious within the meaning of § 103(a) in view of the teaching of Lehat, Sonne and Meezan. Withdrawal of the § 103(a) rejection is respectfully requested.

CONCLUSION

Applicants timely submit these remarks in response to the Office Communication dated March 13, 2015. In the event that fees are due in connection with the filing of this response, please charge the necessary fees to Deposit Account No. 23-2415 referencing Docket No. 35401-716.201. Applicants encourage the Examiner to contact the undersigned attorney, should there be any remaining issues that may be addressed by a telephonic interview.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: September 11, 2015

By: / Matthew V. Grumbling/
Matthew V. Grumbling
Registration No. 44,427

650 Page Mill Road
Palo Alto, CA 94304
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Customer No. 021971

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Jeffrey W. Guise./Misty Elam
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
RCE- 2nd and Subsequent Request	2820	1	850	850
		Total in USD ($)		**1550**

Electronic Acknowledgement Receipt

EFS ID:	23468182
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Jeffrey W. Guise./Misty Elam
Filer Authorized By:	Jeffrey W. Guise.
Attorney Docket Number:	35401-716.201
Receipt Date:	11-SEP-2015
Filing Date:	27-MAR-2009
Time Stamp:	14:50:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1550
RAM confirmation Number	1118
Deposit Account	232415
Authorized User	ELAM, MISTY
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	35401-716-201RCE.pdf	697834 eb8ccc679c873b413624eee0fe48bef646e90621	no	3
Warnings:					
Information:					
2		35401-716-201Response.pdf	44072 f6d407a3103395451e5eaa69501f7645ca7a3d81	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Submitted/Entered with Filing of CPA/RCE	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	9

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32556 8ad5652779c55982d0f2eca9966f64ea650d6253	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	774462	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	March 27, 2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	1	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2004-0101482	5/1/2004	Sanders, Mark	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	2.	CN-1303674A	07/18/2001	Shan-N		X
	3.	EP-1208863	5/1/2002	Ohki et al.		
	4.	WO-2003-004015	01/16/2003	West Pharm Serv Drug Res LTD		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	5.	EP12801372.9 Extended EP Search Report dated March 26, 2015	
	6.	Newman. Aerosol deposition consideration in inhalation therapy. Chest 152S-160S (1985)	
	7.	SUN, et al. Nasal spray for curing status epilepticus (SE) and epilepsy, comprises alprazolam and carriers. Database WPI, Section Ch, Week 200164. Thomson Scientific	
	8.	U.S. Serial No. 14/021,988 Office Action mailed May 22, 2015	
	9.	U.S. Serial No. 12/116,842 Office Action mailed July 8, 2015	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt

EFS ID:	23472726
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Rose Flanagan
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	CN1303674A.pdf	1331296 63012aa861b928fd7363eef85dc5cb3400385947	no	16

Warnings:	
Information:	

2	Foreign Reference	CN1303674A_trans_18Jul2001.pdf	2021264 8559852ac40805a838c6f607878097130ece5b57	no	39
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3	Foreign Reference	WO2003004015.pdf	2132991 617b5f926f0ecc6296ef3cd94d4f3b32e6dcc747	no	28
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Information:					
4	Non Patent Literature	EP128013729_EESR_26MAR2015.pdf	705907 e58375da74d58848e39353ea521f8d2a3df636c0	no	9
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9		NeurelisIDS.pdf	184133 af725a83bc848eca3b0a1ad1f07c81ab72a905f9	yes	5

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权利要求书2页 说明书12页 附图页数0页

[54]发明名称 阿普唑仑鼻喷剂

[57]摘要

一种苯二氮䓬类药物——阿普唑仑鼻喷剂，由主药阿普唑仑、药用溶剂和其它药用辅料组成。根据药物的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。本发明给药方便，起效快，吸收完全，可用于癫痫持续状态(SE)及癫痫的治疗。

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权利要求书

1.阿普唑仑的鼻喷剂，其特征在于由主药阿普唑仑、溶剂和其它药用辅料组成，在1000ml药液中，阿普唑仑的用量为0.5~10g，其它辅料的用量为0.01~500g。

2.权利要求 1 中所述的鼻喷剂，其特征在于其溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，其用量为5-1000ml。

3.权利要求 1 中所述的鼻喷剂，其特征在于权利要求 1 中所述的其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂和乳化剂，其中助溶剂为环糊精，其用量为0.1～20g；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇和纤维素，其用量为0.1～25g；助悬剂为聚丙烯酸、聚乙烯吡咯烷酮、纤维素和天然胶，其用量为0.5～50g；油脂为油酸和肉蔻酸异丙酯，其用量为 20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆和卡泊姆，其用量为1.5-80。

4.权利要求 1 中所述的鼻喷剂，其特征在于它可制备成溶液型、混悬型、凝胶型、乳液型四种类型；

5.权利要求 4 中所述的鼻喷剂，其特征在于溶液型的主要成分是阿普唑仑和溶剂；在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-950ml。

6.权利要求 4 中所述的鼻喷剂，其特征在于凝胶型的主要成分是阿普唑仑、溶剂、生物粘附性高分子材料，在 1000ml 药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素，可以是其中的一种或几种，其用量为 0.1～25g。

7.权利要求 4 中所述的鼻喷剂，其特征在于混悬型的主要成分是阿普唑仑、溶剂、助悬剂，在1000ml药液中，阿普唑仑的用量为0.5~10g，所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 6-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素、天然

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胶， 可以是其中的一种或几种，其用量为 0.5～50g。

8.权利要求 4 中所述的鼻喷剂，其特征在于乳液型的主要成分是阿普唑仑、溶剂、油脂、乳化剂,在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；油脂为油酸和肉蔻酸异丙酯，可以是其中的一种或几种，其用量为 20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆，可以是其中的一种或几种，其用量为 1.5-80g。

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说 明 书

阿普唑仑鼻喷剂

本发明涉及苯二氮䓬类药物——阿普唑仑鼻喷剂，属于化学和药物制剂领域。

癫痫是一种可由多种不同因素引起的反复发作性的脑功能紊乱现象，又称抽风、羊角风，一般大致可分为全身性发作和部分性发作两类。癫痫持续状态（SE）是指发作时间超过 30 分钟或者发作频繁而在间歇期意识始终未能完全恢复正常的病症，属神经系统危重症之一。发病时常出现缺氧、高热、脑水肿、心血管系统紊乱、低血糖以及呼吸道感染等进一步加重惊厥甚至危及生命的病理生理改变，如不及时治疗，病人即有病死和致残的可能，故应采取果断而有力的治疗措施尽快止惊。目前临床认为理想的止惊药应具备下列性能：（1）脂溶性高，易透过血脑屏障，迅速达到脑内药物峰值；（2）作用强而不会显著抑制呼吸和血压；（3）半衰期长，不必多次用药；（4）用药途径方便，药物起效迅速；（5）与其它止惊药之间无不利的相互作用；（6）苏醒较快；（7）无矛盾反应，即某药效果不佳需加大剂量或换用同类药物时 SE 反而加重的情况。目前控制 SE 一般首选苯二氮䓬类药物，如静脉注射地西泮（安定）、劳拉西泮（氯羟安定）氯硝西泮（氯硝安定）等。

与口服给药、肌肉注射、保留灌肠等给药途径相比，静脉注射药物有吸收好、起效快等特点，但对于 SE 病人，尤其是较严重的强直—阵挛性 SE 病人，由于发病期肢体或不断抽动或木僵，静脉注射有一定困难，此时亦有采用保留灌肠或肌肉注射或舌下给药治疗的情况，但前者由于吸收慢，难以迅速止惊，而后者多数病人强直，无法将药放入舌下而失败，因此上述治疗方法中除静脉注射外其它方法均难以达到较好的治疗效果。

本发明的目的在于针对上述问题,发明一种苯二氮䓬类药物——阿普唑仑鼻喷剂，从而达到治疗迅速、用药方便的目的。

本发明是这样实现的：阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂和其它药用辅料组成,所使用的药用辅料的种类和数量可根据制剂类型进行调整。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，其它辅料的用量为

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0.01~500g。本发明所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂，可以包括其中的一种或几种。其中助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20g；生物粘附性高分子材料包括聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及其衍生物，其中聚丙烯酸包括多种型号的卡泊姆，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。

根据药物的的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。

溶液型的阿普唑仑鼻喷剂由主药阿普唑仑、药用溶剂、助溶剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，药

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用溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-950ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成溶液即得到药液。

凝胶型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助溶剂、生物粘附性高分子材料、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；生物粘附性高分子材料包括：聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及衍生物，其中聚丙烯酸包括卡泊姆-934、974、941、981、TR-2 等型号，纤维素及衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节凝胶溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。用聚丙烯酸等制成亲水凝胶型鼻喷剂，

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可以延长药物与鼻腔粘膜的接触时间，有利于提高生物利用度。其制备过程为将主药与各种适宜的药用辅料混合，制成亲水凝胶溶液即得到药物凝胶液。

混悬型的阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶如明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；渗透压调节剂包括：氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成混悬溶液即得到喷雾药液。

乳液型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g。本发明所用的溶剂为水、聚乙二醇（200、300、400）、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂

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包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g，其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，采用干胶法或湿胶法制成混悬溶液即得到喷雾溶液。

阿普唑仑为新的苯二氮䓬类药物，有与地西泮相似的药理作用，有抗焦虑、抗惊厥、抗抑郁、镇静、催眠及肌肉松弛等作用，其作用比地西泮强 10 倍。将阿普唑仑制成鼻喷剂，药物经鼻腔毛细血管吸收后，直接进入体循环，而不经门—肝系统，避免了肝脏的首过效应，生物利用度高，血药浓度与静脉注射相似，因此阿普唑仑喷鼻治疗 SE 与静脉注射和直肠给药相比，不仅给药方便，而且起效快，吸收完全，可以达到较好的治疗效果。

下面是本发明的实施例，但并不受实施例的限制。

实施例 1

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	5g
乙醇	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 2

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处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
甜味剂	1.0g
香草香精	0.1g
苯甲醇	5 ml
乙醇	200ml
聚乙二醇	600ml
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 3

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
氯甲酚	1 g
乙醇	300ml
甘油	200mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 4

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
新洁尔灭	1g
乙醇	250ml
丙二醇	250mL
水	稀释至 1000ml

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操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 5

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
卡泊姆-934	5 g
β-环糊精	6g
0.1N NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装凝胶喷泵，包装，检验，入库。

实施例 6

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
卡泊姆 941	1.5g
β-环糊精	4g
三乙醇胺	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

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操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 7

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	1 g
卡泊姆-974	10 g
0.1N NaOH	适量
苯甲醇	5 g
乙醇	280ml
丙二醇	200ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于乙醇和丙二醇的混合物中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液(1)和(2)混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 8

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8 g
甲基纤维素	15 g
β-环糊精	10g
0.1NHCl 或 NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将甲基纤维素、EDTA-2Na、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），

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将溶液(1)和(2)混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 9

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
丙二醇	150ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇和丙二醇的混合物中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 10

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8g
卡泊姆 TR-2	1.5 g
β-环糊精	10g
三乙醇胺	适量
苯甲醇	5 g
丙二醇	250ml
甘油	100
水	稀释至 1000ml

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操作：按处方比例将主药与β-环糊精溶于丙二醇和甘油的混合物中，制成溶液（1），将卡泊姆 TR-2、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加三乙醇胺调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 11

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 12

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
微晶纤维素	3 g
氯化钠	9 g
0.1N HCl 或 NaOH	适量
洁尔灭	5 g
水	稀释至 1000ml

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操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、微晶纤维素、氯化钠、洁尔灭及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 13

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
卡泊姆-941	2 g
葡萄糖	55 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、卡泊姆-941、葡萄糖、苯甲醇及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 14

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4g
油酸	80 g
卡泊姆 TR-2	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

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操作：按处方比例将主药、油酸、卡泊姆 TR-2、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 15

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
肉蔻酸异丙酯	90 g
蔗糖酯	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、肉蔻酸异丙酯、蔗糖酯、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

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Alprazolam nasal spray

CN 1303674 A

ABSTRACT

A kind of benyl diazopines medicine-alprazolam nasal spray is comprised of alprazolam as main medicine, medicinal solvent and medicinal auxiliary materials. Said invention can be divided into solution type, suspension type, gel type and emulsion type, and can be used for curing status epilepticus (SE) and epilepsy.

DESCRIPTION translated from Chinese

Alprazolam nasal spray

The present invention relates □ benzodiazepine class of drugs - alprazolam nasal spray, belongs to the field of chemical and pharmaceutical preparations.

Epilepsy is a recurrent phenomenon of a brain dysfunction caused by a variety of different factors, also known as convulsions, epilepsy, generally can be divided into generalized seizures and partial seizures categories. Status epilepticus (SE) refers to the time of onset of frequent seizures more than 30 minutes or in the interim period has been unable to fully return to normal awareness of the disease, one case of severe disease of the nervous system. Onset often appear hypoxia, high fever, brain edema, cardiovascular system disorders, hypoglycemia and respiratory infections further aggravate convulsions and even life-threatening physiological and pathological changes, if not treated, the patient died of illness and disability that is possible, it should be take decisive and effective treatment as soon as possible just scared. Current clinical think the ideal drug only surprise should have the following properties: (1) high fat-soluble, easily through the blood-brain barrier, the brain quickly reached a peak of drugs; (2) the role of a strong and does not significantly inhibit respiration and blood pressure; (3) long half-life, without having to repeatedly medication; convenient (4) the route of administration, rapid onset of drug; (5) other just scared and no adverse drug interactions; (6) wake up fast; (7) non-contradictory reaction that a need to increase the dose of the drug ineffective or change occurs with similar drugs actually worsened the SE. SE currently controls generally preferred benzodiazepine □ drugs, such as intravenous diazepam (Valium), lorazepam (lorazepam) clonazepam (clonazepam) and so on.

Intramuscular injection, enema and other routes of administration compared to oral administration, intravenous drug absorption, rapid onset, etc., but for SE patients, especially more severe tonic-clonic SE patients, due to the incidence of limb or constantly twitching or stupor, intravenous injection will be difficult, at this time also using case enema or intramuscular injection or sublingual administration of treatment, but the former is due to the absorption of slow, difficult to quickly just scared, which most patients rigidity, can not be placed in sublingual drug fails, so in addition to the above-described methods of treatment intravenous other methods are difficult to achieve a better therapeutic effect.

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Object of the present invention is to solve the above problems, an invention benzodiazepine □ drug - alprazolam nasal spray, so as to achieve rapid treatment, facilitate administration purposes.

The present invention is implemented as follows: alprazolam nasal spray is the main drug alprazolam, solvents and other pharmaceutical excipients pharmaceutical composition, the type and amount of pharmaceutical excipients can be adjusted according to the type of formulation. In 1000ml of liquid, the alprazolam dosage 0.5 ~ 10g, the amount of other auxiliary branch of 0.01 ~ 500g. The solvent used in the present invention is water, polyethylene glycol, ethanol, propylene glycol and glycerol, which can be one or more, in an amount of 5-1000ml; Other pharmaceutical excipients include: co-solvents, bioadhesive high molecular materials, suspending agents, oils, emulsifiers, osmotic pressure adjusting agents, aromatic flavoring agents and antimicrobial preservatives, which may comprise one or several. Wherein the co-solvent is a cyclodextrin, including α- cyclodextrin, β- cyclodextrin, hydroxyethyl -β- cyclodextrin, hydroxypropyl -β- cyclodextrin, 3-hydroxypropyl -β- ring dextrin and the like, which may be one or more, in an amount of 0.1 ~ 20g; bioadhesive polymer materials include polyacrylic acid, polyvinyl pyrrolidone, polyethylene glycol, cellulose and derivatives thereof, wherein the poly acrylate, including a variety of types of cards perm, cellulose and its derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, etc., can be one of them or Several, in an amount of 0.1 ~ 25g; suspending agents include polyacrylic acid, polyvinyl pyrrolidone, cellulose and derivatives thereof, natural rubber, etc., wherein a polyacrylic acid include a variety of types of cards perm, etc., cellulose and its derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and the like; natural gums include gelatin, acacia, sodium alginate, etc., which may be one or more in an amount of 0.5 ~ 50g; fats include oleic acid, nutmeg acid and isopropyl, which may be one or more, in an amount of 20 ~ 500g; emulsifiers include glycerol esters, sucrose esters, Tween , poloxamer, cards perm etc., which may be one or more, in an amount of 1.5-80g; osmolality adjusting agents include sodium chloride, dextrose, mannitol, sodium lactate, etc., may be one of a species or more, in an amount of 0.5 ~ 55g; aromatic flavoring agents include sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, which may be one or several, aromatic agents include natural and synthetic fragrances, which may be one or more, in an amount of 0 ~ 1g; PH adjusting agents include inorganic acid and organic acid, for adjusting the PH value of the solution in an amount few, can According to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzyl alcohol, benzyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal, etc., can be one of them or a few species, in an amount of 0.01 ~ 10g.

Effect of the drug according to the characteristics and physical and chemical properties, and the characteristics of nasal administration, the present invention can be classified into solution type, suspension type, gel type, emulsion type.

Solution-based nasal spray alprazolam alprazolam by primary drug, medicinal solvent, solvent, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml of liquid, the alprazolam dosage 0.5 ~

10g, medicinal solvent is water, polyethylene glycol, including 200,300,400 other models, ethanol, propylene glycol and glycerin, which can be one or a few species, an amount of 5-950ml; cosolvent as cyclodextrins, cyclodextrin include α-, β- cyclodextrin, hydroxyethyl -β- cyclodextrin, hydroxypropyl -β- cyclodextrin, 3 - hydroxypropyl -β- cyclodextrin, which can be one or more, in an amount of 0.1 ~ 20g, but in the liquid in the lower alprazolam concentration may not be added; aromatic flavoring agents sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, which can be one or more an amount of from 0 ~ 1g; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzyl alcohol, benzyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal, etc., can be one of them species or more, in an amount of 0.01 ~ 10g. The preparation process for the main drug alprazolam mixed with a variety of suitable pharmaceutical excipients, to prepare a solution to obtain liquor.

Alprazolam gel nasal spray is the main drug alprazolam, a pharmaceutically acceptable solvent, solvent, bioadhesive polymer materials, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml drug solution, the amount of alprazolam 0.5 ~ 10g, the solvent used is water, polyethylene glycol, comprising 200,300,400 models, ethanol, propylene glycol and glycerol, which can be one or several species, an amount 5-1000ml; cosolvent as cyclodextrins, cyclodextrin include α-, β- cyclodextrin, hydroxyethyl -β- cyclodextrin, hydroxypropyl -β- cyclodextrin, 3 - hydroxypropyl -β- cyclodextrin, which can be one or more, in an amount of 0.1 ~ 20g, but in the liquid may not be added at low concentration of alprazolam; bioadhesive polymer materials include: polyacrylic acid, polyvinyl pyrrolidone, polyethylene glycol, cellulose and derivatives thereof, wherein the polyacrylic acid comprises a card perm -934,974,941,981, TR-2 and other models, cellulose and derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and other claims, which can be one or more, in an amount of 0.1 ~ 25g; aromatic flavoring agents include sweet flavoring and perfuming agents, sweetening agents include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, which can be one or several, of its the amount of 0 ~ 1g; PH regulators include inorganic acid and organic acid, used to adjust the PH value of the gel solution, the amount of rare, according to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzene methanol, benzyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal and the like, which may be one or more, in an amount of 0.01 ~ 10g. With polyacrylic acid made hydrophilic gel nasal sprays, drugs can prolong the contact time with the nasal mucosa, help to improve bioavailability. The preparation process for a variety of primary drug is mixed with a suitable pharmaceutical excipients, made of hydrophilic gel solution to obtain the drug gel fluid.

Suspension type alprazolam nasal spray is the main drug alprazolam, a pharmaceutically acceptable solvent, suspending agents, osmotic pressure regulator, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml drug solution, the amount of alprazolam 0.5 ~ 10g, the solvent used is water, polyethylene glycol, comprising 200,300,400 models, ethanol, propylene glycol and glycerol, which can be one or several species, an amount 5-1000ml; suspending agents include polyacrylic acid, polyvinyl

pyrrolidone, cellulose and derivatives thereof, natural rubber, etc., wherein a polyacrylic acid include a variety of types of cards perm, etc., cellulose and its derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and the like; natural gums such as gelatin, acacia, sodium alginate, etc., which may be one or several, in an amount of 0.5 ~ 50g; osmolality adjusting agents include: sodium chloride, dextrose, mannitol, sodium lactate, etc., which may be one or more, in an amount of 0.5 ~ 55g; aromatic flavoring agents include sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, which can be one or more, an amount of 0 ~ 1g; PH regulators include inorganic acid and organic acid, used to adjust the PH value of the solution, the amount of very few, according to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzyl alcohol, benzyl alcohol , cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal and the like, which may be one or more, in an amount of 0.01 ~ 10g. The preparation process for the main drug alprazolam variety of suitable pharmaceutical excipients mixed with a solution that is made to get spray liquid suspension.

Emulsion alprazolam nasal spray is the main drug alprazolam, a pharmaceutically acceptable solvent, suspending agents, oils, emulsifiers, osmotic pressure regulator, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml of liquid, the alprazolam dosage 0.5 ~ 10g. The solvent used in the present invention is water, polyethylene glycol (200,300,400), ethanol, propylene glycol and glycerol, which can be one or more, in an amount of 5-1000ml; suspending agents include polyacrylic acid, slightly polyvinyl pyrrolidone, cellulose and its derivatives, natural rubber, etc., wherein a polyacrylic acid include a variety of types of cards perm, etc., cellulose and its derivatives include methyl cellulose, sodium carboxymethylcellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and the like; natural gums include gelatin, acacia, sodium alginate, etc., which may be one or more, in an amount of 0.5 ~ 50g; fats include oleic acid, meat Kou acid and isopropyl, which may be one or more, in an amount of 20 ~ 500g; emulsifiers include glycerol esters, sucrose esters, polysorbate, poloxamer, cards perm etc., which can be one or more, in an amount of 1.5-80g; osmolality adjusting agents include sodium chloride, dextrose, mannitol, sodium lactate, etc., which may be one or more, in an amount of 0.5 ~ 55g; aromatic straightening flavoring agents including sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, can be one of them or Several, in an amount of 0 ~ 1g; PH regulators include inorganic acid and organic acid, used to adjust the PH value of the solution, the amount of rare, according to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium , benzyl alcohol, phenylethyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal and the like, which may be one or more, in an amount of 0.01 ~ 10g, process for the preparation thereof main drug alprazolam mixed with various suitable pharmaceutical excipients, suspending solution using adhesive or wet glue into the legal system to obtain a spray solution.

Alprazolam is a benzodiazepine □ new drugs, and diazepam have similar pharmacological effects, anxiolytic, anticonvulsant, antidepressant, sedative, hypnotic and muscle relaxation and so on, which is stronger than diazepam 10 times. The nasal spray is made alprazolam, after absorption of the drug through the nasal capillaries directly into the systemic circulation, rather than through the door - liver system, avoiding first-pass effect of the liver, and high bioavailability, plasma concentration and intravenous similar, alprazolam SE nasal spray treatment compared with intravenous and rectal administration, the administration is not only convenient, but also rapid onset of absorption is complete, you can achieve better therapeutic effect.

The following are examples of the present invention, but are not limited to the embodiments of the subject.

Formulation Example 1 (with a volume of solution dubbed 1000ml of dollars) alprazolam 5g ethanol diluted to 1000ml operation: the main prescription drugs mixed with excipients proportion spray liquid preparation, the filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 2

Prescription (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam sweetener 2g 1.0g 0.1g vanilla 5ml ethanol, benzyl alcohol polyethylene glycol 600ml water 200ml to 1000ml operation: the main prescription drugs and excipients proportion mixed to prepare a spray liquid, the filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 3 prescription (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam chlorocresol 2g 1g ethanol glycerol 200mL water 300ml to 1000ml operation: the main mixing prescription drugs and excipients proportion, preparation spray liquid filtration filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Diluted to 1000ml Formulation Example 4 (dubbed the volume of solution to 1000ml of dollars) alprazolam Bromogeramine 2g 1g ethanol glycol 250mL water 250ml

Operation: The main prescription drugs and excipients proportions, preparation spray liquid, the filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 5 (dubbed the volume of solution to 1000ml of dollars) alprazolam 4g card perm -934 5gβ- diluted cyclodextrin 6g0.1N NaOH appropriate amount of propylene glycol, benzyl alcohol 5g water 250ml to 1000ml: Press prescription proportion the main drug and β- cyclodextrin was dissolved in propylene glycol to produce a solution (1), the card perm, benzyl alcohol, and 500ml of pure water were mixed to prepare a hydrogel solution (2), the solution (1) and (2) diluted mix, add water to 1000ml, adding NaOH solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation gel spray pumps, packaging, testing, storage.

Formulation Example 6 (dubbed volume of solution to 1000ml of dollars) alprazolam 2g card perm 941 1.5gβ- cyclodextrin diluted 4g 5g triethanolamine right amount of benzyl alcohol polyethylene glycol water 350ml to 1000ml

Operation: According to the proportion of the main drug prescription with β- cyclodextrin was dissolved in polyethylene glycol, to prepare a solution (1), the card perm, benzyl alcohol and purified water 500ml, prepared hydrogel solution (2), the diluted solution (1) and (2) mixing, add water to 1000ml, adding NaOH solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 7 (dubbed volume of solution to 1000ml of dollars) alprazolam 1g card perm -974 10g0.1N NaOH appropriate amount of benzyl alcohol, propylene glycol 5g ethanol 280ml 200ml to 1000ml water dilution: Press prescription drugs and the proportion of the primary β- cyclodextrin was dissolved in a mixture of ethanol and propylene glycol, to prepare a solution (1), the card perm, benzyl alcohol and purified water 500ml, prepared hydrogel solutions (2), the solution (1) and dilution (2) mixing, add water to 1000ml, adding NaOH solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 8 (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam 8g methylcellulose 15gβ- cyclodextrin 10g0.1NHCl or NaOH appropriate amount of propylene glycol, benzyl alcohol 5g water 250ml to 1000ml: Press prescription proportion the main drug and β- cyclodextrin was dissolved in propylene glycol to produce a solution (1), methyl cellulose, EDTA-2Na, benzyl alcohol, and 500ml of pure water were mixed to prepare a hydrogel solution (2), and the solution dilution (1) and (2) mixing, add water to 1000ml, adding acid or alkali solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 9 Formulation example (with a volume of solution dubbed the meter 1000ml) alprazolam 10g sodium carboxymethyl cellulose 2.5gβ- cyclodextrin 10g0.1N HCl or NaOH 5g appropriate amount of benzyl alcohol glycol polyethylene glycol 350ml water 150ml diluted to 1000ml: Press the mixture ratio of the main drug prescription with β- cyclodextrin was dissolved in polyethylene glycol and propylene glycol to prepare a solution (1), and the mixture of sodium carboxymethyl cellulose, benzyl alcohol and purified water 500ml to prepare a hydrogel solution (2), the diluted solution (1) and (2) were mixed with water to 1000ml, the addition of acid or alkali solution to adjust the PH to 5.0-7.0, determination, filling, sealing, installation spray pump , packaging, testing, storage.

Formulation Example 10 (dubbed the volume of solution to 1000ml of dollars) alprazolam 8g card perm TR-2 1.5gβ- cyclodextrin 10g right amount of benzyl alcohol, triethanolamine diluted 5g propylene glycerol 100 Water 250ml to 1000ml

Operation: According to the proportion of the main drug prescription with β- cyclodextrin was dissolved in a mixture of propylene glycol and glycerol, to make a solution (1), the card perm TR-2, benzyl alcohol, and 500ml of pure water were mixed to prepare a hydrogel gum solution (2), the diluted solution (1) and (2) mixing, add water to 1000ml, plus triethanolamine adjust the PH of 5.0-7.0, determination, filling, sealing, installation of spray pumps, packaging, testing, storage .

Prescription Example 11 (dubbed the volume of solution in the meter 1000ml) alprazolam 10g sodium carboxymethyl cellulose 2.5gβ- cyclodextrin 10g0.1N HCl or dilute NaOH 5g appropriate amount of benzyl alcohol polyethylene glycol to 250ml water 1000ml operation: the ratio of the main drug prescription with β-cyclodextrin was dissolved in polyethylene glycol, to prepare a solution (1), and the mixture of sodium carboxymethyl cellulose, benzyl alcohol, and 500ml of pure water to prepare a hydrogel gum solution (2), the diluted solution (1) and (2) were mixed with water to 1000ml, the addition of acid or alkali solution to adjust the PH to 5.0-7.0, determination, filling, sealing, installation spray pumps, packaging, testing, storage.

Formulation Example 12 (dubbed the volume of solution to 1000ml of dollars) alprazolam 1.0g sodium carboxymethyl cellulose, microcrystalline cellulose 2.5g 3g 9g0.1N HCl or NaOH appropriate amount of sodium chloride benzalkonium 5g dilution water to 1000ml

Operation: The main drug be micronized (5μm or less), the standby; prescription mixing proportions of sodium carboxymethyl cellulose, microcrystalline cellulose, sodium chloride, benzalkonium chloride and 800ml of pure water, swell, and dissolved to prepare an aqueous solution will be diluted with micronized drug master mix, add water to 1000ml, adding acid or alkali solution was adjusted to 5.0-7.0 PH, mix, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 13 Formulation example (with a volume of solution dubbed the meter 1000ml) alprazolam 10g sodium carboxymethyl cellulose 2.5g card perm -941 2g glucose 55g0.1N HCl or NaOH appropriate amount of benzyl alcohol, polyethylene glycol 5g 250ml diluted with water to 1000ml operation: the primary agents for the micronized (5μm or less), the standby; prescription proportion of sodium carboxymethyl cellulose, card perm -941, glucose, benzyl alcohol and 800ml of purified water, the swelling, dissolution system into the aqueous solution, the diluted with micronized drug master mix, add water to 1000ml, adding acid or alkali solution to adjust PH 5.0-7.0, mixing, determination, filling, sealing, installation of spray pumps, packaging, testing, into library.

Diluted to 1000ml Formulation Example 14 (dubbed the volume of solution to 1000ml of dollars) alprazolam 4g oleic acid 80g card perm TR-2 2g0.1N HCl or NaOH appropriate amount of benzyl alcohol, polyethylene glycol 5g 350ml water

Operation: The main drug prescription proportion, oleic acid, card perm TR-2, benzyl alcohol were mixed and dissolved in a water bath, was added slowly with stirring at a high speed mixing of pure water, diluted to

1000ml, homogenized for 30 minutes, adding acid or base PH was adjusted to 5.0-7.0, mixing, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 15 (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam 4g nutmeg 90g sucrose isopropyl ester 2g0.1N HCl or NaOH appropriate amount of benzyl alcohol, polyethylene glycol 5g 350ml to 1000ml water operations: The main drug prescription proportion, nutmeg isopropyl, sucrose esters, benzyl alcohol were mixed and dissolved in a water bath, was added slowly with stirring at a high speed mixing of pure water, diluted to 1000ml, homogenized for 30 minutes, the addition of acid or alkali solution is adjusted PH is 5.0-7.0, mixing, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

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[57]摘要

一种苯二氮䓬类药物——阿普唑仑鼻喷剂，由主药阿普唑仑、药用溶剂和其它药用辅料组成。根据药物的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。本发明给药方便，起效快，吸收完全，可用于癫痫持续状态(SE)及癫痫的治疗。

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权利要求书

1.阿普唑仑的鼻喷剂，其特征在于由主药阿普唑仑、溶剂和其它药用辅料组成，在1000ml药液中，阿普唑仑的用量为0.5~10g，其它辅料的用量为0.01~500g。

2.权利要求 1 中所述的鼻喷剂，其特征在于其溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，其用量为5-1000ml。

3.权利要求 1 中所述的鼻喷剂，其特征在于权利要求 1 中所述的其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂和乳化剂，其中助溶剂为环糊精，其用量为0.1～20g；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇和纤维素，其用量为0.1～25g；助悬剂为聚丙烯酸、聚乙烯吡咯烷酮、纤维素和天然胶，其用量为0.5～50g；油脂为油酸和肉蔻酸异丙酯，其用量为20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆和卡泊姆，其用量为1.5-80。

4.权利要求 1 中所述的鼻喷剂，其特征在于它可制备成溶液型、混悬型、凝胶型、乳液型四种类型；

5.权利要求 4 中所述的鼻喷剂，其特征在于溶液型的主要成分是阿普唑仑和溶剂；在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-950ml。

6.权利要求 4 中所述的鼻喷剂，其特征在于凝胶型的主要成分是阿普唑仑、溶剂、生物粘附性高分子材料，在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-1000ml；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素，可以是其中的一种或几种，其用量为0.1～25g。

7.权利要求 4 中所述的鼻喷剂，其特征在于混悬型的主要成分是阿普唑仑、溶剂、助悬剂，在1000ml药液中，阿普唑仑的用量为0.5~10g，所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素、天然

胶， 可以是其中的一种或几种，其用量为 0.5～50g。

8.权利要求 4 中所述的鼻喷剂，其特征在于乳液型的主要成分是阿普唑仑、溶剂、油脂、乳化剂,在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；油脂为油酸和肉蔻酸异丙酯，可以是其中的一种或几种，其用量为 20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆，可以是其中的一种或几种，其用量为 1.5-80g。

说 明 书

阿普唑仑鼻喷剂

本发明涉及苯二氮䓬类药物——阿普唑仑鼻喷剂，属于化学和药物制剂领域。

癫痫是一种可由多种不同因素引起的反复发作性的脑功能紊乱现象，又称抽风、羊角风，一般大致可分为全身性发作和部分性发作两类。癫痫持续状态（SE）是指发作时间超过 30 分钟或者发作频繁而在间歇期意识始终未能完全恢复正常的病症，属神经系统危重症之一。发病时常出现缺氧、高热、脑水肿、心血管系统紊乱、低血糖以及呼吸道感染等进一步加重惊厥甚至危及生命的病理生理改变，如不及时治疗，病人即有病死和致残的可能，故应采取果断而有力的治疗措施尽快止惊。目前临床认为理想的止惊药应具备下列性能：（1）脂溶性高，易透过血脑屏障，迅速达到脑内药物峰值；（2）作用强而不会显著抑制呼吸和血压；（3）半衰期长，不必多次用药；（4）用药途径方便，药物起效迅速；（5）与其它止惊药之间无不利的相互作用；（6）苏醒较快；（7）无矛盾反应，即某药效果不佳需加大剂量或换用同类药物时 SE 反而加重的情况。目前控制 SE 一般首选苯二氮䓬类药物，如静脉注射地西泮（安定）、劳拉西泮（氯羟安定）氯硝西泮（氯硝安定）等。

与口服给药、肌肉注射、保留灌肠等给药途径相比，静脉注射药物有吸收好、起效快等特点，但对于 SE 病人，尤其是较严重的强直—阵挛性 SE 病人，由于发病期肢体或不断抽动或木僵，静脉注射有一定困难，此时亦有采用保留灌肠或肌肉注射或舌下给药治疗的情况，但前者由于吸收慢，难以迅速止惊，而后者多数病人强直，无法将药放入舌下而失败，因此上述治疗方法中除静脉注射外其它方法均难以达到较好的治疗效果。

本发明的目的在于针对上述问题,发明一种苯二氮䓬类药物——阿普唑仑鼻喷剂，从而达到治疗迅速、用药方便的目的。

本发明是这样实现的：阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂和其它药用辅料组成,所使用的药用辅料的种类和数量可根据制剂类型进行调整。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，其它辅料的用量为

0.01~500g。本发明所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂，可以包括其中的一种或几种。其中助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20g；生物粘附性高分子材料包括聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及其衍生物，其中聚丙烯酸包括多种型号的卡泊姆，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。

根据药物的的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。

溶液型的阿普唑仑鼻喷剂由主药阿普唑仑、药用溶剂、助溶剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，药

用溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-950ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成溶液即得到药液。

凝胶型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助溶剂、生物粘附性高分子材料、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；生物粘附性高分子材料包括：聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及衍生物，其中聚丙烯酸包括卡泊姆-934、974、941、981、TR-2 等型号，纤维素及衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节凝胶溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。用聚丙烯酸等制成亲水凝胶型鼻喷剂，

可以延长药物与鼻腔粘膜的接触时间，有利于提高生物利用度。其制备过程为将主药与各种适宜的药用辅料混合，制成亲水凝胶溶液即得到药物凝胶液。

混悬型的阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶如明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；渗透压调节剂包括：氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成混悬溶液即得到喷雾药液。

乳液型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g。本发明所用的溶剂为水、聚乙二醇（200、300、400）、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂

包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g，其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，采用干胶法或湿胶法制成混悬溶液即得到喷雾溶液。

阿普唑仑为新的苯二氮䓬类药物，有与地西泮相似的药理作用，有抗焦虑、抗惊厥、抗抑郁、镇静、催眠及肌肉松弛等作用，其作用比地西泮强 10 倍。将阿普唑仑制成鼻喷剂，药物经鼻腔毛细血管吸收后，直接进入体循环，而不经门—肝系统，避免了肝脏的首过效应，生物利用度高，血药浓度与静脉注射相似，因此阿普唑仑喷鼻治疗 SE 与静脉注射和直肠给药相比，不仅给药方便，而且起效快，吸收完全，可以达到较好的治疗效果。

下面是本发明的实施例，但并不受实施例的限制。

实施例 1

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	5g
乙醇	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 2

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
甜味剂	1.0g
香草香精	0.1g
苯甲醇	5 ml
乙醇	200ml
聚乙二醇	600ml
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 3

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
氯甲酚	1 g
乙醇	300ml
甘油	200mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 4

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
新洁尔灭	1g
乙醇	250ml
丙二醇	250mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 5

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
卡泊姆-934	5 g
β-环糊精	6g
0.1N NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装凝胶喷泵，包装，检验，入库。

实施例 6

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
卡泊姆 941	1.5g
β-环糊精	4g
三乙醇胺	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 7

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	1 g
卡泊姆-974	10 g
0.1N NaOH	适量
苯甲醇	5 g
乙醇	280ml
丙二醇	200ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于乙醇和丙二醇的混合物中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液(1)和(2)混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 8

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8 g
甲基纤维素	15 g
β-环糊精	10g
0.1NHCl 或 NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将甲基纤维素、EDTA-2Na、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），

将溶液(1)和(2)混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 9

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
丙二醇	150ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇和丙二醇的混合物中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 10

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8g
卡泊姆 TR-2	1.5 g
β-环糊精	10g
三乙醇胺	适量
苯甲醇	5 g
丙二醇	250ml
甘油	100
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇和甘油的混合物中，制成溶液（1），将卡泊姆 TR-2、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加三乙醇胺调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 11

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 12

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
微晶纤维素	3 g
氯化钠	9 g
0.1N HCl 或 NaOH	适量
洁尔灭	5 g
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、微晶纤维素、氯化钠、洁尔灭及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 13

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
卡泊姆-941	2 g
葡萄糖	55 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、卡泊姆-941、葡萄糖、苯甲醇及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 14

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4g
油酸	80 g
卡泊姆 TR-2	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、油酸、卡泊姆 TR-2、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 15

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
肉蔻酸异丙酯	90 g
蔗糖酯	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、肉蔻酸异丙酯、蔗糖酯、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

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[57]摘要

一种苯二氮䓬类药物——阿普唑仑鼻喷剂，由主药阿普唑仑、药用溶剂和其它药用辅料组成。根据药物的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。本发明给药方便，起效快，吸收完全，可用于癫痫持续状态(SE)及癫痫的治疗。

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权利要求书

1.阿普唑仑的鼻喷剂，其特征在于由主药阿普唑仑、溶剂和其它药用辅料组成，在1000ml药液中，阿普唑仑的用量为0.5~10g，其它辅料的用量为0.01~500g。

2.权利要求 1 中所述的鼻喷剂，其特征在于其溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，其用量为5-1000ml。

3.权利要求 1 中所述的鼻喷剂，其特征在于权利要求 1 中所述的其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂和乳化剂，其中助溶剂为环糊精，其用量为0.1～20g；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇和纤维素，其用量为0.1～25g；助悬剂为聚丙烯酸、聚乙烯吡咯烷酮、纤维素和天然胶，其用量为0.5～50g；油脂为油酸和肉蔻酸异丙酯，其用量为20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆和卡泊姆，其用量为1.5-80。

4.权利要求 1 中所述的鼻喷剂，其特征在于它可制备成溶液型、混悬型、凝胶型、乳液型四种类型；

5.权利要求 4 中所述的鼻喷剂，其特征在于溶液型的主要成分是阿普唑仑和溶剂；在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-950ml。

6.权利要求 4 中所述的鼻喷剂，其特征在于凝胶型的主要成分是阿普唑仑、溶剂、生物粘附性高分子材料，在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-1000ml；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素，可以是其中的一种或几种，其用量为0.1～25g。

7.权利要求 4 中所述的鼻喷剂，其特征在于混悬型的主要成分是阿普唑仑、溶剂、助悬剂，在1000ml药液中，阿普唑仑的用量为0.5~10g，所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为6-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素、天然

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胶， 可以是其中的一种或几种，其用量为 0.5～50g。

8.权利要求 4 中所述的鼻喷剂，其特征在于乳液型的主要成分是阿普唑仑、溶剂、油脂、乳化剂,在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；油脂为油酸和肉蔻酸异丙酯，可以是其中的一种或几种，其用量为 20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆，可以是其中的一种或几种，其用量为 1.5-80g。

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说 明 书

阿普唑仑鼻喷剂

本发明涉及苯二氮䓬类药物——阿普唑仑鼻喷剂，属于化学和药物制剂领域。

癫痫是一种可由多种不同因素引起的反复发作性的脑功能紊乱现象，又称抽风、羊角风，一般大致可分为全身性发作和部分性发作两类。癫痫持续状态（SE）是指发作时间超过 30 分钟或者发作频繁而在间歇期意识始终未能完全恢复正常的病症，属神经系统危重症之一。发病时常出现缺氧、高热、脑水肿、心血管系统紊乱、低血糖以及呼吸道感染等进一步加重惊厥甚至危及生命的病理生理改变，如不及时治疗，病人即有病死和致残的可能，故应采取果断而有力的治疗措施尽快止惊。目前临床认为理想的止惊药应具备下列性能：（1）脂溶性高，易透过血脑屏障，迅速达到脑内药物峰值；（2）作用强而不会显著抑制呼吸和血压；（3）半衰期长，不必多次用药；（4）用药途径方便，药物起效迅速；（5）与其它止惊药之间无不利的相互作用；（6）苏醒较快；（7）无矛盾反应，即某药效果不佳需加大剂量或换用同类药物时 SE 反而加重的情况。目前控制 SE 一般首选苯二氮䓬类药物，如静脉注射地西泮（安定）、劳拉西泮（氯羟安定）氯硝西泮（氯硝安定）等。

与口服给药、肌肉注射、保留灌肠等给药途径相比，静脉注射药物有吸收好、起效快等特点，但对于 SE 病人，尤其是较严重的强直—阵挛性 SE 病人，由于发病期肢体或不断抽动或木僵，静脉注射有一定困难，此时亦有采用保留灌肠或肌肉注射或舌下给药治疗的情况，但前者由于吸收慢，难以迅速止惊，而后者多数病人强直，无法将药放入舌下而失败，因此上述治疗方法中除静脉注射外其它方法均难以达到较好的治疗效果。

本发明的目的在于针对上述问题,发明一种苯二氮䓬类药物——阿普唑仑鼻喷剂，从而达到治疗迅速、用药方便的目的。

本发明是这样实现的：阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂和其它药用辅料组成,所使用的药用辅料的种类和数量可根据制剂类型进行调整。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，其它辅料的用量为

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0.01~500g。本发明所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂，可以包括其中的一种或几种。其中助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20g；生物粘附性高分子材料包括聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及其衍生物，其中聚丙烯酸包括多种型号的卡泊姆，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。

根据药物的的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。

溶液型的阿普唑仑鼻喷剂由主药阿普唑仑、药用溶剂、助溶剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，药

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用溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-950ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成溶液即得到药液。

凝胶型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助溶剂、生物粘附性高分子材料、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；生物粘附性高分子材料包括：聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及衍生物，其中聚丙烯酸包括卡泊姆-934、974、941、981、TR-2 等型号，纤维素及衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节凝胶溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。用聚丙烯酸等制成亲水凝胶型鼻喷剂，

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可以延长药物与鼻腔粘膜的接触时间，有利于提高生物利用度。其制备过程为将主药与各种适宜的药用辅料混合，制成亲水凝胶溶液即得到药物凝胶液。

混悬型的阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶如明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；渗透压调节剂包括：氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成混悬溶液即得到喷雾药液。

乳液型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g。本发明所用的溶剂为水、聚乙二醇（200、300、400）、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂

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包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g，其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，采用干胶法或湿胶法制成混悬溶液即得到喷雾溶液。

阿普唑仑为新的苯二氮䓬类药物，有与地西泮相似的药理作用，有抗焦虑、抗惊厥、抗抑郁、镇静、催眠及肌肉松弛等作用，其作用比地西泮强 10 倍。将阿普唑仑制成鼻喷剂，药物经鼻腔毛细血管吸收后，直接进入体循环，而不经门—肝系统，避免了肝脏的首过效应，生物利用度高，血药浓度与静脉注射相似，因此阿普唑仑喷鼻治疗 SE 与静脉注射和直肠给药相比，不仅给药方便，而且起效快，吸收完全，可以达到较好的治疗效果。

下面是本发明的实施例，但并不受实施例的限制。

实施例 1

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	5g
乙醇	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 2

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处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
甜味剂	1.0g
香草香精	0.1g
苯甲醇	5 ml
乙醇	200ml
聚乙二醇	600ml
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 3

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
氯甲酚	1 g
乙醇	300ml
甘油	200mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 4

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
新洁尔灭	1g
乙醇	250ml
丙二醇	250mL
水	稀释至 1000ml

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操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 5

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
卡泊姆-934	5 g
β-环糊精	6g
0.1N NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装凝胶喷泵，包装，检验，入库。

实施例 6

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
卡泊姆 941	1.5g
β-环糊精	4g
三乙醇胺	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

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操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 7

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	1 g
卡泊姆-974	10 g
0.1N NaOH	适量
苯甲醇	5 g
乙醇	280ml
丙二醇	200ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于乙醇和丙二醇的混合物中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液(1)和(2)混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 8

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8 g
甲基纤维素	15 g
β-环糊精	10g
0.1NHCl 或 NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将甲基纤维素、EDTA-2Na、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），

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将溶液(1)和(2)混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 9

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
丙二醇	150ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇和丙二醇的混合物中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 10

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8g
卡泊姆 TR-2	1.5 g
β-环糊精	10g
三乙醇胺	适量
苯甲醇	5 g
丙二醇	250ml
甘油	100
水	稀释至 1000ml

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操作：按处方比例将主药与β-环糊精溶于丙二醇和甘油的混合物中，制成溶液（1），将卡泊姆 TR-2、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加三乙醇胺调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 11

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 12

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
微晶纤维素	3 g
氯化钠	9 g
0.1N HCl 或 NaOH	适量
洁尔灭	5 g
水	稀释至 1000ml

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操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、微晶纤维素、氯化钠、洁尔灭及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 13

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
卡泊姆-941	2 g
葡萄糖	55 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、卡泊姆-941、葡萄糖、苯甲醇及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 14

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4g
油酸	80 g
卡泊姆 TR-2	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

BNSDOCID: <CN.....1803674A_...1.>

操作：按处方比例将主药、油酸、卡泊姆 TR-2、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 15

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
肉蔻酸异丙酯	90 g
蔗糖酯	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、肉蔻酸异丙酯、蔗糖酯、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

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(54) Title: OIL-IN-WATER EMULSIONS COMPRISING A BENZODIAZEPINE DRUG

(57) Abstract: There is provided oil-in-water emulsion compositions comprising a benzodiazepine drug, such as midazolam, that is dissolved in an oil phase that comprises 1 to 35% (w/w) vitamin E.

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OIL-IN-WATER EMULSIONS COMPRISING A BENZODIAZEPINE DRUG

This invention relates to new oil-in-water emulsion compositions.

Emulsion systems have long been used for pharmaceutical purposes. Such systems include oil-in-water emulsions, water-in-oil emulsions and more complex systems known as multiple emulsions.

Oil-in-water emulsions, in which the continuous phase is aqueous and the dispersed phase is oily in nature, may be used for a variety of purposes and administered *via* a variety of routes, including injection as well as administration to the eye, nose, lung, gastrointestinal tract or vagina.

Benzodiazepine compounds, which act on the central nervous system to cause sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and to prevent convulsions, are widely used in medicine. The benzodiazepine drug midazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5α-][1,4]benzodiazepine) is used as a sedative, especially in a hospital setting and particularly as premedication prior to surgery.

The intranasal administration of aqueous solutions of midazolam as a sedative prior to minor invasive surgical and medical procedures has been widely reported (see, for example, S. Björkman *et al. British Journal of Anaesthesia* 79, 575-580 (1997) and N. C. T. Wilton *et al. Anesthesiology* 69, 972-975 (1988)). It has been especially used in the paediatric patient group. Apart from being a patient group in which alleviation of anxiety is particularly beneficial, the use of intranasal midazolam has been largely confined to children because of limited solubility of the drug substance. The aqueous solubility of midazolam is low, and to deliver a therapeutic dose to an adult by the intranasal route would require a prohibitively large

dose volume. An additional drawback of the intranasal administration of midazolam, and which could limit its use (especially in children), is the irritation and stinging that it causes in the nasal cavity. At least part of the cause of this discomfort is thought to be the acidic pH of the simple aqueous solutions of midazolam that are used.

WO 00/24373 describes oil-in-water emulsions of drugs that are poorly soluble in water, especially non-steroidal anti-inflammatory drugs and drugs for the treatment of pain, erectile dysfunction and Parkinson's disease. Compositions comprising Vitamin E and benzodiazepines are neither disclosed nor suggested.

Compositions comprising benzodiazepines are described in US 4,950,664. The use of vitamin E in such compositions is neither disclosed nor suggested. Further, preferred dosage forms are solutions, suspensions and gels.

A formulation containing 17 mg/mL midazolam, achieved by using sulfobutylether-β-cyclodextrin as a solubilising agent, has been described by Loftsson *et al.* (*Int. J. Pharm.* 212, 29-40, (2001)). Penkler et al describes the use of randomly methylated β-cyclodextrin to produce a solution containing 10 mg/mL midazolam (*AAPS PharmSci. Supplement* 1, S-3642, (1999)).

WO 97/03651 describes emulsion compositions containing vitamin E as a solubilising agent. There is no suggestion in this document of emulsions containing benzodiazepines.

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Emulsion formulations of drug compounds are described in US 6,193,985. The compositions comprise active agent dissolved in an oil phase comprising tocopherol (vitamin E), wherein the vitamin E comprises 20 to 95% w/w of the compositions. The second phase of the emulsion comprises vitamin E TPGS as the emulsifying agent. Vitamin E TPGS is a water soluble derivative of vitamin E and consists of tocopherol esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Compositions in which the oil phase comprises 1 to 35% (w/w) of vitamin E are neither disclosed nor suggested.

Nonetheless, there is an unmet need for benzodiazepine (and especially midazolam) compositions that contain high concentrations of active agent, that give minimal irritation of the nasal cavity on intranasal administration, and that are stable over prolonged periods.

We have found, surprisingly, that the above-mentioned problems may be solved using an emulsion formulation in which both the amount of oil phase in the emulsion as well as the vitamin E content of that oil phase are carefully selected. We have additionally found that emulsion stability may be further enhanced by addition of a non-ionic surfactant and/or a cellulose-based thickening agent. When administered into the nasal cavity, the emulsion is well tolerated.

Thus, according to the invention there is provided oil-in-water emulsion compositions for the delivery of a benzodiazepine drug to a patient comprising:

(a) an oil phase, which phase comprises 10 to 60% (w/v) of the emulsion, and which phase comprises vitamin E in an amount 1 to 35% (w/w of that phase) and a benzodiazepine drug;

(b) an aqueous phase; and

(c) an emulsion stabiliser,

which compositions are referred to hereinafter as "the emulsions according to the invention".

It is preferred that the emulsions according to the invention are adapted for intranasal administration.

When used herein, the term "vitamin E" includes all tocol and tocotrienol derivatives that exhibit vitamin E activity. It is preferred that the vitamin E is water insoluble and/or non-water dispersible. The nomenclature for vitamin E and related compounds is unclear in current practice and can vary when used by different compendia and organisations. The United States Pharmacopoeia describes vitamin E as a form of α-tocopherol. This includes D- or D,L-α-tocopherol, D- or D,L-α-tocopherol acetate and D- or D,L-α-tocopherol succinate. The Association of Official Analytical Chemists (AOAC) states that the term vitamin E should be used as a generic description for all tocol and tocotrienol derivatives that exhibit vitamin E activity. Thus the term tocopherols is synonymous with vitamin E but also for methyl tocols. α-Tocopherol is a trivial name without defined stereochemistry.

The vitamin E is preferably in the form of the free alcohol, but suitable tocopherol derivatives include esters of tocopherol such as the linoleate, nicotinate, acetate or acid succinate ester.

The emulsions according to the invention have an oil phase that comprises one or more pharmaceutically acceptable oils. These oils are preferably non-hydroxylated (i.e. they have a hydroxyl value of less than 20) and as such they include vegetable oils such as soybean oil, sesame oil, safflower

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oil, canola oil, corn oil, cottonseed oil and olive oil as well as marine oils such as cod liver oil and sardine oil. Preferred oils are sesame oil, canola oil, corn oil, cottonseed oil, and, especially, soybean oil.

The emulsions according to the invention preferably have an oil phase that represents 12 to 50% (w/v) and more preferably 15 to 40% (w/v) of the total emulsion. Further, the emulsions according to the invention preferably have an oil phase that comprises 2.5 to 30% (w/w) (such as 5 to 25% (w/w)) vitamin E.

When used herein, the term "benzodiazepine drug" will be understood by those skilled in the art to include all pharmacologically active compounds that possess the benzodiazepine (sub-)structure, and which may act on the central nervous system. See also the definition provided in Goodman & Gilman's "*The Pharmacological Basis of Therapeutics*", 9th Edition (1996), McGraw-Hill at pages 363 and 364, the relevant disclosure in which document is hereby incorporated by reference. Examples of suitable benzodiazepine drugs include alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepic acid, clorazepate, clotiazepam, clozapine, delorazepam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazapem, tetrazepam and triazolam. Preferred benzodiazepine drugs include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, nitrazepam, oxazepam, prazepam, quazepam, temazapem, triazolam and, especially, midazolam.

The benzodiazepine drug content of the emulsions according to the invention is dependent upon the solubility of the benzodiazepine drug in question and the dose that needs to be delivered to the patient. For an intranasal formulation delivered as a liquid, the typical dose volume is in the range 0.1 to 0.4 mL although smaller or larger volumes may also be given. The benzodiazepine drug may be incorporated into the emulsions according to the invention by being dissolved into the oil phase prior to emulsification. The benzodiazepine drug content of the oil phase prior to preparation of the emulsions according to the invention is preferably in the range 1 to 1000 mg/mL, more preferably 2 to 800 mg/mL and most preferably 4 to 600 mg/mL. The benzodiazepine drug content of the final oil-in-water emulsion is preferably in the range 0.1 to 300 mg/mL, more preferably 0.5 to 250 mg/mL and most preferably 1 to 200 mg/mL.

When used herein, the term "emulsion stabiliser" refers to agents that, when present in emulsions according to the invention, either prevent or retard phase separation (i.e. the formation of distinct oil and/or water layers) in the emulsions. The term therefore includes agents that prevent phase separation in the emulsions according to the invention for one or more hours or, preferably, for one or more days (e.g. 3 or more days, such as one or more weeks, and, particularly, one or more months).

The emulsion stabiliser is preferably incorporated into the emulsions according to the invention *via* the aqueous phase. Preferred emulsion stabilisers include one or more thickening and/or, particularly, emulsifying agents. Suitable thickening agents include cellulose-based thickening agents such as methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Suitable emulsifying agents include:

(a) ionic surfactants (e.g. phospholipids such as lecithin); and

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(b) non-ionic surfactants (e.g. polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polyoxyethylene castor oil derivatives and polyoxyethylene alkyl ethers).

Detailed descriptions of the non-ionic surfactants mentioned above may be found in the "*Handbook of Pharmaceutical Excipients*", Kibbe (ed), 3rd edition, American Pharmaceutical Association (Washington) and Pharmaceutical Press (London), 2000.

Principle sources of lecithin are eggs and soybeans. Synonyms for lecithin include egg lecithin; mixed soybean phosphatides; ovolecithin; egg yolk phospholipids; soybean lecithin; soybean phospholipids; vegetable lecithin.

Preferred emulsions according to the invention include those that include an emulsion stabiliser that is an emulsifying agent (e.g. an ionic surfactant such as lecithin). In this respect, preferred emulsions according to the invention also include those in which lecithin is employed as an emulsion stabiliser, and a non-ionic surfactant and/or a thickening agent, as hereinbefore defined, is/are optionally employed as (a) further emulsion stabiliser(s).

The amount of emulsion stabiliser (e.g. lecithin) used in the emulsion according to the invention is preferably in the range 0.01 to 15% (w/v), more preferably 0.05 to 10% (w/v) and most preferably 0.1 to 5% (w/v).

When present in the emulsions according to the invention, the non-ionic surfactant may have a concentration that is preferably in the range 0.01 to 25% (w/v), more preferably 0.05 to 20% (w/v) and most preferably 0.1 to 15% (w/v).

When present in the emulsions according to the invention, the thickening agent may have a concentration that is dependent upon its molecular weight. However, its concentration in an emulsion according to the invention is preferably in the range 0.01 to 20% (w/v), more preferably 0.05 to 15% (w/v) and most preferably 0.1 to 10% (w/v).

The pH of the emulsions according to the invention is an important determinant of how well they are tolerated when administered into the nasal cavity. The emulsion may cause irritation and stinging if the pH is too high or low. Further, when the emulsion according to the invention comprises midazolam, it is also preferable to avoid a low pH in order to minimise drug partitioning from the oil phase into the aqueous phase. High concentrations of midazolam in the aqueous phase may exacerbate irritation.

Measuring accurately the pH of an oil-in-water emulsion may be problematic. Indeed, it may be more convenient to measure the pH of the aqueous phase of the emulsion. This measurement may be performed by centrifugation of the emulsion at a force adequate to separate the oil and aqueous phases into separate layers. The aqueous layer may then be removed and the pH measured. The pH of the aqueous phase of an emulsion according to the invention is preferably in the range pH 5.0 to 8.0, more preferably 5.25 to 7.8 and most preferably pH 5.5 to 7.6.

The pH of the aqueous phase of the emulsions according to the invention may be adjusted and controlled by means well known to those skilled in the art, such as buffer salts, acids and bases. Thus, the aqueous phase may contain one or more of the following pH controlling agents: organic acids (e.g. citric acid and the like) or alkali metal (e.g. sodium) salts thereof, pharmaceutically acceptable salts (e.g. sodium, magnesium or calcium salts) of inorganic acids (such as carbonic acid or phosphoric acid), oxides of

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magnesium, as well as alkali, and alkaline earth, metal (e.g. sodium, calcium, potassium and the like) sulphates, metabisulphates, propionates and sorbates. The aqueous phase may, in particular, comprise a buffered aqueous solution, such as phosphate-buffered saline, that has a pH within any of the above-mentioned ranges (e.g. pH 7.4).

The emulsions according to the invention may, if necessary, be adjusted to approximately the same osmotic pressure as that of the body fluids. This may be desirable where a composition is to be applied to delicate tissue membranes, such as those found in the nasal cavity. A composition that has been adjusted in this manner is said to be isotonic and will not tend to swell or contract the tissues with which it comes into contact and will result in minimal discomfort on application. The formation of isotonic preparations may be achieved by adding an ionic compound, such as sodium chloride, or a non-ionic compound to the composition. Suitable non-ionic compounds include glycerol and mannitol.

The emulsions according to the invention may also contain other ingredients in the oil and/or aqueous phases such as antioxidants, chelating agents, preservatives or other agents generally used in pharmaceutical liquid or emulsion formulations. Such agents are well known to those skilled in the art.

Preferred emulsions according to the invention include those that are stable with respect to phase separation for one or more days (e.g. 3 or more days, such as one or more weeks, and, particularly, one or more months). When used herein, the term "stable with respect to phase separation" includes compositions that, on storage, either do not form a distinct oil layer or form a distinct layer of non-coalesced oil droplets that may be redispersed by

gentle shaking (e.g. shaking by hand) alone. The latter process, by which a layer of stabilised oil droplets separates, is known as "creaming".

In their simplest form, the emulsions according to the invention are prepared by dissolving or dispersing emulsion stabiliser in the aqueous phase. The aqueous phase is then mixed with the oil phase (comprising vitamin E, oil and the benzodiazepine drug) to form a dispersion of oil droplets.

Thus, according to a further aspect of the invention, there is provided a process for the preparation of an emulsion according to the invention, which process comprises:

(i) addition of an emulsion stabiliser, as hereinbefore defined, to an aqueous component (e.g. water) to form the aqueous phase;

(ii) addition of vitamin E, and of a benzodiazepine drug, as hereinbefore defined, to an oil to form the oil phase; and

(iii) mixing the oil phase and the aqueous phase together.

The size and size distribution of the oil droplets in the emulsions according to the invention will depend on the method of mixing. In stable emulsions, the droplet size, as measured by techniques such as light microscopy or laser diffraction, generally lies in the range 0.1 to 10 μm. High shear mixing using equipment such as a homogeniser or a microfluidiser is the preferred method of preparing pharmaceutical emulsions.

According to a further aspect of the invention, there is provided the use of an emulsion according to the invention for the manufacture of a medicament for the administration of a benzodiazepine drug (e.g. midazolam) to a patient in need of such administration.

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Similarly, another aspect of the invention provides a method of administering a benzodiazepine drug (e.g. midazolam) to a patient, which method comprises administering to the patient an emulsion according to the invention.

In another aspect of the invention, there is provided the use of an emulsion according to the invention in the manufacture of a medicament for the treatment of a condition in which benzodiazepine drug treatment is indicated.

Particular conditions where benzodiazepine drug treatment may be indicated include anxiety disorders, convulsive disorders (e.g. febrile convulsions and convulsions from status epilepticus), disturbed behaviour, parasomnias (e.g. insomnia, restless leg syndrome, sleepwalking or night terrors), dyspnoea, muscle spasm (e.g. from spasticity, dystonias, stiff-man syndrome, cerebral palsy, poisoning or tetanus), emesis (e.g. nausea and vomiting associated with, for example, cancer chemotherapy), schizophrenia, vertigo and withdrawal syndromes (e.g. alcohol or opioid withdrawal).

Benzodiazepine drugs may also be given for premedication (e.g. before general anaesthesia or to provide sedative cover for minor surgical or investigative procedures) and/or to induce sedation, hypnosis and/or anterograde amnesia. Preferred indications include the provision of sedative cover for minor surgical or investigative procedures.

The emulsions according to the invention may be administered orally or parenterally. When used herein, the term "parenterally" includes administration to the muscles, subcutaneous tissue, peritoneal cavity, venous system, arterial system, lymphatic system, spinal fluid (intrathecal,

epidural) and joint cavities. Parenteral formulations will be sterile and usually pyrogen-free.

The emulsions according to the invention may also be administered to the gastrointestinal tract or other mucosal surfaces, such as the eye, nose, vagina or rectal cavity.

It is preferred that the emulsions according to the invention are administered intranasally. When adapted for intranasal administration, the emulsions according to the invention may be administered to the nasal cavity in forms including drops or sprays. Spray devices can be single ("unit") dose or multiple dose systems and are available from various commercial sources, including Pfeiffer, Valois, Bespak and Becton-Dickinson.

Emulsions according to the invention have the advantage that they may be more stable than (particularly with respect to phase separation), be better tolerated than, be less toxic than, have fewer side effects than, have better pharmacokinetic properties than, be more easily prepared than, or have any other useful properties over, compositions known in the prior art.

Moreover, emulsions according to the invention also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials that are approved for use in food or pharmaceuticals or are of like regulatory status.

The invention is illustrated, but in no way limited, by the following examples.

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Examples

Example 1

Placebo emulsion comprising 25% w/v oil phase in which oil phase comprises 40% w/w vitamin E

The oil phase was prepared by mixing 10 g of vitamin E (Sigma, Poole, UK) with 15 g of soybean oil (Oleificio SABO, Manno, Switzerland). Into 50 mL of phosphate buffered saline solution (PBS; Sigma) was dispersed 1.2 g of egg yolk phospholipid (lecithin; Kabi Pharmacia, Sweden), followed by the addition of 2.2 g of glycerol (Sigma). A coarse emulsion was prepared by mixing the oil and aqueous phases using a Silverson L4R homogeniser. The coarse emulsion was adjusted to a 100 mL volume with PBS and further emulsified by passing through a Rannie Mini-Lab high pressure valve homogeniser set at 1000 bar pressure.

Example 2

Placebo emulsion comprising 25% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 5 g of vitamin E with 20 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 3

Placebo emulsion comprising 33.3% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 6.66 g of vitamin E with 26.64 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 4

Placebo emulsion comprising 40% w/v oil phase in which oil phase comprises 20% w/w vitamin E

The oil phase was prepared by mixing 8 g of vitamin E with 32 g of soybean oil. The emulsion was then prepared in an identical manner to Example 1.

Example 5

Stability of emulsions prepared in Examples 1-4

Samples of the emulsions prepared in Examples 1-4 were sealed into 50 mL clear glass injection vials and stored at room temperature. The appearance of the emulsions was recorded over a 7-day period. The results are provided in the table below. Examples 2,3 and 4 showed good physical stability over the test period. Although there was some separation of the two phases (creaming), the uniform appearance of the emulsions could be restored with gentle shaking.

Example 1, with an oil phase comprising 40% w/w vitamin E, had poor stability and the oil phase readily separated. It was not possible to restore the emulsion to its original uniform state by means of shaking.

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Sample	Time of observation				
	Start	3 hours	1 day	3-4 days	7 days
Ex. 1	Stable	Stable	Slight separation, easily redispersed	Separation	Separation
Ex. 2	Stable	Stable	Stable	Stable	Slight separation, easily redispersed
Ex. 3	Stable	Stable	Stable	Slight separation, easily redispersed	Slight separation, easily redispersed
Ex. 4	Stable	Stable	Slight separation, easily redispersed	Slight separation, easily redispersed	Slight separation, easily redispersed

Example 6

Emulsion containing 10 mg/mL midazolam and 25% w/v oil phase

Vitamin E (5 g) and 20 g of soybean oil were weighed into a 50 mL beaker. Midazolam (1 g; R. W. Unwin, Welwyn, UK) was added to the vitamin E/soybean oil and the mixture was warmed and stirred at 30-40°C until the drug had dissolved. Egg yolk phospholipid (1.2 g; lecithin) was weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) was added to the lecithin dispersion. The oil phase was added to the aqueous phase and the two were mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed was made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product was a milky white to off-white emulsion.

Example 7

Emulsion containing 10 mg/mL midazolam and 33% w/v oil phase

Vitamin E (6.66 g) and 26.64 g of soybean oil were weighed into a 50 mL beaker. Midazolam (1 g) was added to the vitamin E/soybean oil and the mixture was warmed and stirred at 30-40°C until the drug had dissolved. The emulsion was then prepared according to Example 6.

Example 8

Emulsion containing 10 mg/mL midazolam with polyoxyethylene 20 sorbitan monooleate as additional emulsifier

Vitamin E (5 g) and 20 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin) and 0.5 g of polyoxyethylene 20 sorbitan monooleate (Sigma) is weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40.C. Glycerol (2.2 g) is added to this aqueous phase. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 9

Emulsion containing 10 mg/mL midazolam with methylcellulose as thickening agent

Vitamin E (6.66 g) and 26.64 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin) and 0.5 g of methylcellulose (Methocel®

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A15LV; Colorcon, Orpington, UK) are weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to the lecithin dispersion. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 10

Emulsion containing 10 mg/mL midazolam with polyoxyl 40 stearate as additional emulsifier and hydroxypropyl methylcellulose as thickening agent

Vitamin E (6.66 g) and 26.64 g of soybean oil are weighed into a 50 mL beaker. Midazolam (1 g) is added to the vitamin E/soybean oil and the mixture is warmed and stirred at 30-40°C until the drug has dissolved. Egg yolk phospholipid (1.2 g; lecithin), 0.5 g of polyoxyl 40 stearate (polyoxyethylene (40) stearate; Sigma) and 0.5 g of hydroxypropyl methylcellulose (Methocel® K4M; Colorcon) are weighed into a 250 mL beaker and dispersed into 50 mL of pH 7.4 phosphate buffered saline solution at 30-40°C. Glycerol (2.2 g) is added to the lecithin dispersion. The oil phase is added to the aqueous phase and the two are mixed together by homogenisation for 1 minute at 7000-8000 rpm using a Silverson L4R mixer. The coarse emulsion thus formed is made up to a volume of 100 mL and then passed three times through a Rannie Mini-Lab homogeniser at a pressure of 1000 bar. The final product will be a milky white to off-white emulsion.

Example 11

Tolerability of midazolam emulsion in sheep

The sheep is an excellent animal model for nasal pharmacokinetic studies with a large nasal cavity and the ability to receive human-sized doses of drugs and formulations. If an irritant drug or formulation is administered intranasally to the sheep, it may cause the animal to sneeze and snort and the extent of sneezing and snorting may be related to the irritancy of the formulation. A group of five sheep were each administered with a midazolam emulsion formulation of identical composition to Example 7 as part of a pharmacokinetic study. Each animal, weighing approximately 55 kg, was administered intranasally with the emulsion at a dose volume of 0.02 mL/kg divided equally between both nostrils i.e. a 55 kg sheep received 0.55 mL of emulsion per nostril. In the 60 minutes following dosing, any incidences of sneezing or snorting were recorded. There were no incidences in any of the five animals during this period, indicating that the formulation was extremely well tolerated.

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Claims

1. An oil-in-water emulsion composition for the delivery of a benzodiazepine drug to a patient comprising:
   (a) an oil phase, which phase comprises 10 to 60% (w/v) of the emulsion, and which phase comprises vitamin E in an amount 1 to 35% (w/w of that phase) and a benzodiazepine drug;
   (b) an aqueous phase; and
   (c) an emulsion stabiliser.

2. A composition as claimed in Claim 1, wherein the benzodiazepine drug is alprazolam, bentazepam, bromazepam, brotizolam, camazepam, chlordiazepoxide, cinolazepam, clobazam, clonazepam, clorazepic acid, clorazepate, clotiazepam, clozapine, delorazepam, diazepam, estazolam, ethyl loflazepate, etizolam, fludiazepam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, metaclazepam, mexazolam, midazolam, nimetazepam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazapem, tetrazepam or triazolam.

3. A composition as claimed in Claim 2, wherein the benzodiazepine drug is alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, oxazepam, prazepam, quazepam, temazapem or triazolam.

4. A composition as claimed in Claim 3, wherein the benzodiazepine drug is midazolam.

5. A composition as claimed in any one of the preceding claims, wherein the oil phase comprises a non-hydroxylated oil.

6. A composition as claimed in Claim 5, wherein the non-hydroxylated oil is soybean oil, sesame oil, safflower oil, canola oil, corn oil, cottonseed oil, olive oil, cod liver oil or sardine oil.

7. A composition as claimed in Claim 6, wherein the non-hydroxylated oil is soybean oil, sesame oil, canola oil, corn oil or cottonseed oil.

8. A composition as claimed in Claim 7, wherein the non-hydroxylated oil is soybean oil.

9. A composition as claimed in any one of the preceding claims, wherein the oil phase represents 12 to 50% (w/v) of the emulsion.

10. A composition as claimed in Claim 9, wherein the oil phase represents 15 to 40% (w/v) of the emulsion.

11. A composition as claimed in any one of the preceding claims, wherein the oil phase comprises 2.5 to 30% (w/w) vitamin E.

12. A composition as claimed in Claim 11, wherein the oil phase comprises 5 to 25% (w/w) vitamin E.

13. A composition as claimed in any one of the preceding claims, wherein the benzodiazepine drug content of the oil-in-water emulsion is in the range 0.1 to 300 mg/mL.

14. A composition as claimed in any one of the preceding claims, wherein the emulsion stabiliser is one or more thickening and/or emulsifying agents.

BNSDOCID: <WO 03004015A1 >

15. A composition as claimed in Claim 14, wherein the emulsion stabiliser is an emulsifying agent.

16. A composition as claimed in Claim 15, wherein the emulsifying agent is an ionic surfactant.

17. A composition as claimed in Claim 16, wherein the ionic surfactant is a phospholipid.

18. A composition as claimed in Claim 17, wherein the phospholipid is lecithin.

19. A composition as claimed in any one of Claims 15 to 18, wherein a non-ionic surfactant and/or a thickening agent is/are optionally employed as (a) further emulsion stabiliser(s).

20. A composition as claimed in Claim 19, wherein the non-ionic surfactant is selected from the group consisting of a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene stearate, a polyoxyethylene castor oil derivative and a polyoxyethylene alkyl ether.

21. A composition as claimed in Claim 19 or Claim 20, wherein the thickening agent is cellulose-based.

22. A composition as claimed in Claim 21, wherein the thickening agent is methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose or hydroxypropyl methylcellulose.

23. A composition as claimed in any one of the preceding claims, wherein the pH of the aqueous phase is in the range pH 5.0 to 8.0.

24. A composition as claimed in any one of the preceding claims, wherein the emulsion is stable with respect to phase separation for one or more days.

25. The use of a composition as defined in any one of Claims 1 to 24 for the manufacture of a medicament for the administration of a benzodiazepine drug to a patient in need of such administration.

26. Use as claimed in Claim 25 wherein the benzodiazepine drug is midazolam.

27. A method of administering a benzodiazepine drug to a patient, which method comprises administering to the patient a composition as defined in any one of Claims 1 to 24.

28. A method as claimed in Claim 27, wherein the emulsion is administered intranasally.

29. The use of a composition as defined in any one of Claims 1 to 24 in the manufacture of a medicament for the treatment of a condition in which benzodiazepine drug treatment is indicated.

30. The use as claimed in Claim 29, wherein the condition to be treated is an anxiety disorder, a convulsive disorder, disturbed behaviour, a parasomnia, dyspnoea, muscle spasm, emesis, schizophrenia, vertigo or a withdrawal syndrome.

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31. The use as claimed in Claim 29, wherein the benzodiazepine drug is given for premedication and/or to induce sedation, hypnosis and/or anterograde amnesia.

32. A process for the preparation of a composition as defined in any one of Claims 1 to 24, which process comprises:

(i) addition of an emulsion stabiliser to an aqueous component to form the aqueous phase;

(ii) addition of vitamin E, and of a benzodiazepine drug, to an oil to form the oil phase; and

(iii) mixing the oil phase and the aqueous phase together.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K31/5513 A61K31/5517 A61K31/355 A61P25/08
A61P25/18 A61P25/20

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

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, BIOSIS, MEDLINE, EMBASE, PASCAL, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 193 985 B1 (SONNE METTE RYDAHL) 27 February 2001 (2001-02-27) cited in the application example 9	1-32
A	EP 0 391 369 A (YISSUM RES DEV CO) 10 October 1990 (1990-10-10) tables I,III	1-32
Y	WO 00 24373 A (DAVIS STANLEY STEWART ;ILLUM LISBETH (GB); WEST PHARM SERV DRUG RE) 4 May 2000 (2000-05-04) cited in the application page 6, line 24-26; claims 1-4,17	1-32

-/--

[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

"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
26 September 2002	07/10/2002

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

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

BNSDOCID: <WO 03013515A1 >

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 03651 A (DANBIOSYST UK ;ILLUM LISBETH (GB); WASHINGTON CLIVE (GB); LAWRENCE) 6 February 1997 (1997-02-06) cited in the application page 15, line 23 -page 16, line 17; claim 6	1-32
A	EP 0 163 924 A (ROSHDY ISMAIL) 11 December 1985 (1985-12-11) claim 1	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/03005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6193985 B1	27-02-2001	AU 697540 B2	08-10-1998
		AU 2670595 A	05-12-1995
		CA 2189328 A1	23-11-1995
		WO 9531217 A1	23-11-1995
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		FI 964583 A	15-11-1996
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EP 0391369 A	10-10-1990	IL 89856 A	13-05-1993
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WO 9703651 A	06-02-1997	AU 712621 B2	11-11-1999
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		WO 9703651 A1	06-02-1997
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		NO 975931 A	17-12-1997
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EP 0163924 A	11-12-1985	DE 3416209 A1	21-11-1985
		AT 70441 T	15-01-1992
		DE 3584909 D1	30-01-1992
		EP 0163924 A1	11-12-1985

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

BNSDOCID: <WO 03004015A1_L_>

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt, et al.	Group Art Unit: 1612
Serial Number: 12/413,439	Examiner: Adam C. Milligan
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: September 11, 2015

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Dear Examiner:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☒ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $900.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $90.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this

information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: September 11, 2015

By: /Matthew V. Grumbling/
Matthew V. Grumbling
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Customer No. 021971

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/413,439	Filing Date 03/27/2009	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/11/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 62	=	X $ =	
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/KATRINA . TURNER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/413,439	03/27/2009	Steve Cartt	35401-716.201	9049

21971 7590 10/05/2015

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/05/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 12/413,439	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/11/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *20-24,27-36,38 and 40-53* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *20-24,27-36,38 and 40-53* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *3/17/15, 9/11/2015*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/2015 has been entered.

Applicants' arguments, filed 9/11/2015, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statement filed 9/11/2015 fails to comply with 37 CFR 1.98(a)(3)(i) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each reference listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

Claims 20-24, 27-36, 38 and 40-53 are objected to because of the following informalities: the claims take the form:

> A method of intranasal administration of a benzodiazepine drug for treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or reoccurrence of seizure in a patient with a seizure disorder, consisting of: administering to one or more nasal mucosal membranes of the patient with a seizure disorder a pharmaceutical solution for nasal administration, consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, in an amount from about 30% to about 95% (w/w), **and** one or more alcohols or glycols, in an amount from about 10% to about 70% (w/w) **and** about 0.01 % (w/v) to about 1% (w/v) of one or more alkyl glycosides.

The use of commas in the middle of a sequential listing of elements renders the elements of the list confusing. This listing within a sentence is often referred to as a parallel structure. The multiple uses of the word “and” add to the confusing claim construction.

Claim Rejections - 35 USC § 112 – 4th paragraph

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

> Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claims 33-36 and 41-44 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Specifically, independent claim 20 is closed-ended as evidenced by the use of the transition phrase "consisting of", while these claims which depend from claim 20 are open-ended as evidenced by the transition phrase comprising. Given that the claims are open ended, they permit unrecited additional components. However, the independent claim does not permit additional components. These additional components are thus included in the dependent claims, but not in the independent claim. Accordingly, the dependent claims fail to include all the limitations of the claim upon which it depends. Applicant may cancel the claims, amend the claims to place the claims in proper dependent form, rewrite the claims in independent form, or present a sufficient showing that the dependent claims comply with the statutory requirements.

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 20-24, 27-36, 38 and 40-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehat (Intranasal midazolam for childhood seizures, The Lancet, vol.352, August 22, 1998 – See IDS dated 10/29/2013) in view of Sonne (U.S. 6,193,985- See IDS dated 9/16/2009) and Meezan (U.S. 2006/0046962).

Lehat teaches diazepam is widely used to treat acute seizures in adults and children and that intranasal administration of benzodiazepine compounds has been demonstrated as an effective way to manage acute childhood seizures (Abstract).

Lehat does not teach suitable excipients for the formulation.

Sonne teaches tocopherol compositions for the delivery of biologically active agents which are only sparingly soluble in water (col. 1, lines 7-13), such as diazepam (col. 1, lines 7-14). One particular nasal formulation contains 5g of diazepam, 44 g Tenox GT2 (70% tocopherol), 5 g Vitamin E TPGS, 1.45 g Pluronic and 0.1g benzalkonium chloride (example 1 at col. 7, lines 32-45). In preparing the formulation, the ingredients are heated slowly until a homogeneous phase is achieved (Sonne also teaches that co-solvent such as ethanol, benzyl alcohol, sesame oil or propylene glycol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, it may be used in an amount of about 11% by weight of the formulation (See example 3 at col.8, lines 28-43). When sesame oil is used, it may be used in an amount of about 44% (example18, col12, lines 37-51) or about 60% (example 16 at col.12, lines 10-17). α-tocopherol may be used in amounts of 20 to 99.9% (col.5, lines 56-61). The active ingredient should be present in an amount of 0.001% to 40% (col.5, lines 55-61). Diazepam may be present at about 5% by weight (example 11 at col. 11, lines 1-13). Preservative as well as odor masking compounds may be included in the (col.7, lines 4-12). The composition may be in the form of a spray formulation (col. 6, lines 28-35). In general, about 100µL can be administered to the nose at a time(col.7, lines 25-30). Sonne teaches that the "compositions of the invention may be used directly as a solution of bioactive agents in the tocopherol solvent" (col.3, lines 60-61) and that the "[v]iscosity can be reduced by the addition of co-solvents such as ethanol (col.3, lines 65-66). Sonne teaches that

“transmucosal delivery is preferred" (col.3, line 54) and "[n]asal...administrations are particularly preferred" (col.3, lines 58-59). The compositions of the invention may contain from 1-99.99% tocopherol (col.5, lines 55-57). Sonne also teaches that a co-solvent such as ethanol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53).

Sonne does not teach the surfactant is an alkyl glycoside.

Meezan teaches that alkyl glycosidase is an absorption enhancing surfactant for drug administration (¶150). Specifically, Meezan demonstrates that the addition of 0.25% of alkyl glycoside can increase drug absorption from about 3% bioavailabilty to about 90% bioavailability when the drug is administered via a nasal spray. Meezan further teaches that the active ingredient for the nasal spray may be in the form of nanoparticles (¶63).

Meezan does not teach using a benzodiazapine active ingredient.

It would have been obvious to one of ordinary skill in the art treating seizures as taught by Lehat to administer the benzodiazepine in the composition taught by Sonne to improve benzodiazepine solubility. Further, it would have been obvious to one of skill in the art administering the nasal spray formulation of Sonne to use the surfactant taught by Meezan to improve the bioavailability of drug administered via a nasal spray.

Applicants present the following argument against the rejection.

Applicants argue that the amended “consisting of" language excludes other components, such as those required to form separate phases, such as in an emulsion.

Thus, the combination of Sonne and Meezan would not have suggested the instantly claimed subject matter.

Examiner disagrees. Sonne teaches that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues (col.2, lines 54-58). The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent (col.3, lines 60-61). However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application (col.3, lines 62-64). To increase viscosity, co-solvents such as ethanol can be added (col.3, lines 65-67). Since ethanol can be irritating to certain mucosal tissue, Sonne alternatively teaches emulsification as a means to lower viscosity (col.4, lines 1-2). Thus, Sonne teaches three formulating alternatives, (1) high viscosity, (2) co-solvent (i.e. ethanol) addition and (3) emulsification. The high viscosity teaching and the co-solvent teaching render obvious the instantly recited claims.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-24, 27-36, 38 and 40-53 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 23, 25-30, 33-56 and 60-65 of copending Application No. 14/527,613 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to choose from the recited components.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

PTO/SB/08a (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	03/27/2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Milligan, Adam C.
Sheet	1	of	1	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US 2015-0065491	03/05/015	Cartt	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	2.	CA 2,723,470 Office Action dated February 19, 2015	
	3.	CN 201280039077.9 Office Action dated December 26,2014	X

Examiner Signature	/Adam Milligan/	Date Considered	09/28/2015

**EXAMINER:* *Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy* of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	March 27, 2009
				First Named Inventor	Steve Cartt
				Art Unit	1612
				Examiner Name	Adam C. Milligan
Sheet	1	of	1	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2004-0101482	5/1/2004	Sanders, Mark	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	2.	CN-1303674A	07/18/2001	Shen, N.		X
	3.	EP-1208863	5/1/2002	Ohki et al.		
	4.	WO-2003-004015	01/16/2003	West Pharm Serv Drug Res LTD		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	5.	EP12801372.9 Extended EP Search Report dated March 26, 2015	
	6.	Newman. Aerosol deposition consideration in inhalation therapy. Chest 152S-160S (1985)	
	7.	SUN, et al. Nasal spray for curing status epilepticus (SE) and epilepsy, comprises alprazolam and carriers. Database WPI, Section Ch, Week 200164. Thomson Scientific	
	8.	U.S. Serial No. 14/021,988 Office Action mailed May 22, 2015	
	9.	U.S. Serial No. 12/116,842 Office Action mailed July 8, 2015	

Examiner Signature	/Adam Milligan/	Date Considered	09/28/2015

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventor(s): Steve Cartt, *et al.* Serial No.: 12/413,439 Filed: March 27, 2009 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Examiner: Adam C. Milligan Confirmation No.: 9049 Customer No.: 21971 Certificate of Electronic Filing I hereby certify that the attached Correspondence is being deposited by Electronic Filing on March 30, 2016 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. By: /Linda Anders/

RESPONSE TO NON-FINAL OFFICE ACTION

Commissioner for Patents
Mail Stop: Amendment
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This Amendment is submitted in response to the Non-Final Office Action dated October 5, 2015. This Amendment is being submitted within the three-month period for response; therefore applicants believe no fee is required. However, the Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Amendments to the Claims begin on page **2**.

Remarks begin on page 7.

CLAIMS

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn/canceled claims in this or any other appropriate patent application.

Listing of Claims:

1-19. (Canceled).

20. (Currently Amended) A method of intranasal administration of a benzodiazepine drug for treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, consisting of:

administering to one or more nasal mucosal membranes of ~~the~~ said patient ~~with a seizure disorder~~ a pharmaceutical solution for nasal administration, said pharmaceutical solution consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols[[,]] in an amount from about 30% to about 95% (w/w), [[and]] one or more alcohols or glycols[[,]] in an amount from about 10% to about 70% (w/w), and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

21. (Canceled).

22. (Currently Amended) The method of claim [[21]] 20, wherein said patient is a human.

23. (Currently Amended) The method of claim 20, wherein ~~the~~ said benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Currently Amended) The method of claim 23, wherein ~~the~~ said benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Canceled)

26. (Canceled)

27. (Currently Amended) The method of claim 20, wherein ~~the~~ said one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

28. (Currently Amended) The method of claim 20, wherein ~~the~~ said one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

29. (Currently Amended) The method of claim 20, wherein ~~the~~ said one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Currently Amended) The method of claim 20, wherein ~~the~~ said benzodiazepine drug is present in ~~the~~ said pharmaceutical solution in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Currently Amended) The method of claim 30, wherein ~~the~~ said benzodiazepine drug is present in ~~the~~ said pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Currently Amended) The method of claim 31, wherein ~~the~~ said benzodiazepine drug is present in ~~the~~ said pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Currently Amended) The method of claim 20, wherein ~~the~~ said ~~pharmaceutical solution comprises~~ one or more natural or synthetic tocopherols or tocotrienols, or any

combinations thereof, are present in said pharmaceutical solution in an amount from about 45% to about 85% (w/w).

34. (Currently Amended) The method claim 33, wherein ~~the~~ said ~~pharmaceutical solution comprises~~ one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 60% to about 75% (w/w).

35. (Currently Amended) The method of claim 20, wherein ~~the~~ said ~~pharmaceutical solution comprises~~ one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 15% to about 55% (w/w).

36. (Currently Amended) The method of claim 35, wherein ~~the~~ said ~~pharmaceutical solution comprises~~ one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 25% to about 40% (w/w).

37. (Canceled)

38. (Currently Amended) The method of claim 20, wherein ~~the~~ said pharmaceutical solution is a pharmaceutically-acceptable spray formulation.

39. (Canceled).

40. (Currently Amended) The method of claim 38, wherein said ~~pharmaceutical solution is a~~ pharmaceutically-acceptable spray formulation ~~having~~ has a volume of from about 10 μL to about 200 μL.

41. (Currently Amended) The method of claim 40, wherein ~~the~~ said administration of ~~the~~ said pharmaceutical solution ~~comprises~~ consists of spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril of said patient.

42. (Currently Amended) The method of claim 40, wherein ~~the~~ said administration of ~~the~~ said pharmaceutical solution ~~comprises~~ consists of spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril of said patient.

43. (Currently Amended) The method of claim [[42]] 40, wherein ~~the~~ said administration of ~~the~~ said pharmaceutical solution ~~pharmaceutical solution comprises~~ consists of spraying a first quantity of ~~the~~ said pharmaceutical solution into ~~the~~ a first nostril, spraying a second quantity of ~~the~~ said pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of ~~the~~ said pharmaceutical solution into ~~the~~ said first nostril.

44. (Currently Amended) The method of claim [[43]] 40, ~~further comprising,~~ wherein said administration of said pharmaceutical solution consists of spraying a first quantity of said pharmaceutical solution into a first nostril, spraying a second quantity of said pharmaceutical solution into a second nostril, after a pre-selected time delay, spraying a third quantity of said pharmaceutical solution into said first nostril, and optionally after a pre-selected time delay, ~~administering~~ spraying at least a fourth quantity of ~~the~~ said pharmaceutical solution [[to]] into the second nostril.

45. (Currently Amended) The method of claim 43, wherein said nasal administration of ~~the~~ said pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with ~~the~~ said pharmaceutical composition.

46. (Canceled).

47. (Canceled).

48. (Currently Amended) The method of claim 20, wherein ~~the~~ said pharmaceutical solution consists of diazepam, vitamin E, ethanol ~~and optionally an~~ said alkyl glycoside.

49. (Currently Amended) The method of claim 48, wherein ~~the~~ said alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, ~~and/or~~ or a combination ~~combinations~~ of two or more thereof.

50. (Currently Amended) The method of claim 49, wherein ~~the~~ said alkyl glycoside is dodecyl maltoside.

51. (Currently Amended) The method of claim 20, wherein ~~the~~ said pharmaceutical solution consists of 1-20 mg diazepam, 45 % (w/w) to 85 % (w/w) vitamin E, 15% (w/w) to 55 % (w/w) of a combination of ethanol and benzyl alcohol, and 0.01 % (w/v) to 1 % (w/v) of alkyl glycoside.

52. (Currently Amended) The method of claim 51, wherein ~~the~~ said alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, ~~and/or~~ or a combination ~~combinations~~ of two or more thereof.

53. (Currently Amended) The method of claim 52, wherein ~~the~~ said alkyl glycoside is dodecyl maltoside

54. (New) The method of claim 35, wherein said one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 25% to about 55% (w/w).

REMARKS

This Amendment is in response to the Non-Final Office Action dated October 5, 2015. Claims 20, 22-24, 27-36, 38, and 40-45 and 48-54 are currently pending. Claims 20, 22-24, 27-36, 38, 40-45 and 48-53 are currently amended. Claims 1-19, 21, 25, 26, 37, 39 , 46 and 47 are cancelled. Claim 54 is new. Applicants respectfully request that the present amendment be entered, and request prompt examination of the present application. Applicants further submit that the application is now in condition for allowance.

Upon entry of this amendment, claims 20, 22-24, 27-36, 38, and 40-45 and 48-54 remain for further consideration for allowance.

Reconsideration is respectfully requested.

Claim Objections

The Office objected to claims 20-24, 27-36, 38, and 40-53 due to the informalities of using "commas in the middle of a sequential listing of elements," and of "multiple uses of the word 'and'" in independent claim 20. Non Final Office Action, dated October 5, 2015, page 3.

Applicant has amended claim 20 to address these informalities. Additionally, Applicant has offered voluntary amendments to address antecedent basis and other formal issues within the claims, without affecting their scope. Claim 54 is presented as a claim of intermediate scope between previously-presented claims. Applicant believes the claim objections to be moot in light of the presented amendments.

Rejections under 35 U.S.C. § 112 (pre-AIA), Fourth Paragraph

The Office rejected claims 33-36 and 41-44 under 35 U.S.C. § 112 (pre-AIA), Fourth Paragraph. Specifically, the Office stated: "independent claim 20 is closed-ended as evidenced by the use of the transition phrase "consisting of", while these claims which depend from claim 20 are open-ended as evidenced by the transition phrase comprising. Given that the claims are open ended, they permit unrecited additional components. However, the independent claim does not permit additional components." Non Final Office Action, dated October 5, 2015, page 4.

Applicant has amended all the pending claims to address antecedent basis and other informalities. Applicant believes the claim rejection to be moot in light of the presented amendments.

Rejections under 35 U.S.C. § 103 (a)

The Office rejected claims 20-24, 27-36, 38 and 40-53 under 35 U.S.C. § 103(a). The Office alleged that the above claims were unpatentable over Lehat ([sic, "Lahat"] (Intranasal midazolam for childhood seizures, The Lancet, vol. 352, August 22, 1998), in view of Sonne (U.S. 6,193,985) and Meezan (U.S. 2006/0046962). Specifically, the Office alleged that Lahat teaches intranasal administration of benzodiazepine compounds has been demonstrated as an effective way to manage acute childhood seizures (Abstract). The Office acknowledges that Lahat does not teach suitable excipients for the formulation. Non Final Office Action, dated October 5, 2015, page 6. The Office alleges that Sonne cures the excipient deficiency by teaching tocopherol compositions as suitable excipients for water insoluble agents. Non Final Office Action, dated October 5, 2015, page 6. The Office further alleges that Sonne teaches that such formulations may also include alcohols, for example, ethanol. Non Final Office Action, dated October 5, 2015, page 6. The Office acknowledges that Sonne does not teach compositions containing alkyl glycoside. Non Final Office Action, dated October 5, 2015, page 7. The Office alleges that Meezan cures the deficiency by teaching that alkyl glycoside enhances drug administration. Non Final Office Action, dated October 5, 2015, page 7.

Applicant respectfully disagrees. Sonne actually teaches away from intranasal administration of formulations of benzodiazepine containing one or more tocopherols and one or more alcohols or glycols. Specifically, Sonne states that bioactive agents dissolved in tocopherol solvents create viscous solutions, such that "the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application." Sonne, col. 3, ll. 62-64. Although Sonne teaches that "[v]iscosity can be reduced by addition of co-solvents such as ethanol," Sonne goes on to teach "but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues." *Id.*, col. 3, ll. 65-67. Although Sonne does not specifically state which tissues would be irritated by alcohol, Sonne presents ethanol-containing

formulations only for oral and rectal administration, but not for intranasal or intravaginal administration.

Thus, one of ordinary skill in the art would not have been motivated to administer an intranasal formulation consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols in an amount from about 30% to about 95% (w/w), one or more alcohols or glycols in an amount from about 10% to about 70% (w/w), and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides, at least because such a formulation would be expected to be unacceptably irritating to the nasal mucosa due to the presence of the alcohol.

Sonne gives 23 examples of various tocopherol preparations. None of the nose drop preparations consists of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and an alkyl glycoside. The only nasal preparations are Examples 1, 2, 4, 8-11, 15-17 and 19. Examples 1, 2, 4-10, 15, 17 and 19 are oil-in-water emulsion formulations. None contains ethanol. Furthermore, emulsion formulations are excluded by the use of "consisting of" language in the pending claims. Examples 11 and 16 are nose drop solutions. They also lack alcohol. In no case does Sonne teach or suggest administering an ethanol-containing solution to the nose.

This lack of teaching is remarkable in that Sonne does teach ethanol-containing formulations for administration to other tissues, such as the mouth and rectum. The example cited in the Non Final Office Action, dated October 5, 2015, page 6, (Example 3 at col. 8, ll. 28-43) as evidence that ethanol may be used in an amount of up to 11% by weight of the formulation, is for "[a] diazepam enema preparation." Sonne, col. 8, ll. 29. (emphasis added). There is no reason given, and none is apparent, why a solution suitable for rectal administration would also be suitable for intranasal administration. Other examples of ethanol-containing formulations are for administration to the oral cavity. *Id.*, Examples 5 and 14. Therefore, Sonne, in addition to not remedying the deficiencies of Lahat, actually teaches away from a method of use consisting of intranasal administration of the claimed alcohol-containing formulations.

Meezan fails to cure the deficiencies of Lahat and Sonne. Meezan is directed to improving drug absorption with, e.g., an alkyl glycoside. However, Meezan does not teach combining benzodiazepine drugs, an alcohol or glycol, and an alkyl glycoside, as required by the

claims. Meezan does not overcome Sonne's teaching that alcohol-containing formulations are too irritating for certain mucosal tissues.

Therefore, Applicant submits that the proposed combination of references not only fail to teach every limitation recited in the instant claims, but Sonne actually teaches away from intranasal administration of an intranasal pharmaceutical solution, wherein the pharmaceutical solution consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols in an amount from about 30% to about 95% (w/w), one or more alcohols or glycols in an amount from about 10% to about 70% (w/w), and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

Provisional Nonstatutory Double Patenting Rejection

The Examiner provisionally rejected claims 20-24, 27-36, 38 and 40-53 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 23, 25-30, 33-56 and 60-65 of co-pending U.S. Patent Application No. 14/527,613.

Without conceding the basis for rejection, Applicant will consider filing a terminal disclaimer over co-pending Application No. 14/527,613, should the claims of the present application be found to be otherwise allowable.

CONCLUSION

Applicants believe that the application is in condition for allowance and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, or should there be any remaining issues of a minor or purely formal nature that may be readily disposed of through a supplemental amendment, or Examiner's amendment, Applicants encourage the Examiner to telephone the undersigned at 858-350-2332.

Applicants hereby authorize the Commissioner to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: March 30, 2016

By: /Matthew V. Grumbling/
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Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Linda Anders
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
			Total in USD ($)	**700**

Electronic Acknowledgement Receipt

EFS ID:	25347918
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Linda Anders
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	30-MAR-2016
Filing Date:	27-MAR-2009
Time Stamp:	15:24:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$700
RAM confirmation Number	2059
Deposit Account	232415
Authorized User	ANDERS, LINDA
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-201-response3.pdf	197319 ed2973b088f9c3032e9b0c3e0603485c0c428273	yes	11

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	11

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30801 c5cd0ae15bd6a1dbbf5af20ffcc93192b2e12e93	no	2

Warnings:

Information:

Total Files Size (in bytes):	228120

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/413,439	Filing Date 03/27/2009	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **03/30/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 28	Minus	** 62	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/EFREM WARREN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/413,439	03/27/2009	Steve Cartt	35401-716.201	9049

21971 7590 07/14/2016
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/14/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 12/413,439	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/30/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *20,22-24,27-36,38,40-45 and 48-54* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *20,22-24,27-36,38,40-45 and 48-54* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Applicants' arguments, filed 3/30/2016, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20, 22-24, 27-36, 38, 40-45 and 48-54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lehat (Intranasal midazolam for childhood seizures, The Lancet, vol.352, August 22, 1998 – See IDS dated 10/29/2013) in view of Sonne (U.S. 6,193,985- See IDS dated 9/16/2009) and Meezan (U.S. 2006/0046962).

Lehat teaches diazepam is widely used to treat acute seizures in adults and children and that intranasal administration of benzodiazepine compounds has been demonstrated as an effective way to manage acute childhood seizures (Abstract).

Lehat does not teach suitable excipients for the formulation.

Sonne teaches tocopherol compositions for the delivery of biologically active agents which are only sparingly soluble in water (col. 1, lines 7-13), such as diazepam

(col. 1, lines 7-14). One particular nasal formulation contains 5g of diazepam, 44 g Tenox GT2 (70% tocopherol), 5 g Vitamin E TPGS (glycol), 1.45 g Pluronic and 0.1g benzalkonium chloride (example 1 at col. 7, lines 32-45). In preparing the formulation, the ingredients are heated slowly until a homogeneous phase is achieved (Sonne also teaches that co-solvent such as ethanol, benzyl alcohol, sesame oil or propylene glycol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, it may be used in an amount of about 11% by weight of the formulation (See example 3 at col.8, lines 28-43). When sesame oil is used, it may be used in an amount of about 44% (example18, col12, lines 37-51) or about 60% (example 16 at col.12, lines 10-17). α-tocopherol may be used in amounts of 20 to 99.9% (col.5, lines 56-61). The active ingredient should be present in an amount of 0.001% to 40% (col.5, lines 55-61). Diazepam may be present at about 5% by weight (example 11 at col. 11, lines 1-13). Preservative as well as odor masking compounds may be included in the (col.7, lines 4-12). The composition may be in the form of a spray formulation (col. 6, lines 28-35). In general, about 100µL can be administered to the nose at a time (col.7, lines 25-30). Sonne teaches that the “compositions of the invention may be used directly as a solution of bioactive agents in the tocopherol solvent” (col.3, lines 60-61) and that the "[v]iscosity can be reduced by the addition of co-solvents such as ethanol (col.3, lines 65-66). Sonne teaches that “transmucosal delivery is preferred" (col.3, line 54) and "[n]asal...administrations are particularly preferred" (col.3, lines 58-59). The compositions of the invention may contain from 1-99.99% tocopherol (col.5, lines 55-57). Sonne also teaches that a co-

solvent such as ethanol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53).

Sonne does not teach the surfactant is an alkyl glycoside.

Meezan teaches that alkyl glycosidase is an absorption enhancing surfactant for drug administration (¶150). Specifically, Meezan demonstrates that the addition of 0.25% of alkyl glycoside can increase drug absorption from about 3% bioavailabilty to about 90% bioavailability when the drug is administered via a nasal spray. Meezan further teaches that the active ingredient for the nasal spray may be in the form of nanoparticles (¶63).

Meezan does not teach using a benzodiazapine active ingredient.

It would have been obvious to one of ordinary skill in the art treating seizures as taught by Lehat to administer the benzodiazepine in the composition taught by Sonne to improve benzodiazepine solubility. Further, it would have been obvious to one of skill in the art administering the nasal spray formulation of Sonne to use the surfactant taught by Meezan to improve the bioavailability of drug administered via a nasal spray.

Applicants present the following argument against the rejection.

Applicants argue that Sonne teaches away from the instantly claimed methodby stating that bioactive agents dissolved in tocopherol solvents create viscous solutions such that "the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application." Sonne does teach that the viscosity can be reduces by the addition of co-solvents such as ethanol...but this is less desired since

solutions of this type tend to be irritating to certain mucosal tissues". Though Sonne does not teach which types of tissue may be irritated by alcohol, Sonne presents ethanol containing formulations only for oral and rectal administration, not for intranasal administration. Thus, Applicants request the rejection be withdrawn.

Examiner disagrees. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including non-preferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Here, while ethanol addition is not listed as a most preferred method for viscosity reduction, it is taught as a suitable method for such. A prior art reference must be considered for all that it teaches or suggests to one of ordinary skill in the art. It should not be limited to the exemplary formulations. It is further noted that nasal formulations are not limited to sprays, which may require higher amounts of ethanol, but can be in the form of drops, which can be more viscous.

Applicants reiterate that no exemplary formulations of Sonne teach the presence of ethanol and nasal administration. Examiner previously cited to a rectal formulation for providing an amount of ethanol, but has not given a reason why a solution suitable for rectal administration would also be suitable for nasal administration. Thus, the rejection should be withdrawn.

Examiner disagrees. Sonne teaches that the compositions may be administered to mucosal membranes, for example in the nose or rectum (col.3, lines 54-59). In fact, nasal and rectal administrations are particularly preferred (Id.).

Applicants argued that the “consisting of" language excludes other components, such as those required to form separate phases, such as in an emulsion. Thus, the combination of Sonne and Meezan would not have suggested the instantly claimed subject matter.

Examiner disagrees. Sonne teaches that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues (col.2, lines 54-58). The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent (col.3, lines 60-61). However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application (col.3, lines 62-64). To increase viscosity, co-solvents such as ethanol can be added (col.3, lines 65-67). Since ethanol can be irritating to certain mucosal tissue, Sonne alternatively teaches emulsification as a means to lower viscosity (col.4, lines 1-2). Thus, Sonne teaches three formulating alternatives, (1) high viscosity, (2) co-solvent (i.e. ethanol) addition and (3) emulsification. The high viscosity teaching and the co-solvent teaching render obvious the instantly recited claims.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20, 22-24, 27-36, 38, 40-45 and 48-54 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 23, 25-30, 33-56 and 60-65 of copending Application No. 14/527,613 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to choose from the recited components.

Applicants state they will consider filing a terminal disclaimer over the copending application when present claims are found otherwise allowable.

Accordingly, the rejection is maintained.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/413,439	Filing Date	2009-09-27	Docket Number (if applicable)	35401-716.201	Art Unit	1612
First Named Inventor	Steve Cartt			Examiner Name	Adam C. Milligan		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 232415

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Matthew V. Grumbling/	Date (YYYY-MM-DD)	2017-01-10
Name	Matthew V. Grumbling	Registration Number	44427

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Erin Allen
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	850	850
		Total in USD ($)		**1550**

Electronic Acknowledgement Receipt

EFS ID:	28025103
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Erin Allen
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	10-JAN-2017
Filing Date:	27-MAR-2009
Time Stamp:	16:18:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1550
RAM confirmation Number	011117INTEFSW00002733232415
Deposit Account	232415
Authorized User	Matthew Grumbling

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-201-Response-FINAL.pdf	514062 ab86e37b60f7fbbb996cc7054258fe383dacbd64	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	9	
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	35401-716-201-RCE.pdf	1353179 6e91c706efd9f110e90f695d0a479d80e64eb422	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32585 e7cdfa9ea995a63e974389f1afb495d78fba73c2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1899826		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventor(s): Steve Cartt, *et al.* Serial No.: 12/413,439 Filed: March 27, 2009 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Examiner: Adam C. Milligan Confirmation No.: 9049 Customer No.: 21971 Certificate of Electronic Filing I hereby certify that the attached Correspondence is being deposited by Electronic Filing on **January 10, 2017** by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. By: /Erin Allen/ **Erin Allen**

RESPONSE TO FINAL OFFICE ACTION

PURSANT TO A REQUEST FOR CONTINUED EXAMINATION

Commissioner for Patents
Mail Stop: RCE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This Amendment is submitted in response to the Final Office Action dated July 14, 2016. This Amendment is being submitted along with extension of time fees and a Request for Continued Examination ("RCE"). The Commissioner is authorized to charge any additional fees which may be required to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Amendments to the Claims begin on page **2**.

Remarks begin on page 7.

CLAIMS

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in this application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Applicants reserve the right to pursue the subject matter of the withdrawn/canceled claims in this or any other appropriate patent application.

Listing of Claims:

1-19. (Canceled).

20. (Currently Amended) A method of intranasal administration of a benzodiazepine drug for treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure in a patient with a seizure disorder, consisting of:

administering to one or more nasal mucosal membranes of said patient a pharmaceutical nasal spray solution ~~for nasal administration~~, said pharmaceutical nasal spray solution consisting of 1 to 20 mg of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols in an amount from about 30% to about 95% (w/w), one or more alcohols or glycols in an amount from about 10% to about 70% (w/w), and about 0.01 % (w/v) to about 1 % (w/v) of one or more alkyl glycosides.

21. (Canceled).

22. (Previously Presented) The method of claim 20, wherein said patient is a human.

23. (Previously Presented) The method of claim 20, wherein said benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

24. (Previously Presented) The method of claim 23, wherein said benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

25. (Canceled)

26. (Canceled)

27. (Previously Presented) The method of claim 20, wherein said one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

28. (Previously Presented) The method of claim 20, wherein said one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

29. (Previously Presented) The method of claim 20, wherein said one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

30. (Previously Presented) The method of claim 20, wherein said benzodiazepine drug is present in said pharmaceutical solution in a concentration from about 1 mg/mL to about 600 mg/mL.

31. (Previously Presented) The method of claim 30, wherein said benzodiazepine drug is present in said pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

32. (Previously Presented) The method of claim 31, wherein said benzodiazepine drug is present in said pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

33. (Previously Presented) The method of claim 20, wherein said one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 45% to about 85% (w/w).

34. (Previously Presented) The method claim 33, wherein said one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 60% to about 75% (w/w).

35. (Previously Presented) The method of claim 20, wherein said one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 15% to about 55% (w/w).

36. (Previously Presented) The method of claim 35, wherein said one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 25% to about 40% (w/w).

37. (Canceled)

38. (Canceled)

39. (Canceled).

40. (Currently Amended) The method of claim [[38]] 20, wherein said pharmaceutical~~ly acceptable spray formulation~~ solution has a volume of from about 10 μL to about 200 μL.

41. (Previously Presented) The method of claim 40, wherein said administration of said pharmaceutical solution consists of spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril of said patient.

42. (Previously Presented) The method of claim 40, wherein said administration of said pharmaceutical solution consists of spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril of said patient.

43. (Previously Presented) The method of claim 40, wherein said administration of said pharmaceutical solution consists of spraying a first quantity of said pharmaceutical

solution into a first nostril, spraying a second quantity of said pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of said pharmaceutical solution into said first nostril.

44. (Previously Presented) The method of claim 40, wherein said administration of said pharmaceutical solution consists of spraying a first quantity of said pharmaceutical solution into a first nostril, spraying a second quantity of said pharmaceutical solution into a second nostril, after a pre-selected time delay, spraying a third quantity of said pharmaceutical solution into said first nostril, and optionally after a pre-selected time delay, spraying at least a fourth quantity of said pharmaceutical solution into the second nostril.

45. (Previously Presented) The method of claim 43, wherein said nasal administration of said pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with said pharmaceutical composition.

46. (Canceled).

47. (Canceled).

48. (Previously Presented) The method of claim 20, wherein said pharmaceutical solution consists of diazepam, vitamin E, ethanol said alkyl glycoside.

49. (Previously Presented) The method of claim 48, wherein said alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, or a combination of two or more thereof.

50. (Previously Presented) The method of claim 49, wherein said alkyl glycoside is dodecyl maltoside.

51. (Previously Presented) The method of claim 20, wherein said pharmaceutical solution consists of 1-20 mg diazepam, 45 % (w/w) to 85 % (w/w) vitamin E, 15% (w/w) to 55 % (w/w) of a combination of ethanol and benzyl alcohol, and 0.01 % (w/v) to 1 % (w/v) of alkyl glycoside.

52. (Previously Presented) The method of claim 51, wherein said alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, or a combination of two or more thereof.

53. (Previously Presented) The method of claim 52, wherein said alkyl glycoside is dodecyl maltoside

54. (Previously Presented) The method of claim 35, wherein said one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from about 25% to about 55% (w/w).

REMARKS

This Amendment is filed with an RCE in response to the Final Office Action dated July 14, 2016. Claims 20, 22-24, 27-36, 40-45 and 48-54 are currently pending. Claims 20 and 40 are currently amended. Claim 38 is cancelled herein. No claims are new. Applicants respectfully request that the present amendment be entered, and request prompt examination of the present application. Applicants further submit that the application is now in condition for allowance.

Upon entry of this amendment, claims 20, 22-24, 27-36, 40-45 and 48-54 remain for further consideration for allowance.

No new matter is presented by any amendment made herein. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 103 (a)

The Office rejected claims 20, 22-24, 27-36, 38, 40-45, and 48-54 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lehat ([sic, "Lahat"] (Intranasal midazolam for childhood seizures, The Lancet, vol. 352, August 22, 1998), in view of Sonne (U.S. 6,193,985) and Meezan (U.S. 2006/0046962). Specifically, the Office alleged that Lehat teaches diazepam is used to treat acute seizures, Sonne teaches tocopherol can be used to deliver agents which are only sparingly soluble in water, and Meezan teaches alkyl glycoside is an absorption enhancing surfactant. July 14, 2016, Final Office Action at 2-4.

Applicant respectfully disagrees for at least the following reasons. Sonne and Meezan teach away from the pending claims by teaching different properties for the claimed excipients. Sonne teaches that surfactants may be used "[t]o optimize the stability of emulsions," and further lists "surfactants well known in the art, or other stabilisers such as xanthan gum, or propylene glycol alginate." Sonne, col. 6, ll. 54-59. Thus, a person of skill in the art, in reading Sonne, would understand that if the emulsion is not stable, adding a surfactant "or other stabiliser" might improve stability. Sonne does not suggest that surfactants could be used to increase absorption or bioavailability of a drug. Sonne, however, does suggest that tocopherols may serve to improve bioavailability of a drug. For example, "[a] study has shown that cinnarizine has a

higher oral bioavailability, if it is dissolved in a vehicle before administration . . . an example of such a vehicle could be α-tocopherol." Sonne, col. 11, ll. 25-29. Thus, Sonne teaches away from combining tocopherols and alkyl glycosides, presumably because tocopherol already serves to increase bioavailability of a drug. Additionally, Meezan teaches "therapeutic compositions comprising of least one drug and at least one surfactant, wherein the surfactant is comprised of at least one alkyl glycoside." Meezan, paragraph [0048]. Meezan does not teach benzodiazepine or tocopherol. Thus, Meezan does not provide any counter instruction to Sonne's teaching away. Therefore, a person of skill in the art looking at Sonne would not be motivated to apply the teachings of Sonne and Meezan to develop the claimed excipient combination for benzodiazepine administration. In light of the above, Applicant respectfully requests withdrawal of the rejection.

Provisional Nonstatutory Double Patenting Rejection

The Examiner provisionally rejected claims 20-24, 27-36, 38 and 40-53 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 23, 25-30, 33-56 and 60-65 of co-pending U.S. Patent Application No. 14/527,613.

Without conceding the basis for rejection, Applicant will consider filing a terminal disclaimer over co-pending Application No. 14/527,613, should the claims of the present application be found to be otherwise allowable.

CONCLUSION

Applicants believe that the application is in condition for allowance and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, or should there be any remaining issues of a minor or purely formal nature that may be readily disposed of through a supplemental amendment, or Examiner's amendment, Applicants encourage the Examiner to telephone the undersigned at 858-350-2332.

Applicants hereby authorize the Commissioner to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: January 10, 2017

By: /Matthew V. Grumbling/
Matthew V. Grumbling.
Reg. No. 44,427

Kathryn Grey
Reg. No. 69,591

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PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/413,439	Filing Date	2009-09-27	Docket Number (if applicable)	35401-716.201	Art Unit	1612
First Named Inventor	Steve Cartt			Examiner Name	Adam C. Milligan		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

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☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 232415

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Signature of Registered U.S. Patent Practitioner			
Signature	/Matthew V. Grumbling/	Date (YYYY-MM-DD)	2017-01-10
Name	Matthew V. Grumbling	Registration Number	44427

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/413,439	03/27/2009	

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**165**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**165**

APPLICATION AS AMENDED – PART II

AMENDMENT **01/10/2017**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 27	Minus	** 62	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
GLORIA J. TRAMMELL

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	JP-2011516425-A	05-26-2011	HALE BIOPHARMA VENTURES LLC [US], et al.	See WO-2009121039-A2 For English	☒
	002	WO-2009121039-A2	10-01-2009	HALE BIOPHARMA VENTURES LLC [US], et al.		☐
	003	CN-1303674A	12-02-1999	INST. OF MEDICAL INDUSTRY SHAND [CN]	English abstract provided	☒

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	Chinese Patent Application No. 201280039077.9 Office Action dated November 21, 2016.	☒
	002	Chinese Patent Application No. 201280039077.9 Third Office Action dated March 17, 2016.	☒
	003	European Patent Application No. 12801372.9 Communication dated July 5, 2016.	☐
	004	Japanese Patent Application No. 2014-515967 Office Action dated March 30, 2016.	☒
	005	Japanese Patent Application No. 2014-515967 Office Action dated November 28, 2016.	☒
	006	U.S. Patent Application No. 14/527,613 Office Action dated July 14, 2016.	☐
	007	U.S. Patent Application No. 14/948,081 Office Action dated October 31, 2016.	☐
	008	Canadian Patent Application No. 2756690 Examiner's Report dated October 20, 2015	☐
	009	Chinese Patent Application No. 2012800390779 Second Office Action dated August 11, 2015	☒

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt

EFS ID:	28036925
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/diane garcia
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	11-JAN-2017
Filing Date:	27-MAR-2009
Time Stamp:	17:03:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	JP2011516425A.pdf	2842225 b35520d9c2d6c1325e92f6998761e97c2bc51dde	no	66

Warnings:

Information:					
2	Foreign Reference	WO09121039.pdf	3135090 f0c21c07099618f5e2526477e91d861ff425154f	no	71
Warnings:					
Information:					
3	Foreign Reference	CN1303674A_trans_18Jul2001.pdf	2021264 8559852ac40805a838c6f607878097130ece5b57	no	39
Warnings:					
Information:					
4	Non Patent Literature	CN2012800390779_OA_ENG_21NOV2016.pdf	226014 75f3bb85caaec3c7015bc53c3cd15085a1fed4c6	no	5
Warnings:					
Information:					
5	Non Patent Literature	CN2012800390779_OATRANS_17MAR2016.pdf	171227 9efea0a5e696c582464d17cb5bb97a718de57c90	no	6
Warnings:					
Information:					
6	Non Patent Literature	EP128013729_Communication_05JUL2016.pdf	599614 142ceb9be3bf14de19d4dbdbf638e3b54501654a	no	7
Warnings:					
Information:					
7	Non Patent Literature	JP2014_515967_OA_ENG_30MAR2016.pdf	122321 fcffe208dae06bab79385c4040929a5d923aa597	no	6
Warnings:					
Information:					
8	Non Patent Literature	JP2014515697_OA_ENG_28NOV2016.pdf	80750 1fd57ce9d050d86f1ab09204d98ab484a05dc409	no	4
Warnings:					
Information:					

9	Non Patent Literature	US14527613_OA_14JUL2016.pdf	88878 d48538a8ba92350cd904ecf5c0ec744b18f88d90	no	1
Warnings:					
Information:					
10	Non Patent Literature	US14948081_OA_31OCT2016.pdf	45621 359b543c5dc75bb82b5e027af762ac85f7263b59	no	1
Warnings:					
Information:					
11	Non Patent Literature	CA2756690_OA_20OCT2015.pdf	140749 584fa1ed84865ad14bab86ab8f15ea3a0bd788db	no	3
Warnings:					
Information:					
12	Non Patent Literature	CN2012800390779_OA_ENG_11AUG2015.pdf	98075 0047551ef72812fc8743c85b404eb3eda58a7910	no	2
Warnings:					
Information:					
13		35401-716-201.pdf	262604 766bffcdb4129654e37be4bd53bf4c18d8392399	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	4
	Information Disclosure Statement (IDS) Form (SB08)	5	6

Warnings:	
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Total Files Size (in bytes):	9834432

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

(19)日本国特許庁(JP)　(12)公表特許公報(A)　(11)特許出願公表番号
特表2011-516425
(P2011-516425A)
(43)公表日　平成23年5月26日(2011.5.26)

(51)Int.Cl.		F I		テーマコード（参考）
A61K 31/4174	***(2006.01)***	A61K	31/4174	4C076
A61K 47/22	***(2006.01)***	A61K	47/22	4C086
A61K 47/10	***(2006.01)***	A61K	47/10	
A61K 31/551	***(2006.01)***	A61K	31/551	
A61K 31/5513	***(2006.01)***	A61K	31/5513	

審査請求 未請求　予備審査請求 未請求　（全 66 頁）　最終頁に続く

(21)出願番号　特願2011-502124 (P2011-502124)
(86)(22)出願日　平成21年3月27日 (2009.3.27)
(85)翻訳文提出日　平成22年11月25日 (2010.11.25)
(86)国際出願番号　PCT/US2009/038696
(87)国際公開番号　WO2009/121039
(87)国際公開日　平成21年10月1日 (2009.10.1)
(31)優先権主張番号　61/040,558
(32)優先日　平成20年3月28日 (2008.3.28)
(33)優先権主張国　米国(US)

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最終頁に続く

(54)【発明の名称】ベンゾジアゼピン組成物の投与

(57)【要約】
【課題】本発明は、経鼻投与用の１以上のベンゾジアゼピン薬を含む医薬組成物、このような組成物を製造及び使用するための方法に関する。
【解決手段】　経鼻投与用の医薬組成物であって、組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せと、を備える。

【特許請求の範囲】
【請求項１】
経鼻投与用の医薬組成物であって、
該組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、
（ａ）ベンゾジアゼピン薬と、
（ｂ）約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、
（ｃ）約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せと、を備えることを特徴とする医薬組成物。
【請求項２】
前記ベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せ、及び約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せに溶解されることを特徴とする請求項１記載の医薬組成物。
【請求項３】
前記ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、これらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せからなる群から選択されることを特徴とする請求項２に記載の医薬組成物。
【請求項４】
前記ベンゾジアゼピン薬は、ジアゼパム又はその任意の薬学的に許容可能な塩であることを特徴とする請求項３に記載の医薬組成物。
【請求項５】
前記ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備えることを特徴とする請求項１記載の医薬組成物。
【請求項６】
前記ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を備えることを特徴とする請求項５記載の医薬組成物。
【請求項７】
前記１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せからなる群から選択されることを特徴とする請求項１記載の医薬組成物。
【請求項８】
前記１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せからなる群から選択されることを特徴とする請求項１記載の医薬組成物。
【請求項９】
前記１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択されることを特徴とする請求項１記載の医薬組成物。
【請求項１０】
前記ベンゾジアゼピン薬は、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で、前記医薬組成物中に存在することを特徴とする請求項１記載の医薬組成物。
【請求項１１】

前記ベンゾジアゼピン薬は、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で、前記医薬組成物中に存在することを特徴とする請求項１記載の医薬組成物。
【請求項１２】
前記ベンゾジアゼピンは、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で、前記医薬組成物中に存在することを特徴とする請求項１１記載の医薬組成物。
【請求項１３】
前記１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せは、約４５％から約８５％（Ｗ／Ｗ）までの量であることを特徴とする請求項１記載の医薬組成物。
【請求項１４】
前記１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せは、約６０％から約７５％（Ｗ／Ｗ）までの量であることを特徴とする請求項１３記載の医薬組成物。
【請求項１５】
前記１以上のアルコール又はグリコール、あるいはそれらの任意の組合せは、約１５％から約５５％（Ｗ／Ｗ）までの量であることを特徴とする請求項１記載の医薬組成物。
【請求項１６】
前記１以上のアルコール又はグリコール、あるいはそれらの任意の組合せは、約２５％から約４０％（Ｗ／Ｗ）までの量であることを特徴とする請求項１５記載の医薬組成物。
【請求項１７】
前記医薬組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる薬剤からなる群から選択される、少なくとも１つの付加的成分をさらに備えることを特徴とする請求項１乃至１６いずれかに記載の医薬組成物。
【請求項１８】
前記薬学的に許容可能な製剤は、少なくとも約０．０１％（Ｗ／Ｗ）のアルキルグリコシドを備えることを特徴とする請求項１記載の医薬組成物。
【請求項１９】
前記薬学的に許容可能な製剤は、約０．０１％から約１％（Ｗ／Ｗ）までのアルキルグリコシドを備えることを特徴とする請求項１８記載の医薬組成物。
【請求項２０】
ベンゾジアゼピン薬で治療可能な疾患のある患者を処置する方法であって、
該方法は、
（ａ）ベンゾジアゼピン薬を含む経鼻投与用の医薬組成物と、約３０％から約９５％（Ｗ/Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、及び約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを患者の１以上の鼻粘膜に投与する工程を含むことを特徴とする方法。
【請求項２１】
前記ベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、及び約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せに溶解されることを特徴とする請求項２０記載の方法。
【請求項２２】
前記患者がヒトであることを特徴とする請求項２１記載の方法。
【請求項２３】
前記ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、

オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、これらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せからなる群から選択されることを特徴とする請求項２０記載の方法。

【請求項２４】

前記ベンゾジアゼピン薬は、ジアゼパム又はその任意の薬学的に許容可能な塩であることを特徴とする請求項２３記載の方法。

【請求項２５】

前記ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備えることを特徴とする請求項２０記載の方法。

【請求項２６】

前記ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を備えることを特徴とする請求項２５記載の方法。

【請求項２７】

前記１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せからなる群から選択されることを特徴とする請求項２０記載の方法。

【請求項２８】

前記１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せからなる群から選択されることを特徴とする請求項２０記載の方法。

【請求項２９】

前記１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択されることを特徴とする請求項２０記載の方法。

【請求項３０】

前記ベンゾジアゼピン薬は、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で、前記医薬組成物中に存在することを特徴とする請求項２０記載の方法。

【請求項３１】

前記ベンゾジアゼピン薬は、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で、前記医薬組成物中に存在することを特徴とする請求項３０記載の方法。

【請求項３２】

前記ベンゾジアゼピン薬は、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で、前記医薬組成物中に存在することを特徴とする請求項３１記載の方法。

【請求項３３】

前記医薬組成物が、約４５％から約８５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備えることを特徴とする請求項２０記載の方法。

【請求項３４】

前記医薬組成物が、約６０％から約７５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備えることを特徴とする請求項３３記載の方法。

【請求項３５】

前記医薬組成物が、約１５％から約５５％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備えることを特徴とする請求項２０記載の方法。

【請求項３６】

前記医薬組成物が、約２５％から約４０％（Ｗ／Ｗ）までの量の１以上のアルコール又

はグリコール、あるいはそれらの任意の組合せを備えることを特徴とする請求項３５記載の方法。

【請求項３７】

前記組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる薬剤からなる群から選択される、少なくとも１つの付加的成分を備えることを特徴とする請求項２０記載の方法。

【請求項３８】

前記組成物は、薬学的に許容可能なスプレー製剤中に存在することを特徴とする請求項２０記載の方法。

【請求項３９】

前記ベンゾジアゼピンが、約１ｍｇから約２０ｍｇまでの治療的に効果的な量で、投与されることを特徴とする請求項３８記載の方法。

【請求項４０】

前記医薬組成物は、約１０μＬから約２００μＬまでの量を有する薬学的に許容可能なスプレー製剤中に存在することを特徴とする請求項３９記載の方法。

【請求項４１】

前記医薬組成物の投与は、前記ベンゾジアゼピンの治療的に効果的な量の少なくとも一部を、少なくとも１つの鼻孔中に噴霧する工程を備えることを特徴とする請求項４０記載の方法。

【請求項４２】

前記医薬組成物の投与は、前記ベンゾジアゼピンの治療的に効果的な量の少なくとも一部を、夫々の鼻孔中に噴霧する工程を備えることを特徴とする請求項４０記載の方法。

【請求項４３】

前記医薬組成物の投与は、第１の量の前記医薬組成物を第１の鼻孔中に噴霧する工程と、第２の量の前記医薬組成物を第２の鼻孔中に噴霧する工程と、任意に、事前に選択した時間遅延の後、第３の量の前記医薬組成物を前記第１の鼻孔中に噴霧する工程を備えることを特徴とする請求項４２記載の方法。

【請求項４４】

任意に事前に選択した時間遅延の後、少なくとも第４の量の前記医薬組成物を前記第２の鼻孔の中へ投与する工程をさらに備えることを特徴とする請求項４３記載の方法。

【請求項４５】

前記医薬組成物の経鼻投与は、前記医薬組成物により処置可能となり得る疾患の症状の発病前又は発病後の任意の時点で開始することを特徴とする請求項４３記載の方法。

【請求項４６】

前記薬学的に許容可能な製剤は、少なくとも約０．０１％（Ｗ／Ｗ）のアルキルグリコシドを備えることを特徴とする請求項２０記載の組成物。

【請求項４７】

前記薬学的に許容可能な製剤は、約０．０１％から約１％（Ｗ／Ｗ）までのアルキルグリコシドを備えることを特徴とする請求項２１記載の医薬組成物。

【発明の詳細な説明】

【技術分野】

【０００１】

本出願は２００８年３月２８日に出願された米国の仮特許出願第６１／０４０，５５８号の３５Ｕ．Ｓ．Ｃ．§１１９（ｅ）優先権の利益を主張する。この出願の全ての内容は、それを参照することにより本出願に組み込まれる。

【０００２】

本発明は、ベンゾジアゼピン薬及びそれらの組成物の経鼻投与に関する

【背景技術】

【０００３】

限定するものではないが、ベンゾジアゼピンファミリーは、例えばジアゼパム、ロラゼパム、及びメダゼパム等の薬からなる。このファミリーの薬は、鎮静作用特性、精神安定特性及び筋弛緩特性を有するものとして認められる。これら薬は、精神安定弛緩薬及び骨格筋弛緩薬としてしばしば分類される。これらの薬は、不安定神経症、不眠症、激越、発作（例えば癲癇により引起されるもの等）、筋痙攣及び筋硬直（テタヌスにより引き起きされる）の症状、中枢神経抑制剤の継続的な乱用に関係する薬物離脱症候群、及び神経ガスへの暴露を抑制し、処置し、又は改善に有益であると考えられる。

【０００４】

ベンゾジアゼピンは、ニューロンのＧＡＢＡ$_A$受容体に結合することにより作用すると考えられ、おそらく、その受容体に形状の変化を引き起こし、ＧＡＢＡ$_A$受容体をガンマーアミノ酪酸（ＧＡＢＡ）にさらに近づきやすくしている。

【０００５】

ＧＡＢＡは、ＧＡＢＡ$_A$受容体に結合する場合、ＧＡＢＡ$_A$受容体が結合するニューロン中へのＣｌ$^-$イオン洪水を促進する抑制性の神経伝達物質である。Ｃｌ$^-$イオンの増加は、ニューロンの細胞膜を過分極させる。これは、活動電位を伝えるニューロンの能力を完全に又は実質的に減少させる。この受容体を標的とすることは、神経系を通過する過度な活動電位に起因する、例えばテタヌス及び癲癇等の多くの疾患を処置するのに有益である。

【０００６】

ベンゾジアゼピン薬の現在の製剤は、経口で、直腸に、又は非経口で投与され得る。これら及び他の製剤のタイプを利用する能力は、溶解性チャレンジ（ｃｈａｌｌｅｎｇｅ）に起因して、多くの場合大きく限定される。

【０００７】

経口投与は、いくつかの不都合に起因して次善として考慮され得る。例えば、経口投与のベンゾジアゼピン薬の血漿中の治療的関連性のある濃度を達成するのに要求される時間は、かなり長く、例えば１時間又はそれ以上である。その上、ベンゾジアゼピン薬は、肝臓を通り抜けるので、多くの量が代謝される。従って、治療的な血漿中濃度を達成するには、多い用量が必要となる。さらに、発作及び筋痙攣の特性に起因して、患者又は介護人のいずれかは、ベンゾジアゼピン薬を経口投与することが非常に困難となる。

【０００８】

静脈内投与は、しばしば高速に投与する経路を提供する。しかしながら、静脈内投与は、一般的には厳重に制御された臨床状況における訓練された医療従事者に限定される。その上、無菌が維持されなければならない。さらに、任意の薬を静脈内に投与することは、苦痛であり、そして針恐怖症に苦しむ患者にとっておそらく実質的ではない。

【０００９】

ベンゾジアゼピン薬の坐薬組成物は、作用が速やかに始まる。しかしながら、坐薬の不便さは、患者の親しい知人及び患者の専門医療介護人の非常に少ないグループ以外の誰かにより投与される場合、明らかに障害となる。

【発明の概要】

【課題を解決するための手段】

【００１０】

いくつかの実施形態において、経鼻投与用の医薬組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを備える。いくつかの実施形態において、ベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せ、及び約５％から約７０％（Ｗ／Ｗ）までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）ま

での量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部は、ミクロ粒子、ナノ粒子又はそれらの組合せを含む形態である。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００１１】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、これらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せからなる群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼパム、又はその薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を備える。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００１２】

いくつかの実施形態において、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、合成トコフェロールは、ビタミンＥ　ＴＰＧＳ（ビタミンＥポリエチレングリコールコハク酸）を含み得る。いくつかの実施形態において、他方、合成トコフェロールは、例えばポリエチレングリコール等のグリコールポリマーと共有結合又は連結する（例えば２塩基酸の連結基を介して）トコフェロールを除外する。従って、いくつかの実施形態において、本明細書中に記載される組成物はビタミンＥ　ＴＰＧＳを除外する。

【００１３】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択される。好適な実施形態において、グリコールは、グリコールポリマーを除外する。いくつかの好適な実施形態において、グリコールは、２００を超える平均分子量を備えるグリコールポリマーを除外する。いくつかの実施形態において、グリコールは、２００を超える平均分子量を備えるポリエチレングリコールを除外する。

【００１４】

いくつかの実施形態において、ベンゾジアゼピン薬は、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で、担体系中に存在する。いくつかの実施形態において、ベンゾジアゼピン薬は、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で、担体系中に存在する。いくつかの実施形態において、ベンゾジアゼピンは、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で、担体系中に存在する。

【００１５】

いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％か

ら約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。

【００１６】

いくつかの実施形態において、担体系は、約１０％から約７０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約１５％から約５５％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せ備える。

【００１７】

いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調整し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる剤からなる群から選択される少なくとも１つの付加的な成分を備える。

【００１８】

いくつかの実施形態において、組成物は、１以上の追加の賦形剤、例えば１以上のパラベン、１以上のポビドン、及び／又は１以上のアルキルグリコシドを備える。

【００１９】

本発明は、また、ベンゾジアゼピン薬で治療可能な疾患のある患者を処置する方法を開示する。いくつかの実施形態において、患者はヒトである。いくつかの実施形態において、方法は、ベンゾジアゼピン薬を含む経鼻投与用の医薬組成物と、約３０％から約９５％（Ｗ/Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、及び約５％から約７０％（Ｗ/Ｗ）までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを患者の１以上の鼻粘膜に投与する工程を含む。いくつかの実施形態において、ベンゾジアゼピンは、約３０％から約９５％（Ｗ／Ｗ）までの量の１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せ、及び約５％から約７０％までの量、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子又はそれらの組合せを含む。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００２０】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、又はこれらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せからなる群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼピン又はその任意の薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール並びに１以上のアルコール又はグリコールを含む単相に完全に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、組成物は、さらに水を備える。いくつかのこのような実施形態において、ベン

ゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を備える。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００２１】

いくつかの実施形態において、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せからなる群から選択される。

【００２２】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せからなる群から選択される。いくつかの実施形態において、アルコール又はグリコールは水がない（無水、ＵＳＰ）。いくつかの実施形態において、アルコールはエタノールである（無水、ＵＳＰ）。

【００２３】

いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で存在する。

【００２４】

いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％から約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロール又は天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。

【００２５】

いくつかの実施形態において、担体系は、約１５％から約５５％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せ備える。

【００２６】

いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる薬剤からなる群から選択される少なくとも１つの付加的成分を備える。

【００２７】

いくつかの実施形態において、組成物は、薬学的に許容可能なスプレー製剤中に存在し、さらに、１以上の患者の鼻粘膜に組成物を投与することを備える。いくつかの実施形態において、治療的に効果的な量は、約１ｍｇから約２０ｍｇまでのベンゾジアゼピンである。いくつかの実施形態において、医薬組成物は、約１０μＬから約２００μＬまでの量を有する薬学的に許容可能なスプレー製剤中に存在する。

【００２８】
いくつかの実施形態において、組成物の投与は、組成物の治療的に効果的な量の少なくとも一部を、少なくとも１つの鼻孔中に噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、組成物の治療学的に効果的な量の少なくとも一部を、それぞれの鼻孔中に噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、第１の量の組成物を、第１の鼻孔中に噴霧する工程と、第２の量の組成物を第２の鼻孔中に噴霧する工程と、任意に、事前に選択した時間遅延の後、第３の量の組成物を第１の鼻孔中に噴霧する工程を備える。いくつかの実施形態は、任意に事前に選択した時間遅延の後、少なくとも第４の量の組成物を第２の鼻孔の中へ投与する工程をさらに備える。
【００２９】
いくつかの実施形態において、組成物の投与は、組成物により処置可能となり得る疾患の症状の発病前又は発病後の任意の時点で開始する。
【００３０】
本発明の追加の実施形態、使用、及び効果は、本明細書中に記載される開示の考察に基づき、当該分野の当業者にとって明らかである。
【発明を実施するための形態】
【００３１】
本明細書中に言及される、全ての出版物、特許、及び特許出願は、それぞれの個別の出版物、特許、又は特許出願が、特に及び個別に、参照により組み込まれるものと示された場合と同様の程度に、参照されることにより本明細書中に組み込まれるものとする。
【００３２】
本明細書中に提供されるのは、１以上のベンゾジアゼピン薬の医薬組成物及び、このような医薬組成物を用いる方法である。このような医薬組成物は経鼻的に投与される。
【００３３】
いくつかの実施形態において、経鼻投与用の医薬組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを備える。いくつかの実施形態においてベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約１０％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部は、ミクロ粒子、ナノ粒子、又はそれらの組合せの形態である。いくつかの実施形態において組成物には、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。
【００３４】
いくつかの実施形態において、経鼻投与用の医薬組成物は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、ベンゾジアゼピン薬と、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとを備える。いくつかの実施形態においてベンゾジアゼピン薬は、約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の１以上のアルコール又はグリコール、あるいはそれらの任意の組合せとに溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は、担体系に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部は、ミクロ粒子、ナノ粒子、又はそれらの組合せの形態である。いくつかの実施形態において組成物には、ベンゾジアゼピンミクロ粒

子、ナノ粒子、又はそれらの組合せが実質的にない。

【００３５】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、これらの任意の薬学的に許容可能な塩、及びこれらの任意の組合せから成る群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼパム、又はその薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を有する。いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。

【００３６】

いくつかの実施形態において、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン（ｔｏｃｏｐｈｅｒｓｏｌａｎ）、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、担体系は、ビタミンＥ　ＴＰＧＳなどの、トコフェロールコアと共有結合又は連結するグリコールポリマーを有する、１以上の合成トコフェロールを含み、このことは米国特許第６，１９３，９８５号に記載されており、これは全体として参照することにより本明細書中に組み込まれる。特に、ベンゾジアゼピンがトコフェロールの相には溶解していない、いくつかのベンゾジアゼピンの粒子懸濁液中では、ビタミンＥ　ＴＰＧＳが、粒子（ミクロ粒子、ナノ粒子、又は組合せ）の懸濁液を安定させるための所望の賦形剤であり得るということが見出されている。いくつかの実施形態において、他方では、担体系は、ビタミンＥ　ＴＰＧＳなどの、トコフェロールコアと共有結合又は連結するグリコールポリマーを有する合成トコフェロールを特に除外し、このことは米国特許第６，１９３，９８５号に記載されており、これは全体として参照することにより本明細書中に組み込まれる。

【００３７】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、アルコールはエタノール（無水、ＵＳＰ）である。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、グリコールはプロピレングリコールＵＳＰである。いくつかの実施形態において、合成トコフェロールはビタミンＥ　ＴＰＧＳ（ビタミンＥポリエチレングリコールスクシネート）を含むことができる。いくつかの実施形態において、他方では、合成トコフェロールは、ポリエチレングリコールなどのグリコールポリマーと（例えば２塩基酸の連結基を介して）共有結合又は連結するトコフェロールを除外する。従って、いくつかの実施形態において、本明細書中に記載の組成物はビタミンＥ　ＴＰＧＳを除外する。

【００３８】

いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で存在する。

【００３９】
いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％から約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、合成トコフェロールはビタミンＥ　ＴＰＧＳ（ビタミンＥポリエチレングリコールスクシネート）を含むことができる。いくつかの実施形態において、他方では、合成トコフェロールは、ポリエチレングリコールなどのグリコールポリマーと（例えば２塩基酸の連結基を介して）共有結合又は連結するトコフェロールを除外する。従って、いくつかの実施形態において、本明細書中に記載の組成物はビタミンＥ　ＴＰＧＳを除外する。

【００４０】
いくつかの実施形態において、担体系は１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを、約１０％から約５５％まで、約１０％から約４０％まで、約１０％から約３５％まで、約１２％から約５５％まで、約１２％から約４０％まで、約１２％から約３５％まで、約１５％から約５５％まで、約１５％から約４０％まで、約１５％から約３５％まで、約１０％、約１２．５％、約１５％、約１７．５％、約２０％、約２２．５％、約２５％、約２７．５％、約３０％、約３２．５％、約３５％、約３７．５％、約４０％、約４２．５％、約４５％、約４７．５％、約５０％、約５２．５％、又は約５５％（Ｗ／Ｗ）の量で備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、アルコールはエタノールである、又はエタノールを含有する。いくつかの好ましい実施形態において、グリコールはグリコールポリマーを除外する。いくつかの好ましい実施形態において、グリコールは２００より大きい平均分子量を有するグリコールポリマーを除外する。いくつかの実施形態において、グリコールは約２００より大きい平均分子量を有するポリエチレングリコールを除外する。

【００４１】
いくつかの実施形態において、担体系は、約１５％から約５５％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せ備える。

【００４２】
いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調整し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる剤から成る群から選択される少なくとも１つの付加的な成分を備える。

【００４３】
いくつかの実施形態において、組成物は少なくとも１つのアルキルグリコシドを備える。いくつかの実施形態において、少なくとも１つのアルキルグリコシドは、米国特許第５，６６１，１３０号に記載のものであり、これは参照することにより本明細書中に組み込まれる。

【００４４】
いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを備える溶媒中に完全に溶解し

ているベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを備える溶媒中に完全に溶解しているベンゾジアゼピン薬を備え、そこで溶液は実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）

【００４５】

いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを有する溶媒中に完全に溶解しているベンゾジアゼピン薬を備える。従って、いくつかの実施形態において、組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せが実質的にない。いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールを有する溶媒中に完全に溶解しているベンゾジアゼピン薬を備え、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に完全に溶解している、ベンゾジアゼピン薬から必須のものとして構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有することを示す。）いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成される。いくつかの実施形態において、組成物は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及び任意に１以上のアルキルグリコシドから成る溶媒中に溶解している、ベンゾジアゼピンから構成され、そこで溶液は少なくとも実質的に水がない。（いくつかの実施形態において、「実質的に水がない」とは、溶液が約１％未満、約０．５％未満、約０．２５％未満、又は約０．１％未満の水を含有す

ることを示す。）

【００４６】

いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及び１以上のアルコール又はグリコールを含有する担体系中に、少なくとも部分的に微粒子型で懸濁したベンゾジアゼピン薬を含有する。いくつかの実施形態において、実質的に全てのベンゾジアゼピン薬は微粒子形態である。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部はミクロ粒子又はナノ粒子の形態である。担体系は、その中で組成物中に存在する少なくとも１つのベンゾジアゼピンの量が、担体系中のその溶解性を超えるものである。いくつかの実施形態において、このような組成物中の担体系は水を含む。いくつかの実施形態において、このような液体担体系は、水及び１以上の賦形剤を含有する。いくつかの実施形態において、１以上の賦形剤は、担体系中に溶解又は懸濁されている。いくつかの実施形態において、少なくとも１つのこのような賦形剤は、担体系中のベンゾジアゼピンの粒子の懸濁液を安定させる。いくつかの実施形態において、担体系は様々な濃度のパラベン（例えば、メチルパラベン、プロピルパラベン等）、及び／又は、ポビドン（ポリビニルピロリドン）などの、様々な量の１以上の界面活性剤を含有し得る。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、ポリエチレングリコールなどの、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、２００ｇ／ｍｏｌより大きい分子量を有する、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、組成物は、合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、１以上の界面活性剤及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、ポビドン及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、ポビドン及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、１以上の界面活性剤及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、ポビドン及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、ポビドン及び水から必須のものとして成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、１以上の界面活性剤及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、ポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、ポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。

【００４７】
いくつかの実施形態において、組成物は、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、１以上のアルコール又はグリコール、及びアルキルグリコシドを含有する担体系中に、少なくとも部分的に微粒子型で懸濁されたベンゾジアゼピン薬を含有する。いくつかの実施形態において、実質的に全てのベンゾジアゼピン薬は微粒子型である。いくつかの実施形態において、ベンゾジアゼピン薬の少なくとも一部はミクロ粒子又はナノ粒子の形態である。担体系は、その中で組成物中に存在する少なくとも１つのベンゾジアゼピンの量が、担体系中のその溶解性を超えるものである。いくつかの実施形態において、このような組成物中の担体系は水を含む。いくつかの実施形態において、このような液体担体系は、水及び１以上の賦形剤を含有する。いくつかの実施形態において、１以上の賦形剤は、担体系中に溶解又は懸濁されている。いくつかの実施形態において、少なくとも１つのこのような賦形剤は、担体系中のベンゾジアゼピンの粒子の懸濁液を安定させる。いくつかの実施形態において、担体系は様々な濃度のパラベン（例えば、メチルパラベン、プロピルパラベン等）、及び／又は、ポビドン（ポリビニルピロリドン）などの、様々な量の１以上の界面活性剤を含有し得る。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、ポリエチレングリコールなどの、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、ベンゾジアゼピンの粒子懸濁液は、２００ｇ／ｍｏｌより大きい分子量を有する、１以上のグリコール重合体を特に除外する。いくつかの実施形態において、組成物は、合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、アルキルグリコシド及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、アルキルグリコシド及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、アルキルグリコシド及び水を備える担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬を備える。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、アルキルグリコシド、任意に界面活性剤及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、アルキルグリコシド、任意にポビドン及び水から必須のものとして構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、アルキルグリコシド、任意にポビドン及び水から基本的に構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から必須のものとして構成される。いくつかの実施形態において、組成物は合成トコフェロール、１以上のパラベン、１以上のアルコール又はグリコール、アルキルグリコシド、任意に１以上の界面活性剤、及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベンとプロピルパラベンの１もしくは両方、少なくとも１つのグリコール、アルキルグリコシド、任意にポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒子又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。いくつかの実施形態において、組成物はビタミンＥ　ＴＰＧＳ、メチルパラベン、プロピルパラベン、プロピレングリコール、アルキルグリコシド、任意にポビドン及び水から構成される担体系中に懸濁されたベンゾジアゼピンのミクロ粒

子及び／又はナノ粒子を含む形態におけるベンゾジアゼピン薬から構成される。

【００４８】

本発明はまた、ベンゾジアゼピン薬を用いて処置可能であり得る疾患の患者を処置する方法を開示する。いくつかの実施形態において、患者はヒトである。いくつかの実施形態において、方法は、ベンゾジアゼピン薬を備える経鼻投与用の医薬組成物と、約３０％から約９５％（Ｗ／Ｗ）までの量の、１またはそれより多い天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、又はそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の、１又はそれより多いアルコール又はグリコール、又はそれらの任意の組合せとを、患者の１以上の鼻粘膜に投与する工程を備える。いくつかの実施形態において、ベンゾジアゼピンは約３０％から約９５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、約５％から約７０％（Ｗ／Ｗ）までの量の、好ましくは約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せの中に溶解される。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に溶解される。他の実施形態において、ベンゾジアゼピン薬の少なくとも一部はミクロ粒子、ナノ粒子、又はそれらの組合せを含む形態である。いくつかの実施形態において、組成物は実質的にベンゾジアゼピンのミクロ粒子、ナノ粒子、又はそれらの組合せがない。

【００４９】

いくつかの実施形態において、ベンゾジアゼピン薬は、アルプラゾラム、ブロチゾラム、クロルジアゼポキシド、クロバザム、クロナゼパム、クロラゼパム、デモキサゼパム、ジアゼパム、フルマゼニル、フルラゼパム、ハラゼパム、ミダゾラム、ノルダゼパム、メダゼパム、ニトラゼパム、オキサゼパム、メダゼパム、ロラゼパム、プラゼパム、クアゼパム、トリアゾラム、テマゼパム、ロプラゾラム、又はこれらの薬学的に許容可能な任意の塩、及びこれらの任意の組合せから成る群から選択される。いくつかの実施形態において、ベンゾジアゼピン薬は、ジアゼパム、又はその薬学的に許容可能な塩である。いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを備える。いくつかの実施形態において、ベンゾジアゼピンナノ粒子は、約５０００ｎｍ未満の有効平均粒径を有する。

【００５０】

いくつかの実施形態において、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、δ－トコトリエノール、トコフェルソラン、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、及びそれらの任意の組合せから成る群から選択される。合成トコフェロールは、ポリエチレングリコール基などの親水基を含むよう修飾されたトコフェロールを含み得、２塩基酸などの共有結合性の連結基を介してトコフェロールと共有結合あるいはトコフェロールと連結し得る。この型の例示的な合成トコフェロールは、当該分野の当業者は、同様の二塩基酸及び／又は親水基を有する他の合成トコフェロールを想像することができるが、ビタミンＥポリエチレングリコールスクシネート（ビタミンＥ　ＴＰＧＳ）である。

【００５１】

いくつかの実施形態において、１以上のアルコールは、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、１以上のグリコールは、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、及びそれらの任意の組合せから成る群から選択される。いくつかの実施形態において、１以上のグリコールは、ポリエチレングリコールなどのグリコール重合体を特に除外する。いくつかの実施形態において、１以上のグリコールは、２００ｇ／ｍｏｌより大きい分子量を有するグリコール重合体を特に除外

する。

【００５２】

いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１ｍｇ／ｍＬから約６００ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で存在する。いくつかの実施形態において、ベンゾジアゼピン薬は担体系中に、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で存在する。

【００５３】

いくつかの実施形態において、担体系は、約４５％から約８５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約６０％から約７５％（Ｗ／Ｗ）までの量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は、約７０％（Ｗ／Ｗ）の量の、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、特にベンゾジアゼピン薬の粒子懸濁液を考慮する場合、組成物はトコフェロール、特にトコフェロールと共有結合的に連結する親水基を有する合成トコフェロールを含み得る。他の実施形態において、特にベンゾジアゼピン薬の溶液を考慮する場合、トコフェロールは実質的に又は完全にビタミンＥ　ＴＰＧＳがない。

【００５４】

いくつかの実施形態において、担体系は約１０％から約５５％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約２５％から約４０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系は約３０％（Ｗ／Ｗ）の量の、１以上のアルコール又はグリコール、あるいはそれらの任意の組合せを備える。いくつかの実施形態において、担体系における１以上のアルコール又はグリコール、あるいはそれらの任意の組合せの量は、約１０％から約５５％まで、約１０％から約４０％まで、約１０％から約３５％まで、約１２％から約５５％まで、約１２％から約４０％まで、約１２％から約３５％まで、約１５％から約５５％まで、約１５％から約４０％まで、約１５％から約３５％まで、約１０％、約１２．５％、約１５％、約１７．５％、約２０％、約２２．５％、約２５％、約２７．５％、約３０％、約３２．５％、約３５％、約３７．５％、約４０％、約４２．５％、約４５％、約４７．５％、約５０％、約５２．５％、又は約５５％（Ｗ／Ｗ）の量で備える。

【００５５】

いくつかの実施形態において、組成物は、医薬品有効成分、賦活剤、賦形剤、及びｐＨを調節し、組成物を緩衝し、分解を防ぎ、そして外観、匂い、又は味を改善するために用いられる剤から成る群から選択される、少なくとも１つの付加的な成分を備える。

【００５６】

いくつかの実施形態において、組成物はベンゾジアゼピン薬、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールに加えて、少なくとも一つの透過賦活剤を備える。いくつかの実施形態において、透過賦活剤はアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、任意の疎水性アルキルにつなぎ合わされる任意の糖を指し、このことは米国特許第５，６６１，１３０号に記されており、これは全体として参照することにより本明細書中に組み込まれる。疎水性アルキルは、任意の適切な長さであることができ、例えば、炭鎖長が約９から約２４の炭素、特に炭鎖長が約１０から約１４の炭素であり得る。疎水性アルキルは、分岐であり得、及び／又は部分的に又は全体的に不飽和であり得る。アルキルは例えばカルボニル基を介してサッカライドコアにつなぎ合わされ、それによってエステル基が形成され得る。適切なアルキルグリコシドは、無毒性であり、非イオン性であり、本明細書中に記載されるように鼻腔内にベンゾジアゼピン薬が投与されるとその吸収を増大させることが

できるという特徴を有する。本発明に係るアルキルに共有結合的につなぎ合され得る例示的な糖類は、グルコース、マルトース、マルトトリオース、マルトテトロース、スクロース、及びトレハロースを含む。使用され得る例示的なアルキルグリコシドは、オクチル－、ノニル－、デシル－、ウンデシル－、ドデシル、トリデシル、テトラデシル、ペンタデシル、オクタデシルα－又はβ－Ｄ－マルトシド、－グルコシド、又はスクロシドを含む。いくつかの実施形態において、好ましいグリコシドは、９、１０、１２、１４、１６、１８、又は２０炭素原子のアルキル鎖にグリコシド結合により連結される、マルトース、スクロース、又はグルコースを含む。存在する場合、組成物中のアルキルグリコシドの量は、鼻腔内経路により投与されるベンゾジアゼピン薬の吸収を高めるために十分な量である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、ベンゾジアゼピン薬の吸収を高めるために選択され、同時に鼻粘膜を著しく刺激しない。いくつかの実施形態において、組成物中のアルキルグリコシドの量は約０．０１％（Ｗ／Ｖ）から約１％（Ｗ／Ｖ）までの範囲内である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は約０．０５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）まで、又は約０．１２５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）までの範囲内である。

【００５７】

いくつかの実施形態において、組成物は薬学的に許容可能なスプレー製剤中にあり、さらに、１以上の、患者の鼻粘膜に組成物を投与することを備える。いくつかの実施形態において、治療的に効果的な量は約１ｍｇから約２０ｍｇまでのベンゾジアゼピンである。いくつかの実施形態において、医薬組成物は約１０μＬから約２００μＬまでの容量を有する、薬学的に許容可能なスプレー製剤中にある。

【００５８】

いくつかの実施形態において、組成物の投与は、組成物の治療的に効果的な量の少なくとも一部を、少なくとも１つの鼻孔の中へ噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、組成物の治療的に効果的な量の少なくとも一部を、それぞれの鼻孔の中へ噴霧する工程を備える。いくつかの実施形態において、組成物の投与は、第１の量の組成物を第１の鼻孔の中へ噴霧する工程と、第２の量の組成物を第２の鼻孔の中へ噴霧する工程と、任意に事前に選択した時間遅延の後、第３の量の組成物を第１の鼻孔の中へ噴霧する工程とを備える。いくつかの実施形態は、任意に事前に選択した時間遅延の後、少なくとも第４の量の組成物を第２の鼻孔の中へ投与する工程を更に備える。

【００５９】

いくつかの実施形態において、組成物の投与は、組成物を用いて処置可能であり得る疾患の症状の発病前又は発病後の任意の時点で開始する。

【００６０】

定義

本明細書中に用いられるように、語句「治療的に効果的な量（又はより単純に「効果的な量」）」は、特定の治療応答を提供するのに十分な量を含み、この特定の治療応答を得るために、特定の処置を必要とする患者に薬が投与される。一般的な技術を有する臨床医は、薬の治療的に効果的な量は、患者、指示、及び投与される特定の薬に左右されることを認めるであろう。

【００６１】

本明細書中に用いられるように、修飾語句「約」は、その正式に認識された、おおよそという意味を有するよう意図されている。いくつかの実施形態において、用語は、修飾される値の特定の百分率内を意味するよう、より正確に解釈され得る。例えば、「約」はいくつかの実施形態において、±２０％、±１０％、±５％、±２％、又は±１％、又はそれ未満を意味し得る。

【００６２】

本明細書中に用いられるように、語句「アナログ又は誘導体」は、１又はそれより多い原子又は官能基が、異なる原子又は官能基と置換されているため、もう１つ別の分子とは異なる分子を含む。これにより同様の化学式を有するが異なる化学的及び／又は生物学的

特性を有する分子がもたらされ得る。

【００６３】

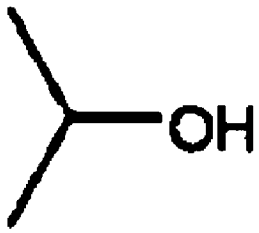
本明細書中に用いられるように、用語「異性体」は、同一の化学式を有する分子を含むが、それらの間で分子の配置は異なり得る。これらの異なる配置により、同一の化学式を有するが、異なる化学的特性を有する分子がもたらされ得る。制約のない例として、プロパノールは化学式C_3H_7OHを有する。それはプロパン－１－オールとして見出され得るが、その場合、－ＯＨは末端炭素に付着して見出される。代替的に、それはプロパン－２－オールとして見出され得るが、その場合－ＯＨは第２炭素に付着して見出される。

【００６４】

【化１】



プロパン-1-オール



プロパン-2-オール

【００６５】

本明細書中に用いられるように、用語「発作」は、一般に認められる型の発作を含み、欠神発作、ミオクローヌス発作、間代発作、強直性発作、強直間代発作、及び脱力発作を含む。しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆により予測される。それぞれの患者は一般的に異なる型の前兆を経験する。それらは患者に特有のものである。しかしながら、前兆は、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は少なくともしばしば患者が発作を経験することより先に起こる。（発作を患う全ての患者が前兆を経験するわけではない。しかしながら前兆は最悪の型の発作、特に強直間代発作を患う人の間では珍しいものではない。）

【００６６】

本明細書中に用いられるように、用語「予防」は、疾患の発病を未然に防ぐことを指し、一時的に未然に防ぐことを含む。発作の場合には、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで起こり得る。

【００６７】

本明細書中に用いられるように、用語「処置」は、疾患の強さ及び／又は持続時間を減じること、又は同様の効果を指す。用語はまた、このような「処置」の副作用をも包含する。

【００６８】

本明細書中に用いられるように、別段に制限された場合を除き、用語「一つの（ａ）」又は「一つの（ａｎ）」は１またはそれより多くを意味し得る。

【００６９】

本明細書中に用いられるように、用語「備える（ｃｏｍｐｒｉｓｉｎｇ）」は、その全ての変形において、請求項において用いられる移行句であり、本発明が、特に列挙された請求項要素を含む、又は含有するがそれらに限定されないということを示す。

【００７０】

本明細書中に用いられるように、用語「必須のものとして構成される」は、請求項において用いられる移行句であり、次に続く成分、部分、又は処理工程の一覧が、主張される組成物、機械、又は工程に存在せねばならないが、この請求項は、本発明の基礎的及び新

規の特性に実質的に影響を及ぼさない、一覧に記載されていない成分、部分、又は処理工程を受け入れる。

【００７１】

本明細書中に用いられるように、用語「構成される」は、請求項において用いられる移行句であり、主張される発明が請求項において説明されるそれらの要素のみを含むことを示す。

【００７２】

ベンゾジアゼピン薬

本発明の文脈において、用語「ベンゾジアゼピン薬」は、任意の治療上効果的なベンゾジアゼピン化合物、又は薬学的に許容可能な塩、又はそれらの組合せを含む。いくつかの実施形態において、ベンゾジアゼピンは　アルプラゾラム、ジアゼパム、フルラゼパム、ロラゼパム、メダゼパム、メキサゾラム、ミダゾラム、テマゼパム及び薬学的に許容可能な塩、及びそれらの組合せから成る群の部材を備える。

【００７３】

付加的なベンゾジアゼピン化合物は、低いバイオアベイラビリティ、乏しい薬物動態学的特性、又は乏しい薬力学的特性のいずれかのため、わずかな治療上の恩恵を有する、又はほとんど治療的な恩恵を有さないとこれまで見なされてきたが、以下を提供することができる、本発明を介した利用を見出し得るということは、当該分野の当業者によって認識されるべきである。それらは、ベンゾジアゼピン薬の改善されたバイオアベイラビリティ、経鼻経路を介するより高濃度のベンゾジアゼピン薬の送達、血漿中のベンゾジアゼピンの治療レベルのより速い達成、肝門脈（ｌｉｖｅｒ　ｐｏｒｔａｌ　ｖｅｉｎ）の回避、及び、付随する初回通過効果の回避、及び／又は、ベンゾジアゼピン薬の脳へのより速い提示である。

【００７４】

例えば、大抵のベンゾジアゼピンはごくわずかに水に溶けるにすぎないため、治療的に効果的な量は、粘膜への塗布に適した水性溶媒の容量には溶解されることができない。いくつかの実施形態においてベンゾジアゼピン薬を溶解する改善された能力を提供する、本担体系を用いることにより、本発明は、ベンゾジアゼピン薬が、鼻粘膜を含む１以上の粘膜に投与されることを可能にする。これにより、入院又は不要な不快感なく、薬を投与することが可能となる。その上、経鼻投与などの、本発明のいくつかの実施形態において、消化器系は大部分は迂回され得る。この後者の改善により、改善されたバイオアベイラビリティ、血漿中のベンゾジアゼピンの治療レベルのより速い達成、肝門脈（ｌｉｖｅｒ　ｐｏｒｔａｌ　ｖｅｉｎ）の回避、及び／又は、付随する初回通過効果の回避を生じさせることができる。

【００７５】

組成物の経鼻投与により、膜と脳の近い近接性のため、１以上のベンゾジアゼピン薬のより速い脳への提示がもたらされることができる。例えば、発病している患者は、硬直した筋肉及び制御できない動きに苦しむ。これが経口及び／又は静脈内投与を困難又は不便にし得る。しかしながら、経鼻通路は開いたままであり、容易に利用可能であり、従って本発明の有用な投与経路である。

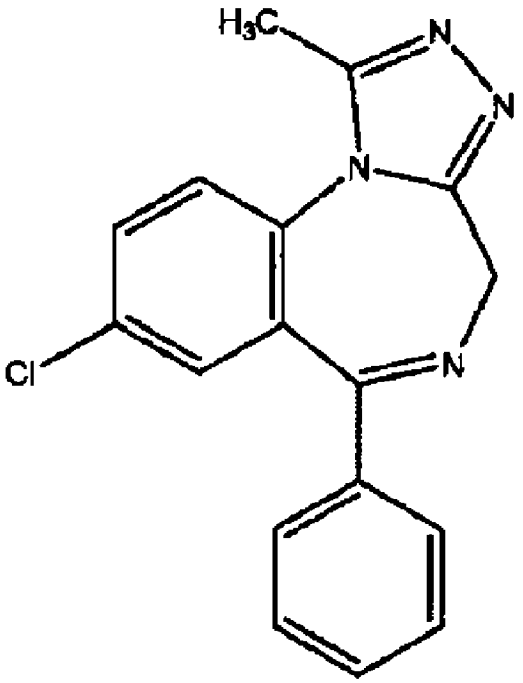
【００７６】

いくつかの実施形態において医薬組成物は、１以上の効果的な量のベンゾジアゼピン薬を用いた処置又は予防を受け入れる疾患に苦しむ患者を処置するために用いられる。制約のない例としてはこのような疾患は、不眠症、不安症、発作、筋痙攣及び硬直、並びに退薬症状を含むことができる。

【００７７】

いくつかの実施形態において、１以上のベンゾジアゼピン薬は、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。

【００７８】
アルプラゾラム（８－クロロ－６－フェニル－１－メチル－４Ｈ－１，２，４－トリアゾロ［４，３－ａ］［１，４］ベンゾジアゼピン）
【００７９】
【化２】



【００８０】
アルプラゾラムは、鎮静の、精神安定の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。アルプラゾラムは、パニック障害の処置に有用であるとも示されている。アルプラゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．５から約４まで、好ましくは約１から約２ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。アルプラゾラムは、米国特許第３，９８７，０５２号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【００８１】
いくつかの実施形態において、アルプラゾラムは、抗不安効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。
【００８２】
いくつかの実施形態において、アルプラゾラムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、アルプラゾラムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、アルプラゾラムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、アルプラゾラムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、アルプラゾラムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、抗痙攣効果又は相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がアルプラゾラムと組み

合わせられ得る。

【００８３】

アルプラゾラムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のアルプラゾラム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のアルプラゾラム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者に治療上有益な薬を便利に投与することをもまた提供する。

【００８４】

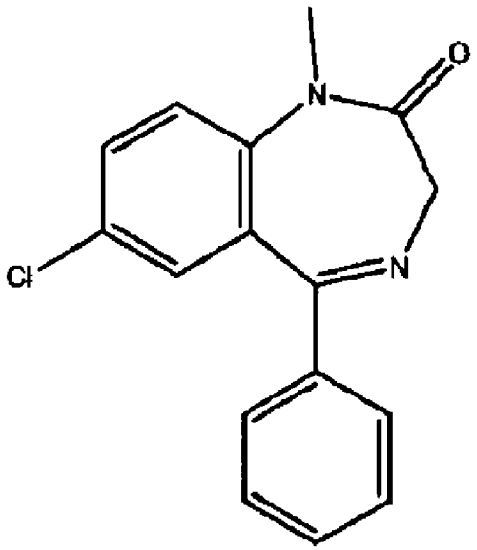
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【００８５】

ジアゼパム（７－クロロ－１－メチル－５－フェニル－１，３－ジヒドロ－２Ｈ－１，４－ベンゾジアゼピン－２－オン）

【００８６】

【化３】



【００８７】

ジアゼパムは、鎮静の、精神安定の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬、及び骨格筋弛緩薬として分類される。これは、抗不安の、抗痙

攣性の、鎮静の、骨格筋弛緩性の、及び健忘性の特性を有する。ジアゼパムの投薬量は、指示により異なり得るが、しかしながら、治療量は投与量あたり約１から約２０まで、好ましくは約２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ジアゼパムは、米国特許第３，３７１，０８５号、第３，１０９，８４３号、第３，１３６，８１５号、又は第３，１０２，１１６号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【００８８】

いくつかの実施形態において、ジアゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【００８９】

いくつかの実施形態において、ジアゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、ジアゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、ジアゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、ジアゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、ジアゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がジアゼパムと組み合わせられ得る。

【００９０】

ジアゼパムはまた、患者が発作の状態にある間、もう１人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のジアゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のジアゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【００９１】

しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

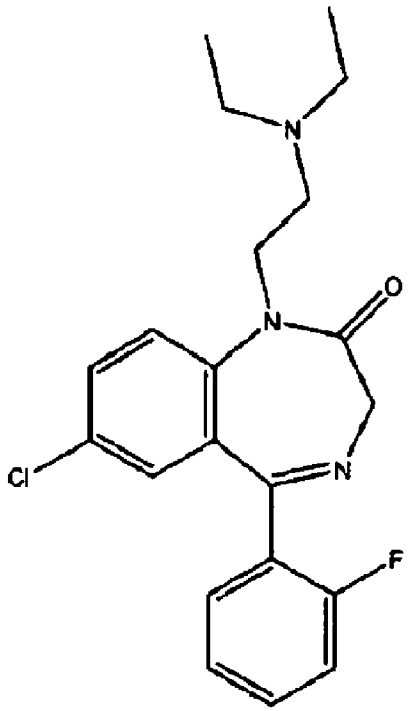
【００９２】

フルラゼパム（７－クロロ－５－（２－フルロフェニル）－２，３－ジヒドロ－１－（

２－（ジエチルアミノ）エチル）－１Ｈ－１，４－ベンゾジアゼピン－２－オン）

【００９３】

【化４】



【００９４】

フルラゼパムは、鎮静の（特に、催眠性の、及び催眠状態の）、抗不安の、抗痙攣性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは鎮静薬、睡眠薬として分類される。フルラゼパムは、不眠症の処置に有用であると示されてきた。フルラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約５から約４０まで、好ましくは約２０から約３５ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。フルラゼパムは、米国特許第３，５６７，７１０号、又は第３，２９９，０５３号に開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【００９５】

いくつかの実施形態において、フルラゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【００９６】

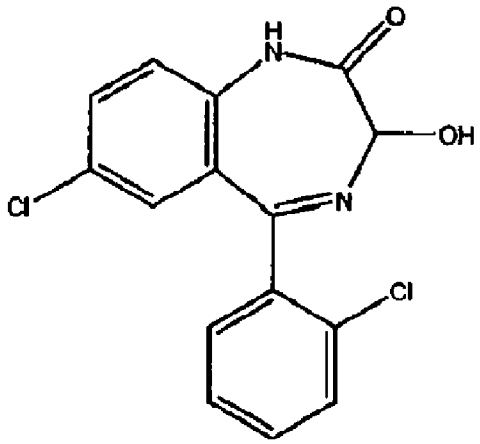
いくつかの実施形態において、フルラゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、フルラゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、フルラゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、フルラゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、フルラゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がフルラゼパムと組み合わせられ得る。

【００９７】
フルラゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のフルラゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のフルラゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【００９８】
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【００９９】
ロラゼパム（７－クロロ－５－（２－クロロフェニル）－３－ヒドロキシ－１，３－ジヒドロ－２Ｈ－１，４－ベンゾジアゼピン－２－オン）

【０１００】
【化５】



【０１０１】
ロラゼパムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。ロラゼパムはまた、吐き気の処置に有用であると示されてきた。ロラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまで

の範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ロラゼパムは、米国特許第３，２９６，２４９号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１０２】

いくつかの実施形態において、ロラゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１０３】

いくつかの実施形態において、ロラゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、ロラゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、ロラゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、ロラゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、ロラゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がロラゼパムと組み合わせられ得る。

【０１０４】

ロラゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のロラゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のロラゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１０５】

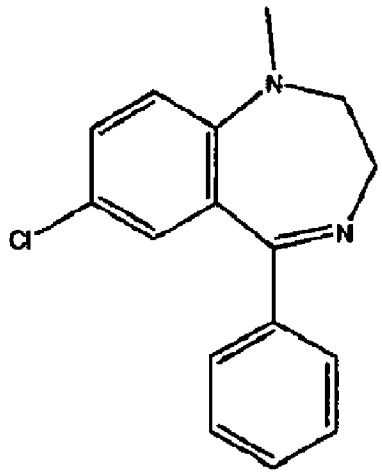
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１０６】

メダゼパム（７－クロロ－１－メチル－５－フェニル－２，３－ジヒドロ－１Ｈ－１，４－ベンゾジアゼピン）

【０１０７】

【化６】



【０１０８】
メダゼパムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。メダゼパムはまた、吐き気の処置に有用であると示されてきた。メダゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メダゼパムは、米国特許第３，２４３，４２７号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【０１０９】
いくつかの実施形態において、メダゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。
【０１１０】
いくつかの実施形態において、メダゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、メダゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、メダゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、メダゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、メダゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がメダゼパムと組み合わせられ得る。
【０１１１】
メダゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の

間隔の拡大がある。従って、本発明のメダゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のメダゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１１２】

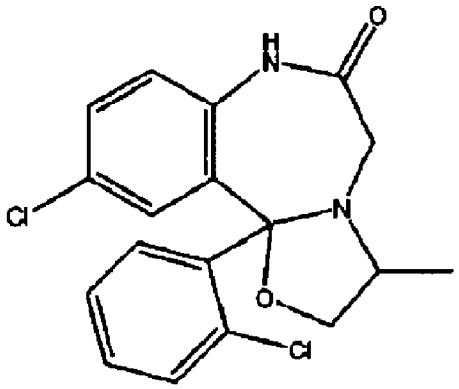
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１１３】

メキサゾラム（１０－クロロ－１１ｂ－（２－クロロフェニル）－１，３，７，１１ｂ－テトラヒドロ－３－メチルオキサゾロ［３，２－ｄ］［１，４］ベンゾジアゼピン－６（５Ｈ）－オン）

【０１１４】

【化７】



【０１１５】

メキサゾラムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。メキサゾラムはまた、吐き気の処置に有用であると示されてきた。メキサゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メキサゾラムは、米国特許第３，７２２，３７１号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１１６】

いくつかの実施形態において、メキサゾラムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１１７】

いくつかの実施形態において、メキサゾラムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再

発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、メキサゾラムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、メキサゾラムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、メキサゾラムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、メキサゾラムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がメキサゾラムと組み合わせられ得る。

【０１１８】

メキサゾラムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のメキサゾラム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のメキサゾラム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１１９】

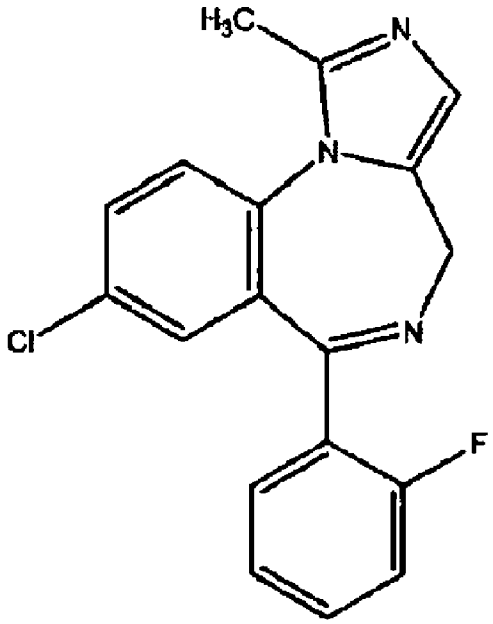
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１２０】

ミダゾラム（８－クロロ－６－（２－フルオロフェニル）－１－メチル－４Ｈ－イミダゾ（１，５－ａ）ベンゾジアゼピン）

【０１２１】

【化８】



【０１２２】

ミダゾラムは、抗不安の、健忘性の、催眠性の、抗痙攣性の、骨格筋弛緩性の、及び鎮静の特性を有する、三環系のベンゾジアゼピンである。ミダゾラムは、約４より低いｐＨで水に溶解できると見なされているが、中性ｐＨ（例えば、約６から８）で大抵の水溶液に比較的に不溶性である。従って、いくつかの実施形態において、ミダゾラムの水性の経鼻用調製物は、約５．５より上、好ましくは約６．０より上、又は約６．５より上のｐＨを有することが好ましい。いくつかの好ましい実施形態において、ｐＨは約６と９の間、約６と８の間である。脂溶性（およそ中性ｐＨで）のミダゾラムは、鼻粘膜中に急速に吸収され、ミダゾラムの能率的な摂取へ導くため、ミダゾラムの調製物は特に経鼻投与に適していると考えられる。更に、ミダゾラムは、ハイドロフルオロカーボン噴射剤、炭化水素噴射剤などといったエアロゾル投与技術において既知であるものなどの、非水性の送達ビヒクルの中に処方され得ると考えられる。

【０１２３】

ミダゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約２０まで、好ましくは約０．２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ミダゾラムは、米国特許第４，２８０，９５７号、又は第５，８３１，０８９号の一つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１２４】

いくつかの実施形態において、ミダゾラムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１２５】

いくつかの実施形態において、ミダゾラムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、ミダゾラムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、ミダゾラムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得

る。いくつかの実施形態において、ミダゾラムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、ミダゾラムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がミダゾラムと組み合わせられ得る。

【０１２６】

ミダゾラムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のミダゾラム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のミダゾラム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１２７】

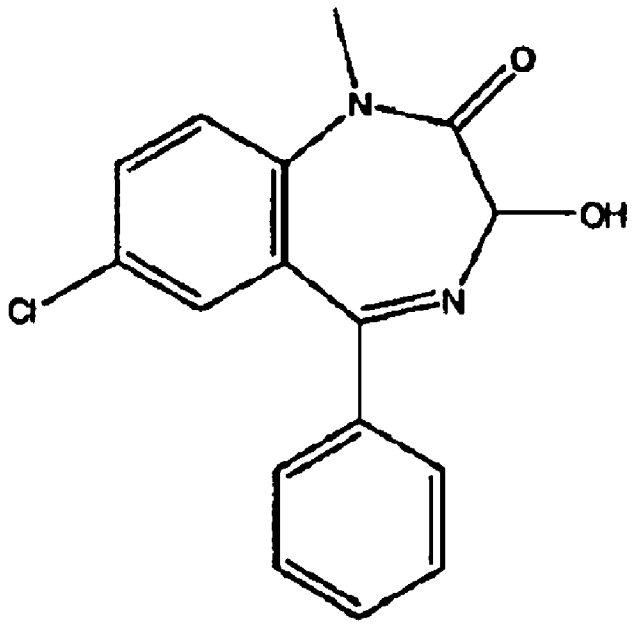
しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

【０１２８】

テマゼパム（７－クロロ－１－メチル－５－フェニル－３－ヒドロキシ－１，３－ジヒドロ－２Ｈ－１，４－ベンゾジアゼピン－２－オン）

【０１２９】

【化９】



【０１３０】

テマゼパムは、鎮静の、精神安定の、抗痙攣性の、健忘性の、及び筋弛緩性の特性を有するベンゾジアゼピン薬である。これは抗不安薬として分類される。テマゼパムはまた、吐き気の処置に有用であると示されてきた。テマゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約１から約５０まで、好ましくは約５から約３０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。テマゼパムは、米国特許第３，３４０，２５３号、又は第３，３７４，２２５号に開示される工程を用いて製造され得、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１３１】

いくつかの実施形態において、テマゼパムは、抗不安効果、抗痙攣効果、鎮静効果、骨格筋弛緩効果、健忘作用、又は前述の効果の組合せを提供するため、単独で、又は他の薬と併用して用いられる。

【０１３２】

いくつかの実施形態において、テマゼパムは、発作を処置し、発作から保護し、発作の強さを減じ又は改善し、発作の頻度を減じ又は改善し、及び／又は、発作の発生又は再発を予防するため、単独で又はもう一つの抗痙攣薬と併用して用いられる。発作から保護するため、患者が発病していない状態にある間、テマゼパムは、患者又は別の人（ヘルスケア専門家など）により投与され得る。発作からの保護が完全でない場合でさえ、テマゼパムの投与は、発作の強さを減じ又は改善し、及び／又は、発作の頻度を減じ又は改善し得る。いくつかの実施形態において、テマゼパムの投与は、発作の発生を予防し得る。いくつかの実施形態において、特に患者が連続的な発作又はてんかん重積状態を経験する傾向がある場合、テマゼパムの投与は、発作の循環を中断することを助け、従って発作の再発を予防し得る。ベンゾジアゼピン（ジアゼパムなど）に加えて、相乗的な抗痙攣効果を提供するため、他の抗痙攣薬がテマゼパムと組み合わせられ得る。

【０１３３】

テマゼパムはまた、患者が発作の状態にある間、もう一人の人（例えば、知人又は友人、家族の一員又はヘルスケア専門家）によって患者に投与されることもあり得る。従って、本発明によると、製剤の利点の一つは、急な治療環境において発作罹病者を処置するために、例えば経鼻的に、それらを投与され得ることである。ベンゾジアゼピン抗痙攣薬を

、例えば経鼻投薬など、急に投薬することにより分け与えられ得る有益な治療効果の中には、発作の重症度の減少（例えば、筋肉の全身におよぶ弛緩、患者が経験する、発作に引き起こされた不安の減少、及び患者に幸福感を一般的に分け与えること）、発作の持続時間の減少、患者が反復発作を経験するであろう確率の減少、現在の発作と次の発作の間の間隔の拡大がある。従って、本発明のテマゼパム製剤、及び特に経鼻製剤は、いくつかの例においては約３０分未満、約１５分未満、約１０分未満、そしていくつかの場合においては約５分未満での、速やかな治療的な恩恵の発現を提供する。本発明のテマゼパム製剤、及び特に経鼻製剤は、静脈内の薬の投与や、直腸の薬の投与を必要としない、患者への治療上有益な薬の便利な投与をもまた提供する。

【０１３４】

しばしば発作、特に重症な強直性発作又は強直間代発作は、患者又は患者をよく知る人によく知られた、１以上の前兆事象により予測される。これらの前兆はそれぞれの患者にほとんど独特であるが、可聴の、視覚の、嗅覚の、又は触覚の感覚として分類され得、通常、又は典型的に患者が発作を経験することより先に起こる。本発明のいくつかの実施形態において、方法は前兆の間に本発明に従ってベンゾジアゼピン薬の調製物を迅速に投与することを含む。いくつかの実施形態において、ベンゾジアゼピン薬のこのような耳内への（ｉｎｔｒａ－ａｕｒａｌ）投与、例えば経鼻投与による投与は、切迫した発作の効果（強さ、持続時間、又は両方）を予防又は少なくとも改善する。従って、本発明の文脈において、発作の予防は、警戒前兆（ｗａｒｎｉｎｇ　ａｕｒａ）の恩恵を受け、又は受けずに、のいずれかで、発作の発病を一時的に未然に防ぐことを指す。

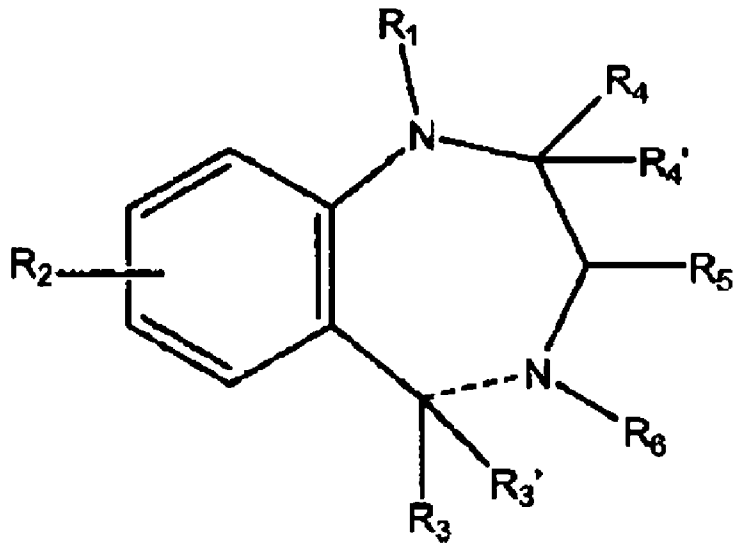
【０１３５】

薬学的に許容可能な塩

ベンゾジアゼピンは、概して式Ｉの塩基性構造を有する。

【０１３６】

【化１０】



式Ｉ

【０１３７】

ここでＲ１からＲ５は置換基である。特定の実施形態において、Ｒ１は任意に置換されたアルキルであるか、又はＲ４とともに環を形成し、Ｒ２はハロゲン（例えばＣｌ、Ｂｒ）であり、Ｒ３は任意に置換されたアリール（例えば、２－クロロ又は２－フルオロフェニル）であり、Ｒ５はＨ又はＯＨであり、Ｒ４及びＲ４’は共に、それらが付いている炭素とともにカルボニル（Ｃ＝Ｏ）を形成する、或いは、Ｒ４及びＲ１はそれらが各々付い

ているジアゼパム環原子とともに任意に置換された複素環式環を形成し、R_3'及びR_6はともに二重結合を形成する、又は、それらが各々付いているジアゼパム環原子とともに任意に置換された複素環式環を形成するよう結合され得る。このような塩基性化合物は、薬学的に許容可能な無機酸及び薬学的に許容可能な有機酸などの薬学的に許容可能な酸を用いて、酸付加塩を形成し得る。

【０１３８】

薬学的に許容可能な無機酸は、ＨＣｌ、H_2SO_4、H_2SO_3、H_3PO_4、H_3PO_3、及び当該分野の当業者に認められる他のものを含む。薬学的に許容可能な有機酸は、酢酸、安息香酸、酒石酸、クエン酸、シュウ酸、マレイン酸、マロン酸等を含む。従って、いくつかの実施形態において、薬学的に許容可能な酸は、１－ヒドロキシ－２－ナフトエ酸、２，２－ジクロロ酢酸、２－ヒドロキシエタンスルホン酸、２－オキソグルタル酸、４－アセトアミド安息香酸、４－アミノサリチル酸、酢酸、アジピン酸、アスコルビン酸（Ｌ）、アスパラギン酸（Ｌ）、ベンゼンスルホン酸、安息香酸、樟脳酸（＋）、カンファー－１０－スルホン酸（＋）、カプリン酸（デカン酸）、カプロン酸（ヘキサン酸）、カプリル酸（オクタン酸）、炭酸、桂皮酸、クエン酸、シクラミン酸、ドデシル硫酸、エタン－１，２－ジスルホン酸、エタンスルホン酸、ギ酸、フマル酸、ガラクタル酸、ゲンチシン酸、グルコヘプトン酸（Ｄ）、グルコン酸（Ｄ）、グルクロン酸（Ｄ）、グルタミン酸、グルタル酸、グリセロリン酸、グリコール酸、馬尿酸、臭化水素酸、塩酸、イソ酪酸、乳酸（ＤＬ）、ラクトビオン酸、ラウリン酸、マレイン酸、リンゴ酸（－　Ｌ）、マロン酸、マンデル酸（ＤＬ）、メタンスルホン酸、ベンゼンスルホン酸（ベシル酸）、ナフタレン－１，５－ジスルホン酸、ナフタレン－２－スルホン酸、ニコチン酸、硝酸、オレイン酸、シュウ酸、パルミチン酸、パモン酸（ｐａｍｏｉｃ　ａｃｉｄ）、リン酸、プロピオン酸、ピログルタミン酸（－　Ｌ）、サリチル酸、セバシン酸、ステアリン酸、コハク酸、硫酸、酒石酸（＋　Ｌ）、チオシアン酸、トルエンスルホン酸（ｐ）及びウンデシレン酸から構成される群から選択され得る。他の薬学的に許容可能な酸は、薬学的に許容可能な酸性（アニオン性）ポリマー、又は薬学的に許容可能な両性ポリマーであり得る。当該分野の当業者は、酸付加塩を作り出すため、他の塩基性の医薬品有効成分が前述の酸と結合され得ることを認める。同様に、当該分野の当業者は、いくつかの実施形態において、いくつか又は全ての加えられた酸がそれ自体で医薬品有効成分となることが好都合であることを認める。

【０１３９】

いくつかの実施形態において、本発明は、１以上の酸性の医薬品有効成分を備える経鼻組成物を提供する。上記の化合物のいずれが酸性であるかを決定することは、当該技術分野の当業者において、十分に考慮されている。このような化合物は、例えば、１以上の無機塩基（例えばＮａＯＨ、ＫＯＨ、$NaHCO_3$、Na_2CO_3、NH_3）、又は有機塩基を加えることにより、塩基付加塩として調製され得る。薬学的に許容化可能な塩基を選ぶことは当該分野の当業者において考慮されている。

【０１４０】

既知のベンゾジアゼピン化合物は、抗不安の、抗痙攣の、鎮静の、及び／又は骨格筋弛緩性の効果を有する。用語「抗痙攣の」は、発作を処置すること、発作から保護すること、発作の強さを減じ又は改善すること、発作の頻度を減じ又は改善すること、及び／又は、発作の発生又は再発を予防することを含む。この点において、発作を処置することは、進行中の発作の休止、進行中の発作の強さの減少、進行中の発作の持続時間の減少を含む。発作から保護することは、接近する発作を未然に防ぐことを含む。

【０１４１】

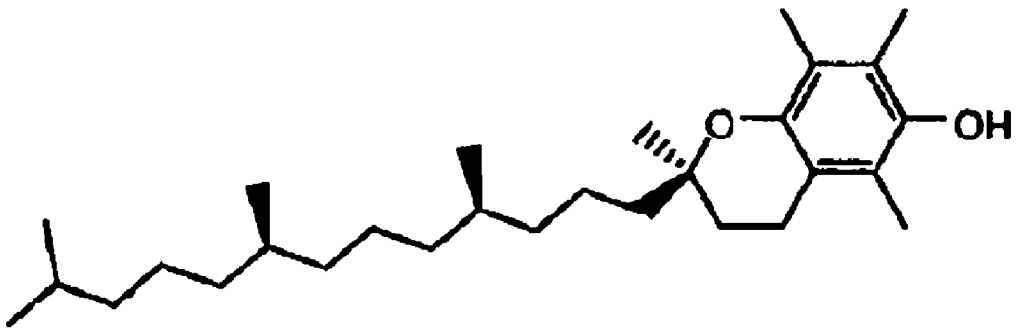
担体系

ビタミンＥは、脂溶性のメチル化されたフェノールである。この分類を備える少なくとも８つの天然由来の化合物が存在し、それらは、α－トコフェロール、β－トコフェロール、γ－トコフェロール、δ－トコフェロール、α－トコトリエノール、β－トコトリエノール、γ－トコトリエノール、及びδ－トコトリエノールで、これらの全ては本発明の

組成物及び方法において用いられ得る。これらの化合物のそれぞれに多数の異性体が存在し、それらの全ては本発明の組成物及び方法において用いられ得る。これらの化合物のそれぞれにまた、トコフェルソランを含む、多数のエステルが存在し、それらのすべては本発明の組成物及び方法において用いられ得る。本明細書中に用いられるように、ビタミンＥは、任意の天然又は合成トコフェロール、トコトリエノール、それらの任意の異性体、それらの任意のエステル、それらの任意のアナログ又は誘導体、又はそれらの任意の組合せを指す。

【０１４２】

【化１１】



【０１４３】

α－トコフェロール

ビタミンＥを備える化合物は抗酸化剤である。それらは、心臓病、癌、白内障、黄斑変性、緑内障、アルツハイマー病、及びパーキンソン病の症状を予防し、それらの発病を遅らせ、又は改善することができるという証拠もまた存在する。

【０１４４】

本発明は、ビタミンＥが、ベンゾジアゼピン薬にとって効果的な担体を供給できることを見出した。いくつかの実施形態において、ベンゾジアゼピンはビタミンＥに溶解できる、又は部分的に溶解できる。いくつかの実施形態において、ビタミンＥは、ミクロ粒子、ナノ粒子、又はそれらの任意の組合せとして存在し得る。更に、ビタミンＥの使用は、敏感な粘膜の炎症を回避すること、及び／又は、炎症を起こしている粘膜を落ち着かせることのいずれかの付加的な恩恵を有す。

【０１４５】

ビタミンＥは、一般的に疎水性に分類され、担体として用いられる時にはエマルションとしての製剤に限定され得る。しかしながら、エマルションは数個の欠点を有し得る。例えば、それらは作りだすのが困難であり、また非常に不安定であり得る。更に、それらは皮膚の表面上に、油の薄膜を残し得る。従って、エマルションの欠点を回避するため、本発明のいくつかの実施形態は、ビタミンＥと、１以上の低級アルキルアルコール又は１以上の低級アルキルグリコール、又はそれらの組合せ中の、１以上のベンゾジアゼピン薬の溶液を備える。

【０１４６】

低級アルキルアルコールは、６以下の炭素原子を有するものである。従って、エタノール、プロピルアルコール、ブチルアルコール、ペンタノール、ベンジルアルコール、それらの任意の異性体、又はそれらの任意の組合せのいずれかが、用いられ得る。

【０１４７】

低級アルキルグリコールは、６以下の炭素原子を有するものである。従って、エチレングリコール、プロピレングリコール、ブチレングリコール、ペンチレングリコール、それらの任意の異性体、又はそれらの任意の組合せのいずれかが、用いられ得る。

【０１４８】

追加の賦形剤

いくつかの実施形態において、組成物はベンゾジアゼピン薬、天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、及びアルコール又はグリコールに加えて、少なくとも１つの透過賦活剤を備える。いくつかの実施形態において、透過賦活剤は少なくとも１つのアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、任意の疎水性アルキルにつなぎ合わされる任意の糖を指し、このことは米国特許第５，６６１，１３０号に記されており、これは全体として参照することにより本明細書中に組み込まれる。疎水性アルキルは、任意の適切な長さであることができ、例えば、炭鎖長が約９から約２４の炭素、特に炭鎖長が約１０から約１４の炭素であり得る。疎水性アルキルは、分岐であり得、及び／又は部分的に又は全体的に不飽和であり得る。アルキルは例えばカルボニル基を介してサッカライドコアにつなぎ合わされ得、それによってエステル基が形成され得る。適切なアルキルグリコシドは、無毒性であり、非イオン性であり、本明細書中に記載されるように鼻腔内に投与されるとベンゾジアゼピン薬の吸収を増大させることができるという特徴を有する。本発明に係るアルキルに共有結合的につなぎ合わされ得る例示的な糖類は、グルコース、マルトース、マルトトリオース、マルトテトロース、スクロース、及びトレハロースを含む。使用され得る例示的なアルキルグリコシドは、オクチルー、ノニルー、デシルー、ウンデシルー、ドデシル、トリデシル、テトラデシル、ペンタデシル、オクタデシルα－又はβ－Ｄ－マルトシド、－グルコシド、又はスクロシドを含む。いくつかの実施形態において、好ましいグリコシドは、９、１０、１２、１４、１６、１８、又は２０炭素原子のアルキル鎖にグリコシド結合により連結される、マルトース、スクロース、又はグルコースを含む。本発明に従って経鼻組成物に使用され得る特定の賦形剤は、アルキルサッカライド（ａｌｋｙｌｓａｃｃｈａｒｉｄｅ）を含み、アルキルサッカライドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２又はそれより多いそれらの組合せを含む。本発明の実施形態において特に有用であるとみなされるアルキルグリコシドは、Ａｅｇｉｓ　Ｔｈｅｒａｐｅｕｔｉｃｓ，ＬＬＣ、サンディエゴ、カリホルニアよりＩｎｔｒａｖａｉｌ（登録商標）の名で販売されているものを含む。他のアルキルグリコシドは、親水性親油性バランス（ＨＬＢ）数が約１０から２０、特に約１１から１５を有するものから選択され得る。ＨＬＢ数は２００９年２月１９日に公開された、米国公開公報２００９／００４７３４７号に説明されるように決定され、この公報の全体、及び特に段落［００７５］から［００７９］は、参照することにより本明細書中に組み込まれる。存在する場合、組成物中のアルキルグリコシドの量は、鼻腔内経路により投与されるベンゾジアゼピン薬の吸収を高めるために十分な量である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、ベンゾジアゼピン薬の吸収を高めるために選択され、同時に鼻粘膜を著しく刺激しない。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、約０．０１％（Ｗ／Ｖ）から約１％（Ｗ／Ｖ）までの範囲内である。いくつかの実施形態において、組成物中のアルキルグリコシドの量は、約０．０５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）まで、又は約０．１２５％（Ｗ／Ｖ）から約０．５％（Ｗ／Ｖ）までの範囲内である。

【０１４９】

用語「透過賦活剤」は、粘膜を介する吸収を増大し、及び／又はバイオアベイラビリティを増大するよう作用する任意の物質を意味する。いくつかの実施形態において、このような物質は、粘液溶解薬、分解性酵素インヒビター、及び粘膜細胞膜の透過性を増大する化合物を含む。所与の化合物が「賦活剤」であるかどうかは、関連のない小さい極性分子を薬として備える、賦活剤を有し、又は有さない２つの製剤を、インビボ又は有効なモデル試験において、比較することにより、及び、薬の摂取が臨床的にかなりの程度まで高められるかどうかを決定することにより、決定される。賦活剤は、慢性毒性の点で、いかなる問題をももたらしてはならない、なぜなら、インビボで、賦活剤は非刺激的であるべきであり、及び／又は、任意の有意な刺激効果を有することなく通常の細胞構成要素に急速に代謝されるべきであるためである。

【０１５０】

いくつかの実施形態において、好ましい賦活物質、リゾリン脂質、例えば、卵又は大豆レシチンから得られるリゾホスファチジルコリンがある。異なるアシル基を有する他のリゾホスファチジルコリンや、同様の膜修飾特性を有する、ホスファチジルエタノールアミン及びホスファチジン酸から産生されるリゾ化合物が用いられ得る。アシルカルニチン（例えばパルミトイル－ｄｌ－カルニチン－クロライド）が選択肢である。いくつかの実施形態において、適切な濃度は０．０２％から２０％Ｗ／Ｖである。

【０１５１】

いくつかの実施形態において、ふさわしい賦活剤は、キレート化剤（ＥＧＴＡ、ＥＤＴＡ、アルギン酸塩）、界面活性剤（特に非イオン性の物質）、アシルグリセロール、脂肪酸及び塩、チロキサポール及び生物学的洗浄剤を含み、これらはシグマカタログ（ＳＩＧＭＡ　Ｃａｔａｌｏｇ）１９８８、ページ３１６から３２１に載っている（これは参照することにより本明細書中に組み込まれる）。また、膜流動性及び透過性を修飾する剤が適切であり、それらは、エナミン（例えば、エチルアセトアセテートのフェニルアラニンエナミン）、マロネート（例えば、ジエチレンオキシメチレンマロネート）サリチル酸塩、胆汁酸塩、及びアナログ並びにフシジン酸塩（ｆｕｓｉｄａｔｅｓ）などである。適切な濃度は、２０％Ｗ／Ｖまでである。

【０１５２】

従って、いくつかの実施形態において、本発明は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、約３０％から約９５％（Ｗ／Ｗ）までの量の、ベンゾジアゼピン薬、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、１以上のアルキルグリコシドと、約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、もしくはそれらの任意の組合せとを備える、経鼻投与用の医薬組成物を提供する。いくつかの実施形態において、アルキルグリコシドはＩｎｔｒａｖａｉｌ（登録商標）ブランドのアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２以上のそれらの組合せである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、テトラデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、スクロースドデカノエイトである。いくつかの実施形態において、アルキルグリコシドは、スクロースモノステアリンである。いくつかの実施形態において、アルキルグリコシドは、スクロースジステアリンである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、又はスクロースジステアリンの、２以上の組合せである。

【０１５３】

従って、いくつかの実施形態において、本発明は、患者の１以上の鼻粘膜への投与用の薬学的に許容可能な製剤中に、約３０％から約９５％（Ｗ／Ｗ）までの量の、ミクロ粒子、ナノ粒子又は両方を備えるベンゾジアゼピン薬、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノール、あるいはそれらの任意の組合せと、１以上のアルキルグリコシドと、約１０％から約７０％（Ｗ／Ｗ）までの量の、１以上のアルコール又はグリコール、もしくはそれらの任意の組合せとを備える、経鼻投与用の医薬組成物を提供する。いくつかの実施形態において、アルキルグリコシドはＩｎｔｒａｖａｉｌ（登録商標）ブランドのアルキルグリコシドである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２以上のそれらの組合せである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、テトラデシルマルトシドである。いくつかの実施形態において、アルキルグリコシドは、スクロースドデカノエイトである。いくつかの実施形態において、アルキルグリコシドは、スクロースモノステ

アリンである。いくつかの実施形態において、アルキルグリコシドは、スクロースジステアリンである。いくつかの実施形態において、アルキルグリコシドは、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、又はスクロースジステアリンの、２以上の組合せである。

【０１５４】

粘膜調製物

粘膜調製物は、２５０μＬ未満の、好ましくは１５０μＬ未満の、及び理想的には２５から１００μＬまでの容量を有する、計量スプレーで一般的に投与される。本発明で禁じられるものではないが、投与量当たり約３００μＬより大きい容量の投与は通常、膜の吸収能力を超える。これにより、薬学的に活性な成分の大部分が失われることとなる。

【０１５５】

調製物、特に鼻用調製物の投薬量の容量は、好ましくは２５から１００μＬに及ぶ。前記の範囲を超える容量は、その過剰分が嚥下されると、洞を迂回し、喉の後ろを流れ落ち得る。

【０１５６】

アルプラゾラム

アルプラゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．５から約４まで、好ましくは約１から約２ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。アルプラゾラムは、米国特許第３，９８７，０５２号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１５７】

経鼻製剤として、アルプラゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、アルプラゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１５８】

ジアゼパム

ジアゼパムの投薬量は、指示により異なり得るが、しかしながら、治療量は投与量あたり約１から約２０まで、好ましくは約２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ジアゼパムは、米国特許第３，３７１，０８５号、第３，１０９，８４３号、第３，１３６，８１５号、又は第３，１０２，１１６号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１５９】

経鼻製剤として、ジアゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ジアゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１６０】

フルラゼパム

フルラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約５から約４０まで、好ましくは約２０から約３５ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。フルラゼパムは、米国特許第３，５６７，７１０号、又は第３，２９９，０５３号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１６１】

経鼻製剤として、フルラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、フルラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１６２】
ロラゼパム
ロラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ロラゼパムは、米国特許第３，２９６，２４９号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【０１６３】
経鼻製剤として、ロラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ロラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１６４】
メダゼパム
メダゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メダゼパムは、米国特許第３，２４３，４２７号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。
【０１６５】
経鼻製剤として、メダゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、メダゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１６６】
メキサゾラム
メキサゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メキサゾラムは、米国特許第３，７２２，３７１号に開示される工程を用いて製造され得、これは全体として参照することにより本明細書中に組み込まれる。
【０１６７】
経鼻製剤として、メキサゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、メキサゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１６８】
ミダゾラム
ミダゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約２０まで、好ましくは約０．２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ミダゾラムは、米国特許第４，２８０，９５７号、又は第５，８３１，０８９号の一つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。
【０１６９】
経鼻製剤として、ミダゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ミダサゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。
【０１７０】
テマゼパム
テマゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約１から約５０まで、好ましくは約５から約３０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予

期される。テマゼパムは、米国特許第３，３４０，２５３号、又は第３，３７４，２２５号に開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１７１】

経鼻製剤として、テマゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、テマゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。

【０１７２】

製剤

いくつかの実施形態は、患者の１以上の粘膜に、治療的に効果的な量の１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を投与することを備える。組成物のいくつかの実施形態は、１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を、約６００ｍｇ／ｍＬまでの濃度で備える組成物を開示する。他の組成物は、１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を、約１０ｍｇ／ｍＬから約２５０ｍｇ／ｍＬまでの濃度で備える組成物を開示する。更に、いくつかの実施形態は、１以上のベンゾジアゼピン薬、又はそれらの薬学的に許容可能な塩を、約２０ｍｇ／ｍＬから約５０ｍｇ／ｍＬまでの濃度で備える組成物を開示する。

【０１７３】

いくつかの実施形態は、約５０％から約９０％（Ｗ／Ｗ）のビタミンＥと約１０％から約５０％（Ｗ／Ｗ）の低級アルコール又は低級アルキルグリコール、又はそれらの任意の組合せである担体系を開示する。いくつかの実施形態は、約６５％から約７５％（Ｗ／Ｗ）のビタミンＥと約２５％から約３５％（Ｗ／Ｗ）の低級アルキルアルコール又は低級アルキルグリコール、又はそれらの任意の組合せである担体系を開示する。更にいくつかの実施形態は、約７０％（Ｗ／Ｗ）のビタミンＥと約３０％（Ｗ／Ｗ）の低級アルキルアルコール又は低級アルキルグリコール、又はそれらの任意の組合せである担体系を開示する。

【０１７４】

本発明のいくつかの実施形態は、ベンゾジアゼピン薬組成物を患者に投与する方法を提供する。好ましい実施形態は、ジアゼパムの使用を備える。方法のいくつかの実施形態は、所望の結果が達成されるまで、約１．０ｍｇから約２０．０ｍｇのジアゼパムの投薬量レベルを開示する。他の投薬量レベルは、所望の結果が達成されるまで約２．０ｍｇから約１５．０ｍｇの投薬量レベルを開示する。いくつかの実施形態は、所望の結果が達成されるまで、約５．０ｍｇから約１０．０ｍｇの投薬量レベルを開示する。

【０１７５】

方法のいくつかの実施形態において、投薬量容量は、約１０μＬから約２００μＬまでに及ぶ。いくつかの実施形態において、投薬量容量は、約２０μＬから約１８０μＬまでに及ぶ。更にいくつかの実施形態は、約５０μＬから約１４０μＬの投薬量容量を開示する。

【０１７６】

製剤工程

いくつかの実施形態において、経鼻投与用の組成物は、ベンゾジアゼピンミクロ粒子、ナノ粒子、又はそれらの組合せを実質的に有さない。いくつかの実施形態において、組成物はビタミンＥを液化するまでゆっくり温める又は熱することにより作られる。次に、１以上のベンゾジアゼピン薬が加えられる。混合物は、１以上のベンゾジアゼピン薬が溶解する又は実質的に溶解されるまで、撹拌され、熱せられる。次に、１以上のアルコールまたはグリコール、もしくはそれらの任意の組合せが、組成物に加えられる。組成物は、粘性の低い組成物が得られるまで撹拌される。

【０１７７】

前述の製剤は、好ましくは無菌であり、ｍｌ当たりとして、許容レベルを１０下回る細菌数を有する。加えて、病原体は好ましくは存在しない。

【０１７８】
いくつかの実施形態において、ベンゾジアゼピン薬は、ベンゾジアゼピンのミクロ粒子及び／又はナノ粒子懸濁液として処方される。ミクロ粒子及びナノ粒子ベンゾジアゼピンの調製は、製粉などの方法によって成し遂げられ得る。このような方法は、当該分野の当業者に知られている。
【０１７９】
いくつかの実施形態において、ベンゾジアゼピン薬は溶液として処方される。製剤を調製する工程の間、ミクロ粒子及び／又はナノ粒子ベンゾジアゼピン薬を使用することにより、溶媒系におけるベンゾジアゼピン薬の全体的な溶解度を改善することができることが、本発明の１つの態様として考慮される。
【０１８０】
追加の活性及び不活性成分
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、活性成分から選択される組成物中の追加の成分を備える。制約のない例として、このような活性成分は、インスリン、カルシトニン（例えば、豚の、ヒトの、サケの、ニワトリの、又はウナギの）及びそれらの合成修飾物、エンケファリン、ＬＨＲＨ及びアナログ（ナファレリン、ブセレリン、ゾリデックス（Ｚｏｌｉｄｅｘ））、ＧＨＲＨ（成長ホルモン放出ホルモン）、ニフェジピン、ＴＨＦ（胸腺液性因子）、ＣＧＲＰ（カルシトニン遺伝子関連ペプチド）、心房性ナトリウム利尿ペプチド、抗生物質、メトクロプラミド、エルゴタミン、ピゾチジン（Ｐｉｚｏｔｉｚｉｎ）、経鼻ワクチン（特にＨＩＶワクチン、麻疹、ライノウイルス１３型及び呼吸器合胞体ウイルス）、ペンタミジン、ＣＣＫ（コレシストキニン）、ＤＤＶＡＰ、インターフェロン、成長ホルモン（ソラトトロピア（ｓｏｌａｔｏｔｒｏｐｉｒ）ポリペプチド又はそれらの誘導体（好ましくは１０００から３００００までの分子量を有する）、セクレチン、ブラジキニンアンタゴニスト、ＧＲＦ（成長放出因子）、ＴＨＦ、ＴＲＨ（甲状腺刺激ホルモン放出ホルモン）、ＡＣＴＨアナログ、ＩＧＦ（インスリン様成長因子）、ＣＧＲＰ（カルシトニン遺伝子関連ペプチド）心房性ナトリウム利尿ペプチド、バソプレシン及びアナログ（ＤＤＡＶＰ、リプレシン）、メトクロプラミド、偏頭痛処置（ジヒドロエルゴタミン、エルゴメトリン、エルゴタミン、ピゾチジン（Ｐｉｚｏｔｉｚｉｎ））、経鼻ワクチン（特にエイズワクチン）第ＶＩＩＩ因子、コロニー刺激因子、Ｇ－ＣＳＦ（顆粒球コロニー刺激因子）、ＥＰＯ（エリスロポエチン）ＰＴＨ（副甲状腺ホルモン）又はそれらの薬学的に許容可能な塩、又はそれらの組合せを含む。
【０１８１】
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、他の抗痙攣薬から選択される組成物中の追加の成分を備える。制約のない例として、このような活性成分は、パラアルデヒド；芳香族アリルアルコール（スチリペントールなど）；バルビツール酸塩（例えば、フェノバルビトール（ｐｈｅｎｏｂａｒｂｉｔｏｌ）、プリミドン、メチルフェノバルビタール、メタルビタール及びバルベキサクロン）；臭化物（臭化カリウムなど）；カルバミン酸塩（フェルバメートなど）；カルボキサミド（カルバマゼピン及びオクスカルバゼピン）；脂肪酸（バルプロ酸、バルプロ酸ナトリウム、及びジバルプロエクスナトリウム、ビガバトリン、プロガビド、チアガビン）；フルクトース、トピラマート、ギャバ（Ｇａｂａ）アナログ（例えば、ガバペンチン及びプレガバリン）；ヒダントイン（例えばエトトイン、フェニトイン、メフェニトイン及びホスフェニトイン）；オキサゾリジンジオン（パラメタジオン、トリメタジオン、エタジオン）；プロピオン酸塩（例えばベクラミド）、ピリミジンジオン（例えばプリミドン）；ピロリジン（例えばブリバラセタム、レベチラセタム及びセレトラセタム）；コハク酸イミド（例えばエトスクシミド、フェンスクシミド及びメスクシミド）；スルホンアミド（例えばアセタゾラミド、スルチアム、メタゾラミド及びゾニサミド）；トリアジン（ラモトリジンなど）；尿素（フェネツリド、フェナセミド）；バルプロイルアミド（ｖａｌｐｒｏｙｌａｍｉｄｅｓ）（バルプロミド及びバルノクタミド）；及び他の抗痙攣薬、又は薬学的に許容可能な塩又はそれらの組合せを含む。

【０１８２】
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、他の抗痙攣薬から選択される組成物中の追加の成分を備える。制約のない例として、このような活性成分は、テトラサイクリン塩酸塩、ロイコマイシン、ペニシリン、ペニシリン誘導体、エリスロマイシン、ゲンタマイシン、スルファチアゾール及びニトロフラゾンなどの抗生物質及び抗菌剤；ベンゾカインなどの局所麻酔剤；フェニレフリン塩酸塩、塩酸テトラヒドロゾリン、硝酸ナファゾリン、塩酸オキシメタゾリン及びトラマゾリン塩酸塩などの血管収縮剤；ジギタリス及びジゴキシンなどの強心剤；ニトログリセリン及びパパベリン塩酸塩などの血管拡張剤；塩酸クロルヘキシジン、ヘキシルレゾルシノール、塩化デカリニウム及びエタクリジンなどの消毒剤；塩化リゾチーム、デキストラナーゼなどの酵素；ビタミンＤ、活性ビタミンＤ及びビタミンＣなどの骨代謝調節剤；性ホルモン；降圧剤；鎮静剤；抗腫瘍薬；ヒドロコルチゾン、プレドニゾン、フルチカゾン、プレドニゾロン、トリアムシノロン、トリアムシノロンアセトニド、デキサメタゾン、ベタメタゾン、ベクロメタゾン、及びジプロピオン酸ベクロメタゾンなどのステロイド性抗炎症剤；アセトアミノフェン、アスピリン、アミノピリン、フェニルブタゾン、メダナミック（ｍｅｄａｎａｍｉｃ）酸、イブプロフェン、ジクロフェナクナトリウム、インドメタシン（ｉｎｄｏｍｅｔｈａｃｉｎｅ）、コルヒチン、及びプロベノシド（ｐｒｏｂｅｎｏｃｉｄ）などの非ステロイド性抗炎症剤；キモトリプシン及びブロメラインセラチオペプチダーゼ（ｂｒｏｍｅｌａｉｎ　ｓｅｒａｔｉｏｐｅｐｔｉｄａｓｅ）などの酵素的な抗炎症剤；塩酸ジフェンヒドラミン、クロロフェニラミンマレイン酸塩（ｃｈｌｏｒｏｐｈｅｎｉｒａｍｉｎｅ　ｍａｌｅａｔｅ）及びクレマスチンなどの抗ヒスタミン剤；クロモグリク酸ナトリウム、コデインリン酸塩、及び塩酸イソプロテレノールなどの抗アレルギー剤及び鎮咳－去痰、抗ぜんそく薬、又はそれらの薬学的に許容可能な塩又はそれらの組合せを含む。

【０１８３】
更に、組成物、及び組成物を使用する方法のいくつかの実施形態は、組成物中の追加の不活性成分を備える。制約のない例として、安定剤、着色剤、ｐＨ調整剤、緩衝剤、分解を防ぎ得る薬剤などの保存剤、湿潤剤、及び香味剤などの少量の成分もまた存在し得る。着色剤の例には、β－カロチン、赤色２号及び青色１号が含まれる。保存剤の例にはステアリン酸、ステアリン酸アスコルビル及びアスコルビン酸が含まれる。矯味薬の例には、メントール及び柑橘類香料が含まれる。

【０１８４】
いくつかの実施形態において、本発明の薬送達システムは、好都合に吸収賦活剤を備える。用語「賦活剤」は、粘膜を介する吸収を増大し、及び／又は、バイオアベイラビリティを増大させるよう作用する任意の物質を意味する。いくつかの実施形態において、このような物質は、粘液溶解薬、分解性酵素インヒビター、及び粘膜細胞膜の透過性を増大する化合物を含む。所与の化合物が「賦活剤」であるかどうかは、関連のない小さい極性分子を薬として備える、賦活剤を有し、又は有さない２つの製剤を、インビボ又は有効なモデル試験において、比較することにより決定され、薬の摂取が臨床的にかなりの程度まで高められるかどうかを決定することにより決定される。賦活剤は、慢性毒性の点で、いかなる問題をももたらしてはならない、なぜなら、インビボで、賦活剤は非刺激的であるべきであり、及び／又は、任意の有意の刺激効果を有さない正常な細胞構成要素に急速に代謝されるべきである。

【０１８５】
いくつかの実施形態において、好ましい賦活物質、リゾリン脂質、例えば、卵又は大豆レシチンから得られるリゾホスファチジルコリンがある。異なるアシル基を有する他のリゾホスファチジルコリンや、ホスファチジルエタノールアミン及びホスファチジン酸から産生され、同様の膜修飾特性を有するリゾ化合物が用いられ得る。アシルカルニチン（例えばパルミトイル－ｄｌ－カルニチン－クロライド）が選択肢である。いくつかの実施形態において、適切な濃度は０．０２％から２０％Ｗ／Ｖである。

【０１８６】

いくつかの実施形態において、ふさわしい賦活剤は、キレート化剤（ＥＧＴＡ、ＥＤＴＡ、アルギン酸塩）、界面活性剤（特に非イオン性の物質）、アシルグリセロール、脂肪酸及び塩、チロキサポール及び生物学的洗浄剤を含み、これらはシグマカタログ（ＳＩＧＭＡ　Ｃａｔａｌｏｇ）１９８８、ページ３１６から３２１に載っている（これは参照することにより本明細書中に組み込まれる）。また、膜流動性及び透過性を修飾する剤が適切であり、それらは、エナミン（例えば、エチルアセトアセテートのフェニルアラニンエナミン）、マロネート（例えば、ジエチレンオキシメチレンマロネート）、サリチル酸塩、胆汁酸塩、及びアナログ並びにフシジン酸塩（ｆｕｓｉｄａｔｅｓ）などである。適切な濃度は、２０％Ｗ／Ｖまでである。

【０１８７】

いくつかの実施形態において、本発明は、追加の薬学的アジュバントを備える生体接着ミクロスフェア中に又は生体接着ミクロスフェア上に組み込まれる薬の送達を利用し、活性薬及び粘液溶解薬、ペプチダーゼインヒビター又は非薬物ポリペプチド基質を単独で又は組合せで含有するシステムに適用する。適宜、粘液溶解薬は、Ｎ－アセチルシステイン、及びその誘導体などのチオール含有化合物である。ペプチドインヒビタには、アクチノニン、アマスタチン、ベスタチン、クロロアセチル－ＨＯＬｅｕ－Ａｌａ－Ｇｌｙ－ＮＨ．ｓｕｂ．２、ジプロチンＡ及びＢ、エベラクトンＡ及びＢ、Ｅ－６４、ロイペプチン、ペプスタチンＡ、ホスホラミドン、Ｈ－Ｔｈｒ－（ｔＢｕ）－Ｐｈｅ－Ｐｒｏ－ＯＨ、アプロチニン、カリクレイン、キモスタチン、ベンズアミジン、キモトリプシン及びトリプシンが含まれる。適切な濃度は、０．０１％から１０％Ｗ／Ｖである。当該分野の当業者は、賦活剤が含まれるべきかどうかを容易に決定することができる。

【０１８８】

投与

いくつかの実施形態において、組成物の投与は、治療的に効果的な量の組成物の少なくとも一部を、少なくとも１つの粘膜上に投与することを備える。いくつかの実施形態において、組成物の投与は、治療的に効果的な量の組成物の少なくとも一部を、少なくとも１つの鼻孔中に噴霧することを備える。いくつかの実施形態において、組成物の投与は、治療的に効果的な量の組成物の少なくとも一部を、それぞれの鼻孔中に噴霧することを備える。いくつかの実施形態において、組成物の投与は、組成物の第１の量を第１の鼻孔中に噴霧すること、組成物の第２の量を第２の鼻孔中に噴霧すること、及び任意に事前に選択した時間遅延の後、組成物の第３の量を第１の鼻孔中に噴霧することを備える。いくつかの実施形態は、任意に事前に選択した時間遅延の後、少なくとも組成物の第４の量を第２の鼻孔中に投与することを更に備える。

【０１８９】

アルプラゾラム

アルプラゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．５から約４まで、好ましくは約１から約２ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。アルプラゾラムは、米国特許第３，９８７，０５２号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１９０】

経鼻製剤として、アルプラゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、アルプラゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増

加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９１】

ジアゼパム

ジアゼパムの投薬量は、指示により異なり得るが、しかしながら、治療量は投与量あたり約１から約２０まで、好ましくは約２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ジアゼパムは、米国特許第３，３７１，０８５号、第３，１０９，８４３号、第３，１３６，８１５号、又は第３，１０２，１１６号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１９２】

経鼻製剤として、ジアゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ジアゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切り、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９３】

フルラゼパム

フルラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約５から約４０まで、好ましくは約２０から約３５ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。フルラゼパムは、米国特許第３，５６７，７１０号、又は第３，２９９，０５３号の１つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０１９４】

経鼻製剤として、フルラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、フルラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９５】

ロラゼパム

ロラゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ロラゼパムは、米国特許第３，２９６，２４９号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１９６】

経鼻製剤として、ロラゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ロラゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９７】

メダゼパム

メダゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メダゼパムは、米国特許第３，２４３，４２７号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０１９８】

経鼻製剤として、メダゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、メダゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０１９９】

メキサゾラム

メキサゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約１０まで、好ましくは約０．２から約１ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。メキサゾラムは、米国特許第３，７２２，３７１号に開示される工程を用いて製造され、これは全体として参照することにより本明細書中に組み込まれる。

【０２００】

経鼻製剤として、メキサゾラムは、２５から２５０μＬの計量スプレーで投与され得る

。いくつかの好ましい実施形態において、メキサゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０２０１】

ミダゾラム

ミダゾラムの投薬量は、指示により異なるが、治療量は投与量あたり約０．１から約２０まで、好ましくは約０．２から約１０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。ミダゾラムは、米国特許第４，２８０，９５７号、又は第５，８３１，０８９号の一つに開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０２０２】

経鼻製剤として、ミダゾラムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、ミダゾラムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０２０３】

テマゼパム

テマゼパムの投薬量は、指示により異なるが、治療量は投与量あたり約１から約５０まで、好ましくは約５から約３０ｍｇまでの範囲内で、１日あたり１から８、好ましくは２から８、いくつかの好ましい実施形態においては約４から約６回の範囲内であることが予期される。テマゼパムは、米国特許第３，３４０，２５３号、又は第３，３７４，２２５号に開示される工程を用いて製造され、これらのそれぞれは全体として参照することにより本明細書中に組み込まれる。

【０２０４】

経鼻製剤として、テマゼパムは、２５から２５０μＬの計量スプレーで投与され得る。いくつかの好ましい実施形態において、テマゼパムは、５０から１５０μＬ、特に約１００μＬの計量スプレーで投与される。いくつかの実施形態において、第１の計量スプレーは第１の鼻孔に適用され、必要であれば第２の計量スプレーが第２の鼻孔に適用される。いくつかの任意の実施形態において、第３の計量スプレーが第１の鼻孔に適用される。いくつかの実施形態において、第４の計量スプレーが第２の鼻孔に適用される。いくつかの実施形態において、患者に全ての標的治療量が投与されるまで、追加の計量スプレーが、

交互の鼻孔に適用される。いくつかの実施形態において、ベンゾジアゼピン薬の同じ鼻孔への適用の間に、数秒から５分間、好ましくは約１０秒から約１分間の時間の増加分がある。これにより、薬が鼻粘膜を通過し、血流中に入る時間が与えられる。任意に時間間隔で区切る、それぞれの鼻孔への計量スプレーの多数回適用は、ベンゾジアゼピン薬を血流中に全て吸収することを可能にするために十分少しずつ、全治療量を投与することを可能とし、喉の奥の下への薬の損失を避けることができる。

【０２０５】

当該分野の当業者は、前述の疾患を処置するためのベンゾジアゼピン薬の、体系的な治療的に効果的な量は、疾病の重症度だけでなく、患者の年齢、大きさ、体重、及び一般的な健康状態によって異なるということを承知している。投与の頻度も同様に、組成物の製剤によって異なり、１日当たり任意の数の投与量が用いられるよう調整されることができる。

【０２０６】

実施例

本発明はこれより、以下の例示的な、非限定の実施例を参照して示される。

【０２０７】

実施例１

ジアゼパムを備える医薬組成物が調製される。それは経鼻送達装置を介して送達されるための溶液として処方される。組成物は、成人のてんかんと関連する発作を処置又は予防するために用いられる。処置は、発作が始まった前又は後のいずれかで実施される。患者が発病している場合、それは、任意の経鼻送達装置からの１パフ（５．０ｍｇ／パフ（５．０ｍｇ／０．１ｍＬ、及び、０．１ｍＬ／パフ）で１パフ）として、５分毎に、発作の停止まで投与される。しかしながら、それは、それぞれの鼻孔中に鼻孔当たり１パフ（２．５ｍｇ／パフ（５．０ｍｇ／０．１ｍＬ、及び、０．０５ｍＬ／パフ）で２パフ）として、５分毎に、発作の停止まで与えられ得る。この実施例による組成物は、以下の表に示される。

【０２０８】

【表１】

表 1-1

5.0 mg/0.1mL	ジアゼパム
70.0 mg	α-トコフェロール
0.1 mL	エタノール(適量0.1mLまで)

【０２０９】

実施例２

ジアゼパムを備える医薬組成物が調製される。それは、経鼻送達装置を介して送達されるための溶液として処方される。組成物は、小児のてんかんと関連する発作を処置又は予防するために用いられる。処置は発作が始まった前又は後のいずれかで実施される。患者が発病している場合、それは、経鼻送達装置からの１パフ（２．０ｍｇ／パフ（２．０ｍｇ／０．１ｍＬ、及び、０．１ｍＬ／パフ）で１パフ）として投与される。発作が中止しない場合、５分後もう１投与量が投与され得る。しかしながら、それは、それぞれの鼻孔中に鼻孔当たり１パフ（１．０ｍｇ／パフ（２．０ｍｇ／０．１ｍＬ、及び、０．０５ｍＬ／パフ）で２パフ）として与えられることができる。発作が中止しない場合、５分後もう１投与量が投与され得る。この例による組成物は以下の表に示される。

【０２１０】

【表２】

表 2-1

2.0 mg/0.1mL	ジアゼパム
70.0 mg	α-トコフェロール
0.1 mL	エタノール (適量0.1mLまで)

【０２１１】

実施例３－ジアゼパム溶液の製剤

一般的に、ベンゾジアゼピン溶液は、１以上の天然又は合成トコフェロールもしくは天然又は合成トコトリエノールと１以上の低級アルコール又はグリコールを混合して、均一混合物が形成されるまで混ぜ合わせ、その均一混合物にベンゾジアゼピン薬を加え、ベンゾジアゼピン薬が均一混合物中に完全に溶解するまで成分を熱し及び混ぜ合わせ、混合物を冷却し、混合物を低級アルコール又はグリコールで、最終質量又は容量へともたらすことにより処方され得る。

【０２１２】

前述の工程により、２つの異なるジアゼパム溶液が処方された。ビタミンＥ　ＵＳＰ及び無水エタノール　ＵＳＰが以下の表に示される量で加えられ、混ぜ合わされることにより均一混合物を形成した。以下の表に示される量のジアゼパムがその後、均一混合物に加えられた。成分は、ジアゼパムが完全に溶解するまで、４０から４５℃に混ぜ合わせながら熱せられ、その結果溶液を形成した。溶液は２０から２５℃に冷却され、その結果溶液は無水エタノール　ＵＳＰを用いて最終標的重量となり、溶液は均一性を確実にするため完全に混ぜ合わされた。溶液はその後製造工程の試験用にサンプル抽出され、３ｍＬの琥珀色のガラスバイアルに入れられた。

【０２１３】

【表３】

表3-1: ジアゼパム溶液－70 mg/mL

構成要素	溶液 00 (65% ビタミン E) 濃度 (mg/mL)	溶液 02 (80% ビタミン E) 濃度 (mg/mL)
ジアゼパム USP	70.0	70.0
ビタミン E USP	650.0	800.0
無水エタノール USP	適量1mLまで	適量1mLまで

【０２１４】

ジアゼパムの量と、ビタミンＥ及びエタノールの相対量を変えることにより、追加の様々な濃度のジアゼパム溶液が同様の方法で作られる。他のベンゾジアゼピン溶液は、ジアゼパムの代わりに１以上のベンゾジアゼピンを使うことにより作られる。アルキルグリコシドなどの他の成分が、工程の適切な段階で（例えば、ベンゾジアゼピンの添加の前又は添加と同時に）加えられ得る。

【０２１５】

実施例４－ジアゼパム懸濁液の製剤

一般的に、ベンゾジアゼピン懸濁液は、ベンゾジアゼピンを微粒子化し、ベンゾジアゼピンを担体と混合することにより処方される。担体は、１以上の低級アルコール又はグリ

コールを水と混合し、天然又は合成トコフェロールもしくは天然又は合成トコトリエノールを加え、トコフェロール又はトコトリエノールが溶解するまで混合物を熱し、１以上のパラベンを加えてパラベンが溶解するまで混ぜ合わせ担体を冷却することにより、調製される。ベンゾジアゼピンが担体に加えられるとすぐに、界面活性剤などの追加の賦形剤が任意に加えられ、担体中に溶解されることができる。懸濁液はその後、水を用いて最終質量又は容量へともたらされる。

【０２１６】

２つの異なるベンゾジアゼピン懸濁液が、前述の一般的な工程により処方された。２つの異なるジアゼパムの粒径が調製され、それらは、Ａ：高圧微粒子化により調製される小さい粒径、及びＢ：低圧微粒子化により調製される大きい粒径である。担体は、プロピレングリコールＵＳＰと、精製水ＵＳＰとを混合し、その後ビタミンＥポリエチレングリコールスクシネートＮＦを加え、その後混合された成分を約４５℃に混ぜ合わせ及び熱することにより調製された。混ぜ合わせることはビタミンＥポリエチレングリコールスクシネートが完全に溶解するまで続けられた。担体はその後、２０から２５℃に冷却された。微粒子化されたジアゼパム（Ａ及びＢ）はその後担体に加えられ、ジアゼパムが完全に担体中に分散するまで強く混ぜ合わされた。ポリビニルピロリドンポビドンＵＳＰ／ＮＦがその後混合物に加えられ、完全に溶解するまで混ぜ合わされた。懸濁液はその後、精製水ＵＳＰを用いて重量へともたらされた。懸濁液はその後、均一になるまで混ぜ合わされ、製造工程の試験用にサンプル抽出され、３ｍＬの琥珀色のガラスバイアルに入れられた。

【０２１７】

【表４】

表4-1: ジアゼパム懸濁液製剤

構成要素	懸濁液 03 (200 mg/mL ジアゼパム) 濃度 (mg/mL)	懸濁液 01 (100 mg/mL ジアゼパム) 濃度 (mg/mL)
ジアゼパム USP	200.00	100.00
ビタミンEポリエチレングリコールスクシネート NF	100.0	100.0
メチルパラベン NF	2.0	2.0
プロピルパラベン NF	0.5	0.5
プロピレングリコール USP	100.0	100.0
ポビドン USP/NF	25.0	25.0
精製水 USP/EP	適量1mLまで	適量1mLまで

【０２１８】

ジアゼパム及び任意に他の賦形剤の量を変えることにより、追加の様々な濃度のジアゼパムの懸濁液が、同様の方法で作られる。他のベンゾジアゼピン懸濁液は、ジアゼパムの代わりに１以上のベンゾジアゼピンを使うことにより作られる。アルキルグリコシドなどの他の成分が、工程の適切な段階で加えられることができる。例えば、アルキルグリコシドは、担体の配合中に担体に加えられ得、又はポビドンの添加と同時、或いは添加後に懸濁液混合物に加えられ得る。

【０２１９】

実施例５－ジアゼパム溶液及び懸濁液の安定性

溶液００及び０２（実施例３）及び懸濁液０１及び０３（実施例４）が、２５℃／６０ＲＨ、３０℃／６５％ＲＨ、及び４０℃／７５％ＲＨで安定した状態で提示された。４つの異なる製剤のそれぞれ１回分が、３ｍｌのねじ蓋式の蓋を有するバイアルに入れられ、対応するアクチュエーターとともに、３つの保存条件で提示された。それらは、それらの

対応するＰａｒｔｉｃｌｅ　Ｓｃｉｅｎｃｅの初期サンプル管理番号とともに、表１に列挙される。

【０２２０】

【表５】

表5-1： PSIサンプル管理番号の概要

製剤 #	25°C/60% RH	30°C/65% RH	40°C/75% RH
溶液 00－70 mg/ml 溶液 ，65% ビタミン E	083101.01	083101.02	083101.02
溶液 02－70 mg/ml 溶液 ，80% ビタミン E	083102.01	083102.02	083102.03
懸濁液 01 - 100 mg/ml 懸濁液	083103.01	083103.02	083103.03
懸濁液 03 - 200 mg/ml 懸濁液	083104.01	083104.02	083104.03

【０２２１】

サンプルは、スプレー内容物の均一性、スプレー容量、ジアゼパム含有量、ジアゼパム関連物質、及びメチルパラベン並びにプロピルパラベンアッセイ（懸濁液サンプルのみ）を試験された。単位重量はＵＳＰ＜７５５＞毎として決定された。

【０２２２】

平均アッセイ値の概要及び他の全ての結果は、表５－４、５－５、５－６、及び５－７に与えられる。開始時点、１カ月及び３カ月時点での結果もまた、比較のために示される。個別のスプレー内容物の均一性の結果は、表５－８、５－９、５－１０、５－１１、５－１２、５－１３、５－１４、及び５－１５に与えられる。

【０２２３】

一般的に、アッセイの全て及び他の結果は、ジアゼパム関連化合物Ａ及びＢを除いて、初期データと同様である。

【０２２４】

関連化合物Ａは、いくつかのサンプルについて、多くて（ＮＭＴ）０．０１％という仕様を満たさなかった（表２を参照）。関連化合物Ａは、時間及び温度とともに増大した。

【０２２５】

【表６】

表5-2: 関連化合物A T6M結果の概要

溶液/懸濁液 #	25°C/60% RH	30°C/65% RH	40°C/75% RH
溶液 00	仕様を満たす	0.058%	0.051%
溶液 02	仕様を満たす	仕様を満たす	仕様を満たす
懸濁液 01	0.038%	0.046%	0.157%
懸濁液 03	0.019%	0.029%	0.081%

【０２２６】

関連化合物Ｂもまた、時間及び温度とともに増大しており、現状では懸濁液及び１つの溶液製剤の両方について、４０℃でＮＭＴ０．１％の仕様に満たない。製剤２６０２のみが、全ての不純物の仕様を満たす。

【０２２７】
【表７】

表5-3: 関連化合物B T6M結果の概要

溶液/懸濁液 #	25°C/60% RH	30°C/65% RH	40°C/75% RH
溶液 00	仕様を満たす	仕様を満たす	0.398%
溶液 02	仕様を満たす	仕様を満たす	仕様を満たす
懸濁液 01	仕様を満たす	仕様を満たす	0.289%
懸濁液 03	仕様を満たす	仕様を満たす	0.123%

【０２２８】

【表８】

表５－４：溶液００結果の概要

溶液 ##, 70mg/mL, 65% ビタミンE												
試験	仕様	開始	1ヶ月 25°C/60 %RH	1ヶ月 30°C/65 %RH	1ヶ月 40°C/75 %RH	3カ月 25°C/60 %RH	3カ月 30°C/65 %RH	3カ月 40°C/75 %RH	6ヶ月 25°C/60 %RH	6ヶ月 30°C/65 %RH	6ヶ月 40°C/75 %RH
	黄色からオレンジの溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ シアゼパム (%)	90.0から110.0%	100.1	100.3	93.9	98.8	96.3	96.9	101.2	97.5	94.6	100.6
不純物 (%) (1)											
ノルダゼパム	NMT 0.3%	0.005	0.01	0.014	0.019	0.013	0.013	0.013	0.013	0.013	0.013
関連化合物B	NMT 0.1%	ND	0.002	0.007	0.03	0.008	0.016	0.089	0.024	0.098	0.398
関連化合物A	NMT 0.01%	0.002	0.002	0.004	0.011	0.002	0.002	0.01	0.005	0.058	0.051
未知	NMT 0.1%	0.011	0.012	0.014	0.02	0.037	0.039	0.047	0.035	0.066	0.055
総計	NMT 1.0%	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.1	0.2	0.5
微生物限定	USPを満たす(61)	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量 (g)	報告結果	1.108	1.103	1.111	1.112	1.109	1.109	1.113	1.103	1.111	1.109
全容量 (ml)	報告結果	1.192	1.189	1.195	1.196	1.193	1.193	1.198	1.187	1.195	1.193
スプレー送達 (μl)	報告結果	133.9	140.7	146.0	140.5	149.1	143.5	139.6	131.4	試験せず	136.4
平均スプレー含有量 (%)	報告結果	95.0	101.2	104.4	99.4	99.7	94.6	99.4	95.7	試験せず	103.7
粘度 (Pa*s)	報告結果	0.14	0.086	0.12	0.12	0.096	0.14	0.12	0.12	0.11	0.11

(1) LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２２９】

【表９】

表５－５：溶液０２結果の概要

溶液02, 70mg/mL, 65% ビタミンE	仕様	開始	1ヶ月 25°C/60 %RH	1ヶ月 30°C/65 %RH	1ヶ月 40°C/75 %RH	3カ月 25°C/60 %RH	3カ月 30°C/65 %RH	3カ月 40°C/75 %RH	6ヶ月 25°C/60 %RH	6ヶ月 30°C/65 %RH	6ヶ月 40°C/75 %RH
記載	黄色からオレンジの溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液	琥珀色溶液
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ アジアゼパム(%)	90.0から110.0%	100.5	94.9	96.2	103.3	98.0	97.2	99.6	97.0	94.3	100.3
不純物(%)(1)											
ノルタゼパム	NMT 0.3%	0.003	0.004	0.005	0.006	0.005	0.005	0.006	0.005	0.004	0.005
関連化合物B	NMT 0.1%	ND	0.002	0.003	0.006	0.003	0.005	0.032	0.007	0.020	0.058
関連化合物A	NMT 0.01%	0.003	0.002	0.002	0.003	0.002	0.002	0.004	0.003	0.009	0.007
未知	NMT 0.1%	0.01	0.012	0.014	0.018	0.019	0.025	0.032	0.014	0.020	0.018
総計	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1
微生物限定	USPを満たす(61)	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量(g)	報告結果	1.135	1.117	1.128	1.123	1.116	1.133	1.137	1.124	1.133	1.127
全容量(ml)	報告結果	1.184	1.165	1.177	1.172	1.164	1.182	1.186	1.172	1.183	1.176
スプレー送達(μl)	報告結果	115.0	137.5	137.6	133.1	143.9	136.3	143.8	129.3	試験せず	124.2
平均スプレー含有量(%)	報告結果	98.6	97.6	97.7	100.7	98.7	94.7	100.5	95.8	試験せず	97.1
粘度(Pa*s)	報告結果	0.69	0.68	0.64	0.68	0.63	0.65	0.64	0.61	0.55	0.56

(1) LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２３０】

【表１０】

表５－６：懸濁液０１結果の概要

懸濁液01、100 mg/ml	仕様	開始	1ヶ月 25°C/60 %RH	1ヶ月 30°C/65 %RH	1ヶ月 40°C/75 %RH	3カ月 25°C/60 %RH	3カ月 30°C/65 %RH	3カ月 40°C/75 %RH	6ヶ月 25°C/60 %RH	6ヶ月 30°C/65 %RH	6ヶ月 40°C/75 %RH
記載	濁った色から白色溶液	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	淡黄色分散	黄色分散
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ ジアゼパム（%）	90.0から110.0%	102.8	102.6	100.9	104.3	101.3	101.8	103.6	100.7	104.3	99.4
不純物（%）（1）											
ノルダゼパム	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
関連化合物B	NMT 0.1%	ND	ND	ND	0.004	ND	0.004	0.053	0.005	0.013	0.289
関連化合物A	NMT 0.01%	ND	0.01	0.02	0.034	0.026	0.036	0.08	0.038	0.046	0.157
未知	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.007	0.007	0.008	0.007	0.018
総計	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5
メチルパラベン（%）	80.0%-115.%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
プロピルパラベン（%）	80.0%115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
微生物限定	USPを満たす（61）	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量（g）	報告結果	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235
全容量（ml）	報告結果	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
スプレー送達（μl）	報告結果	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	試験せず	137.6
平均スプレー含有量（%）	報告結果	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	試験せず	95.94
粘度（Pa*s）	報告結果	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

（１）LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２３１】

【表１１】

表５－７：懸濁液Ｏ３結果の概要

懸濁液O3、200mg/mL	仕様	開始	1ヶ月 25℃/60 %RH	1ヶ月 30℃/65 %RH	1ヶ月 40℃/75 %RH	3カ月 25℃/60 %RH	3カ月 30℃/65 %RH	3カ月 40℃/75 %RH	6ヶ月 25℃/60 %RH	6ヶ月 30℃/65 %RH	6ヶ月 40℃/75 %RH
記載	薄クリーム色から白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	白色分散	淡黄色分散	黄色分散
同定－UV	UV及びRT標準品に従う	パス	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
アッセイ、シアゼパム（%）	90.0から110.0%	100.7	101.2	98.9	101.6	102.6	103.6	103.1	100.5	98.9	100.1
不純物（%）（1）											
ノルダゼパム	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
関連化合物B	NMT 0.1%	ND	ND	ND	ND	0.002	ND	0.023	0.002	0.008	0.123
関連化合物A	NMT 0.01%	ND	0.005	0.01	0.017	0.017	0.012	0.039	0.019	0.029	0.081
未知	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.007	0.008
総計	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2
メチルパラベン（%）	80.0%-115.%%	93.4	101.1	93.8	99.7	101.5	101.6	101.2	103.5	97.2	102.1
プロピルパラベン（%）	80.0%-115.0%	95.6	100.2	94	98.4	100.1	101.3	99.2	97.1	91.9	95.9
微生物限定	USPを満たす{61}	パス	N/A	N/A	N/A	N/A	N/A	N/A	パス	試験せず	試験せず
全重量（g）	報告結果	1.276	1.28	1.259	1.272	1.279	1.279	1.276	1.280	1.262	1.260
全容量（ml）	報告結果	1.186	1.19	1.171	1.183	1.19	1.19	1.187	1.190	1.173	1.172
スプレー送達（μl）	報告結果	112.4	137.4	134.3	119.9	138.9	139.3	134.3	149.4	試験せず	138.0
平均スプレー含有量（%）	報告結果	82.8	99.3	97.3	86.7	98.6	102.3	96.2	98.2	試験せず	98.7
粘度（Pa*s）	報告結果	0.021	0.017	0.017	0.019	0.016	0.016	0.018	0.014	0.013	0.015

（1）LOQは約0.006%であり、LODは約0.002%である。LOQ以下の結果が、目的の方向示すためにこの表で報告される。

【０２３２】

【表１２】

表5-8: 溶液00 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
1	0.13061	0.13259	9.59355	97.89
2	0.13217	0.13451	9.78206	99.82
3	0.12365	0.13332	8.85797	90.39
4	0.12761	0.13072	9.39720	95.89
5	0.14702	0.15216	8.91438	90.96
6	0.13414	0.13702	9.22442	94.13
7	0.12959	0.13384	9.84590	100.47
8	0.12367	0.14603	8.88093	90.62
9	0.13367	0.13425	9.92610	101.29
平均	0.13135	0.13716	9.380	95.72
標準偏差	0.0070	0.0071	0.4309	4.3970
% RSD	5.35	5.20	4.59	4.59

【０２３３】

【表１３】

表5-9: 溶液00 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
1	0.14139	0.15111	10.57237	107.88
2	0.14731	0.15146	11.62831	118.66
3	0.14489	0.14684	10.94206	111.65
4	0.14237	0.14873	11.94883	121.93
5	0.12188	0.13415	9.78103	99.81
6	0.12756	0.13047	9.78347	99.83
7	0.13549	0.13841	10.45221	106.66
8	0.12323	0.12543	9.41177	96.04
9	0.14299	0.14517	11.35701	115.89
平均	0.13635	0.14131	10.653	108.70
標準偏差	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

【０２３４】

【表１４】

表5-10: 溶液02 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, mg	作動重量, mg	回収 ジアゼパム, mg	% 回収 ジアゼパム
1	0.12280	0.12611	8.88043	90.62
2	0.13318	0.13549	9.55581	97.51
3	0.13260	0.13452	9.71837	99.17
4	0.12064	0.12305	9.48123	96.75
5	0.13215	0.13582	9.34463	95.35
6	0.13559	0.13790	9.48722	96.81
7	0.13158	0.13371	9.43613	96.29
8	0.13357	0.13495	9.79164	99.91
9	0.12165	0.12443	8.84732	90.28
平均	0.12931	0.13178	9.394	95.85
標準偏差	0.0058	0.0056	0.3303	3.3701
%RSD	4.52	4.25	3.52	3.52

【０２３５】

【表１５】

表5-11: 溶液02 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収 ジアゼパム, mg	% 回収 ジアゼパム
1	0.12336	0.12563	9.02005	92.04
2	0.05723	0.05792	9.43076	96.23
3	0.13554	0.13908	9.93829	101.41
4	0.13619	0.13679	9.87755	100.79
5	0.13227	0.13414	9.64403	98.41
6	0.13331	0.13515	9.80808	100.08
7	0.13455	0.13844	9.31952	95.10
8	0.13314	0.13736	9.28106	94.70
9	0.13249	0.13387	9.32935	95.20
平均	0.12423	0.12649	9.517	97.11
標準偏差	0.0254	0.0260	0.3148	3.2119
%RSD	20.45	20.57	3.31	3.31

【０２３６】

【表１６】

表5-12:懸濁液01 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収 ジアゼパム, mg	% 回収 ジアゼパム
1	0.12873	0.12999	12.85366	91.81
2	0.14011	0.14247	13.68122	97.72
3	0.14515	0.14757	14.09449	100.67
4	0.13205	0.13347	14.18775	101.34
5	0.14554	0.14743	14.48202	103.44
6	0.14473	0.14682	14.39897	102.85
7	0.13229	0.13411	14.87853	106.28
8	0.14357	0.14581	14.82712	105.91
9	0.14741	0.14940	14.86732	106.20
平均	0.13995	0.14190	14.252	101.80
標準偏差	0.0070	0.0074	0.6602	4.7154
%RSD	5.03	5.18	4.63	4.63

【０２３７】

【表１７】

表5-13: 懸濁液01 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収 ジアゼパム, mg	% 回収 ジアゼパム
1	0.14411	0.14869	13.04770	93.20
2	0.14066	0.14151	13.23277	94.52
3	0.13012	0.13485	13.78126	98.44
4	0.14667	0.14879	13.36970	95.50
5	0.14294	0.14338	12.54309	89.59
6	0.13797	0.14253	13.25396	94.67
7	0.13374	0.13594	13.41984	95.86
8	0.12388	0.12559	14.34944	102.50
9	0.13790	0.14011	13.88564	99.18
平均	0.13755	0.14015	13.431	95.94
標準偏差	0.0073	0.0073	0.5223	3.7310
%RSD	5.28	5.19	3.89	3.89

【０２３８】

【表１８】

表5-14: 懸濁液03 25℃/60%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
1	0.13604	0.13897	25.93418	92.62
2	0.14608	0.14792	26.21721	93.63
3	0.15294	0.15425	30.05570	107.34
4	0.14728	0.14910	25.78804	92.10
5	0.15352	0.15493	26.60721	95.03
6	0.15242	0.15401	29.51030	105.39
7	0.15118	0.15254	28.43104	101.54
8	0.15322	0.15556	28.03664	100.13
9	0.15197	0.15393	26.82906	95.82
平均	0.14941	0.15125	27.490	98.18
標準偏差	0.0057	0.0053	1.5812	5.6472
%RSD	3.79	3.50	5.75	5.75

【０２３９】

【表１９】

表5-15: 懸濁液03 40℃/75%RH スプレー内容物均一性結果

サンプル	収集重量, g	作動重量, g	回収ジアゼパム, mg	% 回収ジアゼパム
1	0.13574	0.13797	28.14588	100.52
2	0.13639	0.13803	27.04437	96.59
3	0.14082	0.14195	26.78985	95.68
4	0.12962	0.13249	29.07192	103.83
5	0.12518	0.12683	27.39785	97.85
6	0.14423	0.14541	28.50133	101.79
7	0.13922	0.14096	27.34617	97.66
8	0.14146	0.14313	27.17415	97.05
9	0.14902	0.15344	27.20939	97.18
平均	0.13796	0.14002	27.631	98.68
標準偏差	0.0073	0.0076	0.7642	2.7294
%RSD	5.28	5.43	2.77	2.77

【０２４０】

実施例６

実施例３及び４に記載される溶液及び懸濁液の全ては、本明細書中に記載される追加の適当量のアルキルグリコシド、例えば、ドデシルマルトシド、テトラデシルマルトシド、スクロースドデカノエイト、スクロースモノステアリン、スクロースジステアリン、及び／又は２又はそれより多いそれらの組合せ、あるいはＡｅｇｉｓ Ｔｅｒａｐｅｕｔｉｃｓ，サンディエゴ、カリホルニアにより市販されているＩｎｔｒａｖａｉｌ（登録商標）

等と共に製剤される。添加されたアルキルグリコシドを備える溶液及び懸濁液は、変更すべきところは変更して、実施例５に記載されるように安定性を加える。

【０２４１】

実施例７

実施例３、４及び６の溶液及び懸濁液は、適切な動物モデル例えば、マウス、ラット、ウサギ又は犬等で薬物動態を評価される。先ず、夫々の動物（例えば、ウサギ）がベンゾジアゼピン薬の量を静脈内投与される。静脈内投与されたベンゾジアゼピン薬の量は、より少ない量が選択され、例えば、鼻腔内投与に効果的な投与量と判断される量のおおよそ半分が選択される。例えば、ウサギに投与されるジアゼパムの静脈内投与量は、約０．０５から０．２ｍｇ／ｋｇ、例えば、約０．１ｍｇ／ｋｇである。投与前及び投与後特定時間で血液が直ちに採血される。血漿中の薬物レベルが、夫々の血液サンプルでアッセイされる。少なくとも１日の休薬期間の後、夫々の動物は、実施例３、４及び６に記載される溶液又は懸濁液の量を静脈内に投与される。血液は、投与前及び静脈内投与後と略同じ特定時間に、直ちに採血された。薬物動態曲線は（時間に対する薬物の血漿中濃度）、投与の静注経路で構成されるとともに、鼻腔内投与経路で投与される溶液及び懸濁液の夫々で構成される。

【０２４２】

毒性は、既知の方法により評価される。特に、組織学的試料は、試験動物の鼻粘膜組織から採取される。他の毒物学的方法が同様に任意に用いられる。

【０２４３】

実施例８

実施例３、４及び６の溶液及び懸濁液は、適切な動物モデル例えば、マウス、ラット、ウサギ又は犬等での血液脳関門を越えて薬物を送達する能力が評価される。夫々の動物は、血液脳関門を通過する薬物の能力を決定するために、代用品として使用される造影剤例えば色素を任意に含む溶液又は懸濁液で、実施例３、４及び６に記載の溶液又は懸濁液の量を鼻腔内に投与される。薬物又は造影剤がどのように血液脳関門を通過するのかを決定するために、懸濁液又は溶液の投与後、溶液又は造影剤が選択時間点で検出される。これらの結果は、薬物又は造影剤を含む静脈注射用の溶液で得られた類似の結果と比較された。

【０２４４】

実施例９

上記の溶液及び／又は懸濁液は、ヒトにおける薬物動態で評価され得る。通常、健康なヒト被験者は、薬物の量を静脈内投与される。静脈内投与に選択される量は、任意の量であるが、人の発作を処置するのに効果的と考えられるに都合のよい投与量である。ヒトに投与されるジアゼピンの静脈内投与は、１から１５ｍｇの範囲であり、例えば約７．５ｍｇである。血液は、投与前及び投与後の選択時間点で直ちに採血される。薬物の血漿中濃度が、血液試料の夫々でアッセイされる。少なくとも１日の休薬期間の後、夫々の被験者は、本明細書中に記載される溶液又は懸濁液の量を、静脈内に投与される。血液は、投与前及び静脈内投与後の略同じ特定時間に、直ちに採血される。静脈注射時点と略同じ投与後時点で直ちに採血される。薬物動態曲線は（時間に対する薬物の血漿中濃度）、静脈投与経路及び鼻腔内投与経路で構成される。

【０２４５】

実施例１０

上記溶液及び／又は懸濁液は、適切な動物モデルで有効性が評価される。手短に言うと、試験される溶液又は懸濁液の各投与量に対して、試験動物が、発作誘発刺激で刺激される。刺激は、光刺激、音刺激、化学刺激又は他の刺激であり、効果的にモデル動物において発作を誘導する。動物は、発病するとすぐに、本明細書中に記載される溶液又は懸濁液が、動物に鼻腔内投与される。溶液及び／又は懸濁液の投与量の有効性は、試験投与量に対する動物の反応に基づいて評価される。この手段は、十分量の反復を介して繰り返され、十分な数の投与で繰り返され、薬物の鼻腔内投与により発作を処置するに効果的と考え

られる投与量が確認される。

【０２４６】

本発明の好適な実施形態は、本明細書中に示され、記載されているが、このような実施形態が、限定されることなく提供されることは、当該分野の当業者にとって明らかである。多くの変化、変更、及び置換は、本発明から逸脱することなく、当該分野の当業者に思い浮かぶだろう。本明細書中に記載される本発明の実施形態の様々な代替は、本発明を実行するのに使用されることを理解されるべきである。次の請求項は、本発明の範囲、これら請求項の範囲内の方法及び構造を規定し、それら等価物はそれらによりカバーされることを目的とする。

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038696

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/5513(2006.01)i, A61K 31/355(2006.01)i, A61K 9/16(2006.01)i, A61K 47/10(2006.01)i, A61P 25/22(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)
IPC8 as above

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)
eKOMPASS, Google scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007043057 A2 (TOUITOU, ELKA et. al.) 19 April 2007 See claims 18 and 35, p. 6 (line 1-3), 8 (line 3-11)	1-19
A	WO 2005117830 A1 (CAMURUS AB, SWED) 15 December 2005 See whole document	1-19
A	WO 2006075123 A1 (CAMURUS AB, SWED) 20 July 2006 See whole document	1-19
A	WO 2007144081 A2 (LTS LOHMANN THERAPIE-SYSTEM A.-G.) 21 December 2007 See whole document ----------//	1-19

☐ 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 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
28 SEPTEMBER 2009 (28.09.2009)	**28 SEPTEMBER 2009 (28.09.2009)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer KIM, YONG Telephone No. 82-42-481-8164

Form PCT/ISA/210 (second sheet) (July 2008)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/038696

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.: 20-45
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 20-45 pertain to methods for treatment of the human body by therapy, as well as prevention method, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☒ Claims Nos.: 46, 47
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:
Claims 46 and 47 relate to a composition, and are indicated as referring to claims 20 and 21, respectively. However, the claims 20 and 21 relate to a method of treating a patient. Thus claims 46 and 47 are too unclear to make meaningful search possible

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 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 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.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2008)

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— *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: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

(57) Abstract: The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

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ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

[001] This application claims priority under 35 U.S.C. § 119(e) from United States provisional patent application number 61/040,558, which was filed on March 28, 2008, and which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[002] This application relates to the nasal administration of benzodiazepine drugs and combinations thereof.

BACKGROUND OF THE INVENTION

[003] By way of non-limiting example, the benzodiazepine family consists of drugs such as diazepam, lorazepam, and medazepam. The drugs in this family have been observed as possessing sedative, tranquilizing and muscle relaxing properties. They are frequently classified as an anxiolytic and skeletal muscle relaxants. They are thought to be useful in preventing, treating, or ameliorating the symptoms of anxiety, insomnia, agitation, seizures (such as those caused by epilepsy), muscle spasms and rigidity (which can be caused by tetanus), the symptoms of drug withdrawal associated with the continuous abuse of central nervous system depressants, and exposure to nerve agents.

[004] Benzodiazepines are thought to act by binding to the $GABA_A$ receptor of a neuron, possibly causing the receptor to change shape and making it more accessible to gama-aminobutyric acid (GABA).

[005] GABA is an inhibitory neurotransmitter that, when bound to the $GABA_A$ receptor, facilitates Cl^- ions flooding into the neuron to which the receptor is bound. The increase in Cl^- ions hyperpolarizes the membrane of the neuron. This completely or substantially reduces the ability of the neuron to carry an action potential. Targeting this receptor is particularly useful in treating many disorders, such as tetanus and epilepsy, which may result from too many action potentials proceeding through the nervous system.

[006] Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

[007] The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount may be metabolized. Thus, it may require large doses to achieve therapeutic plasma levels. Furthermore, due to the nature

of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally.

[008] Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.

[009] Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers.

SUMMARY OF THE INVENTION

[010] In some embodiments, the pharmaceutical composition for nasal administration comprises: a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient. In some embodiments the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form comprising benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[011] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the benzodiazepine drug is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[012] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

[013] In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the glycols exclude glycol polymers having an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.

[014] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL.

[015] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

[016] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount of about 30% (w/w).

[017] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents

used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[018] In some embodiments, the composition comprises one or more additional excipients, such as one or more parabens, one or more povidones, and/or one or more alkyl glycosides.

[019] The invention also discloses a method of treating a patient with a disorder that may be treatable with a benzodiazepine drug. In some embodiments, the patient is a human. In some embodiments, the method comprises: administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration comprising a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70%, preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70%, preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, the benzodiazepine drug includes benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[020] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug is fully dissolved in a single phase comprising one or more one or more natural or synthetic tocopherols or tocotrienols and one or more alcohols or glycols. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some such embodiments, the composition further comprises water. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[021] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

[022] In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the alcohol or glycol is free of water (dehydrated, USP). In some embodiments, the alcohol is ethanol (dehydrated, USP).

[023] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 20 mg/mL to about 50 mg/mL.

[024] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

[025] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 30% (w/w).

[026] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[027] In some embodiments, the composition is in a pharmaceutically-acceptable spray formulation, and further comprising administering the composition to one or more nasal mucosal membranes of the patient. In some embodiments, the therapeutically effective amount is from about 1 mg to about 20 mg of the benzodiazepine. In some embodiments, the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 µL to 200 µL.

[028] In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first