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UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	35401-716.301
First Named Inventor	Steve Cartt
Title	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
Express Mail Label No.	Electronically Filed 10/29/14

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [✔] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 86] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✔] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 5]
6. **Inventor's Oath or Declaration** [*Total Pages*] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

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

ACCOMPANYING APPLICATION PAPERS

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

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

19. CORRESPONDENCE ADDRESS

[✔] The address associated with Customer Number: 21971 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Matthew V. Grumbling/	Date	10/29/2014
Name (Print/Type)	Matthew V. Grumbling	Registration No. (Attorney/Agent)	44,427

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Steve		Cartt	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Union City	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	3260 Whipple Road		
Address 2			
City	Union City	State/Province	CA
Postal Code	94587	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David		Medeiros	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	South San Francisco	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	212 Crown Circle		
Address 2			
City	South San Francisco	State/Province	CA
Postal Code	94080	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Garry	Thomas	Gwozdz	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

City	Jim Thorpe	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	432 Pine Street		
Address 2			
City	Jim Thorpe	State/Province	PA
Postal Code	18229	Country i	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Andrew		Loxley	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Philadephia	Country of Residence i	US

Mailing Address of Inventor:

Address 1	126 Market Street, #5		
Address 2			
City	Philadelphia	State/Province	PA
Postal Code	19106	Country i	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mark		Mitchnick	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	East Hampton	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	80 Three Mile Harbor Drive		
Address 2			
City	East Hampton	State/Province	NY
Postal Code	11937	Country i	US

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David		Hale	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

City	San Diego	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	9232 Bernardo Lakes Drive		
Address 2			
City	San Diego	State/Province	CA
Postal Code	92127	Country i	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Edward	T.	Maggio	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	San Diego	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	16870 W. Bernardo Drive		
Address 2	Suite 390		
City	San Diego	State/Province	CA
Postal Code	92127	Country i	US

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City		State/Province		Country of Residence i	

Mailing Address of Inventor:

Address 1			
Address 2			
City		State/Province	
Postal Code		Country i	

Inventor 9 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City		State/Province		Country of Residence	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Mailing Address of Inventor:

Address 1			
Address 2			
City		State/Province	
Postal Code		Country i	

Inventor 10 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City		State/Province		Country of Residence i	

Mailing Address of Inventor:

Address 1			
Address 2			
City		State/Province	
Postal Code		Country i	

Inventor 11 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City		State/Province		Country of Residence i	

Mailing Address of Inventor:

Address 1			
Address 2			
City		State/Province	
Postal Code		Country i	

Inventor 12 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City		State/Province		Country of Residence i	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Mailing Address of Inventor:			
Address 1			
Address 2			
City		**State/Province**	
Postal Code		**Country** i	

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	21971		
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		
Attorney Docket Number	35401-716.301	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

Filing By Reference :

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country i

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	(•) Customer Number	( ) US Patent Practitioner	( ) Limited Recognition (37 CFR 11.9)
Customer Number	21971		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13495942	2012-06-13
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13495942	Continuation in part of	12413439	2009-03-27
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12413439	Claims benefit of provisional	61040558	2008-03-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13495942	Claims benefit of provisional	61497017	2011-06-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13495942	Claims benefit of provisional	61570110	2011-12-13
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Hale Biopharma Ventures

Mailing Address Information:

Address 1	1042-B North El Camino Real, Suite 430		
Address 2			
City	Encinitas	**State/Province**	CA
Country [i]	US	Postal Code	92024
Phone Number		Fax Number	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Email Address	

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Matthew V. Grumbling/			Date (YYYY-MM-DD)	2014-10-29
First Name	Matthew	Last Name	Grumbling	Registration Number	44427

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (12-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.301
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Figure 1

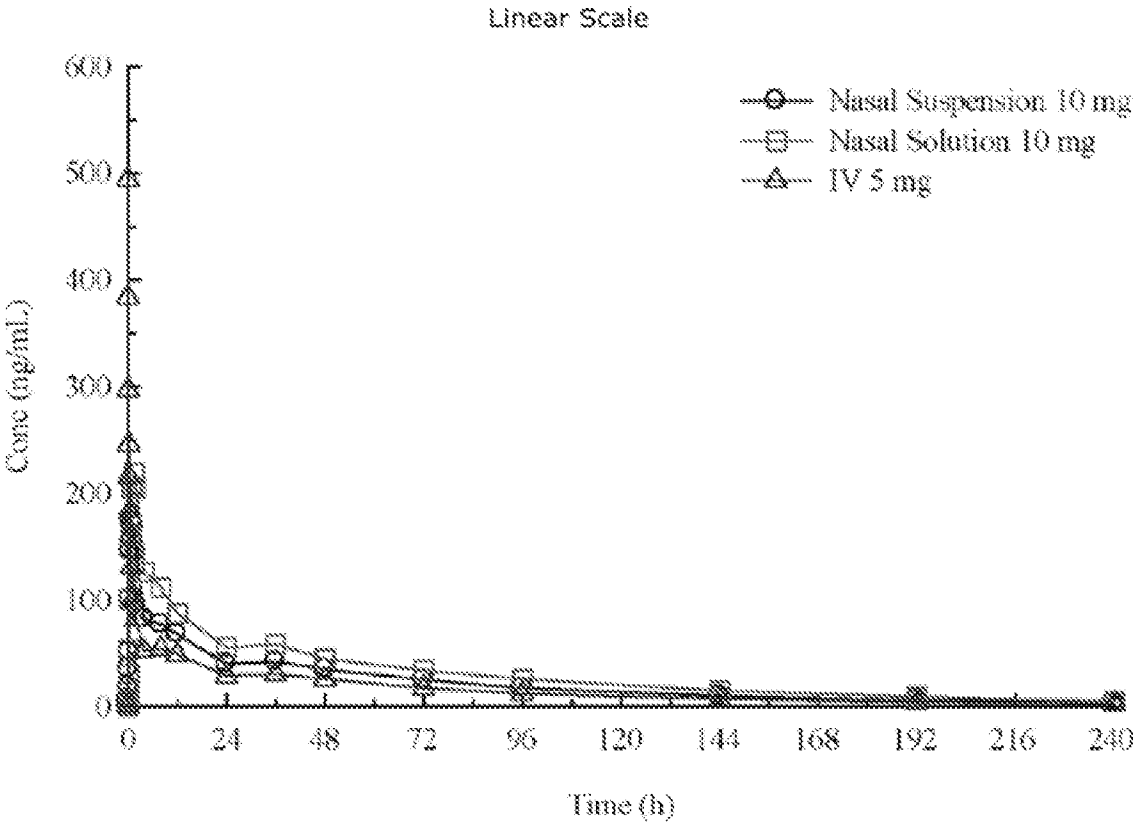

Linear Scale
Nasal Suspension 10 mg
Nasal Solution 10 mg
IV 5 mg
Conc (ng/mL)
600
500
400
300
200
100
0
0
24
48
72
96
120
144
168
192
216
240
Time (h)

Figure 2

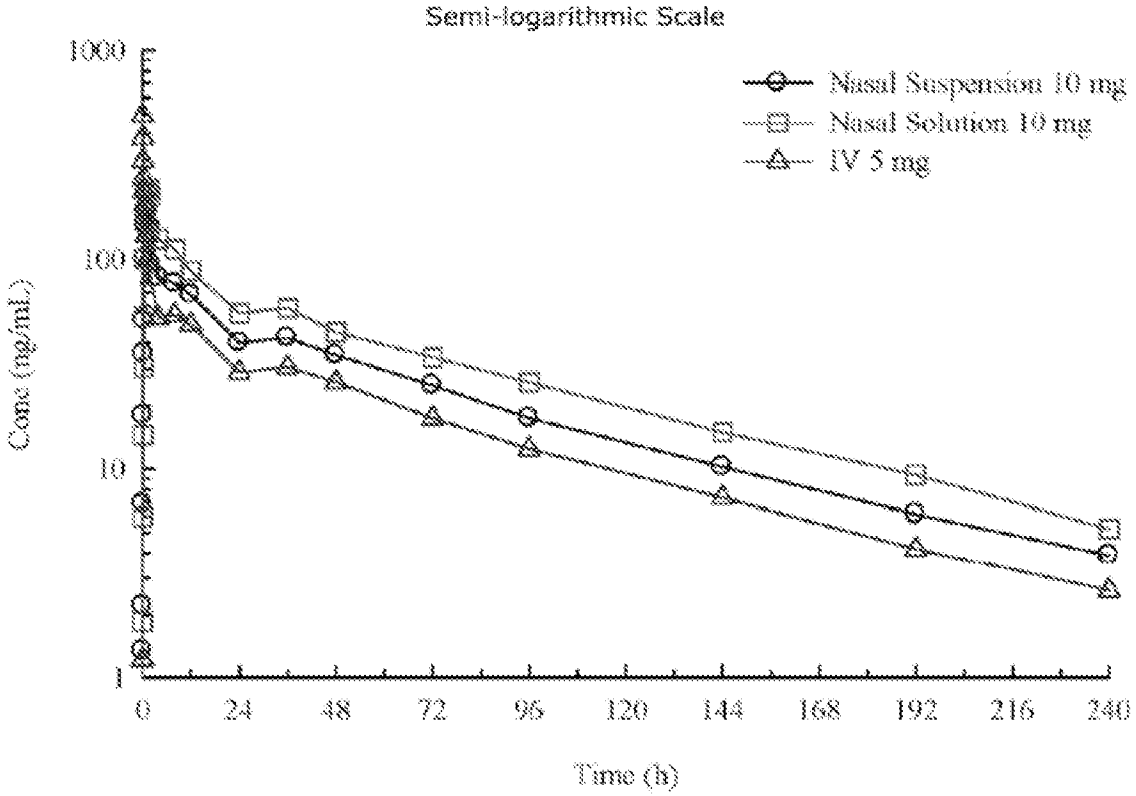

Semi-logarithmic Scale
Nasal Suspension 10 mg
Nasal Solution 10 mg
IV 5 mg
Conc (ng/mL)
1000
100
10
1
0
24
48
72
96
120
144
168
192
216
240
Time (h)

Figure 3

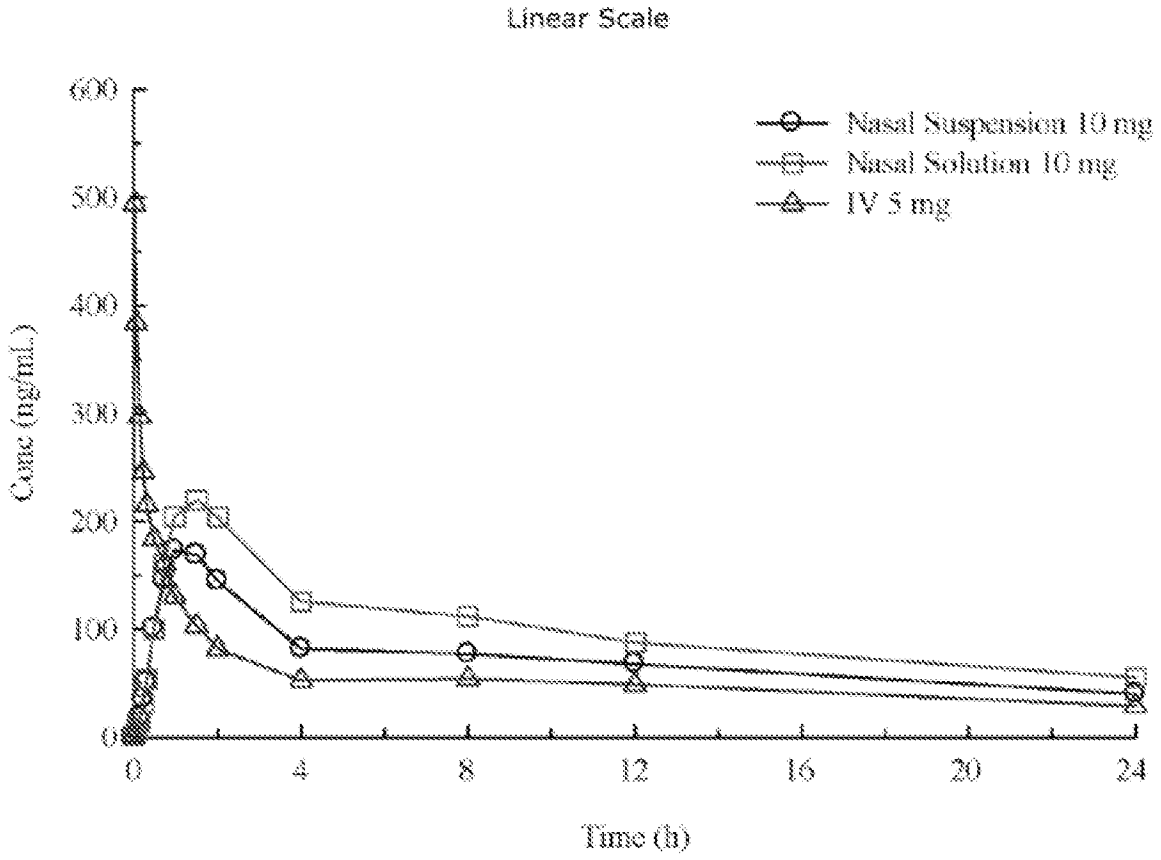

Linear Scale
Nasal Suspension 10 mg
Nasal Solution 10 mg
IV 5 mg
Conc (ng/mL)
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (h)

Figure 4: Flow Diagram for the Manufacture of Diazepam Solution

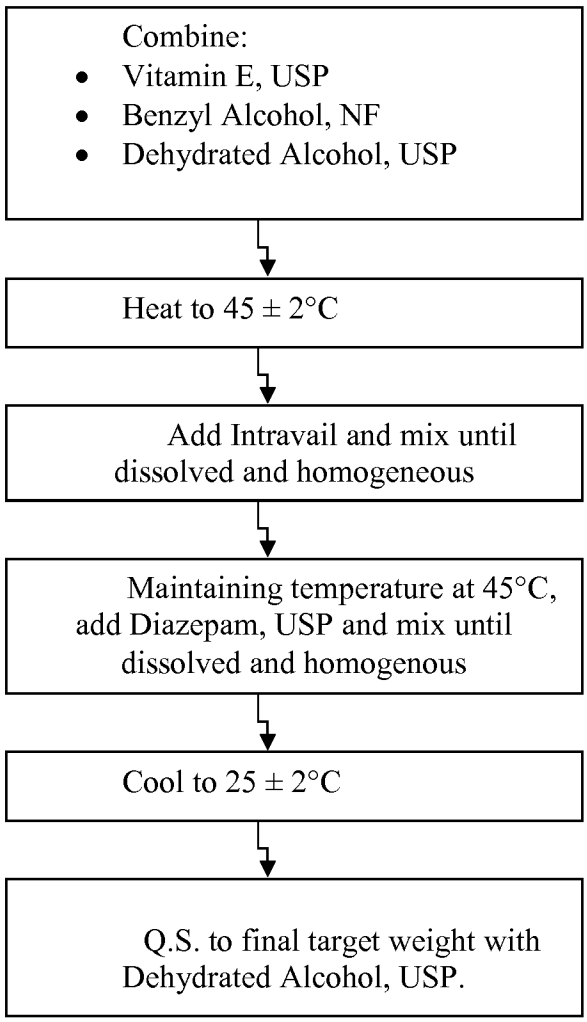
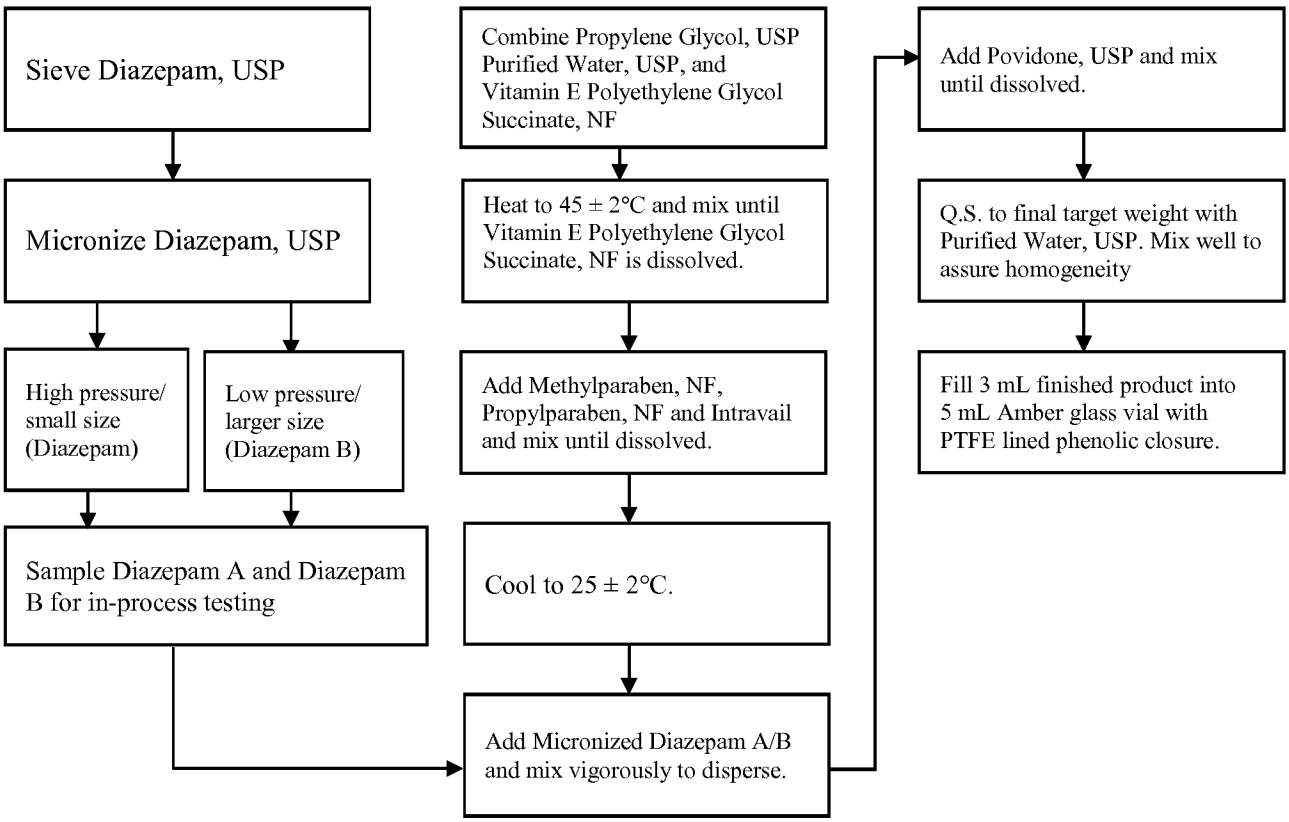


Figure 5: Flow Diagram for Preparation of Diazepam Suspension

Flow Diagram for the Manufacture of NRL-1A



WSGR Docket No. 35401-716.301

PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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By: /Linda Anders/ Date: October 29, 2014

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application is a Continuation of United States Patent Application No. 13/495,942, filed 06/13/2012, which is a Continuation-in-Part of United States Patent Application No. 12/413,439, filed 3/27/2009, published as US 2009/0258865 on October 15, 2009, which is incorporated herein by reference in its entirety, and which claims priority to United States provisional application 61/040,558, filed March 28, 2008, which is incorporated herein by reference; United States Patent Application No. 13/495,942, filed 06/13/2012, also claims priority to United States provisional application 61/497,017, filed June 14, 2011 and United States provisional application 61/570,110, filed December 13, 2011, each of which is incorporated herein by reference 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 midazolam. The drugs in this family have been observed as possessing sedative, tranquilizing and muscle relaxing properties. They are frequently classified as 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, 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 of the drug may be metabolized. Thus, large doses may be required 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 and care-givers may be reluctant to place their hands in patients' mouths.

[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. In addition, intravenous administration of benzodiazepines is associated with respiratory depression. Thus, use of intravenous benzodiazepines is limited to professional health care environments.

[009] Rectal suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of rectally administered drug 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 care-givers.

SUMMARY OF THE INVENTION

[010] In some embodiments, there are provided (non-aqueous) pharmaceutical solutions for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically-acceptable solution for administration to one or more nasal mucosal membranes of a 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 10% to about 70% (w/w). 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, 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 solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. 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, the 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 solution contains two or more alcohols, such as ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may

consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

[011] Some embodiments described herein provide a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of 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); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside. 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 10% to about 70% (w/w). 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, 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 solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. 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, the 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 solution contains two or more alcohols, such as ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w),

e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)). In some embodiments, the patient is human. In some embodiments, the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg. In some embodiments, the benzodiazepine is administered as in a dosage volume from about 10 μL to about 200 μL. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril. In some embodiments, administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril. In some embodiments, the method further comprises, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril. In some embodiments, nasal administration of the pharmaceutical composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition. In some embodiments, the treatment achieves bioavailability that is from about 80-125% (e.g. about 90-110%, or more particularly about 92.5-107.5%) of that achieved with the same benzodiazepine administered intravenously, e.g. In this context, it is intended that bioavailability be determined by a suitable pharmacodynamic method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (e.g. 10 mg of nasal diazepam) with another dose of the

same benzodiazepine administered intravenously (e.g. 5 mg of i.v. diazepam), taking into consideration the difference in dose. Thus, for the sake of illustration, a 10 mg nasal diazepam dose that achieves an AUC that is precisely half of the AUC obtained with 5 mg of i.v. diazepam would have a bioavailability of 100%. In some embodiments, the disorder to be treated is a seizure, such as an epileptic seizure, a breakthrough seizure, or other seizure. In some embodiments, the solution and treatment with the solution are substantially non-irritating and well-tolerated.

[012] 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.

[013] 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, 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.

[014] 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.

[015] 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.

[016] 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.

[017] 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).

[018] 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).

[019] 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.

[020] 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.

[021] 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.

[022] 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, 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.

[023] 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.

[024] 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).

[025] 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.

[026] 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).

[027] 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).

[028] 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.

[029] 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.

[030] 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 nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

[031] In some embodiments, the administration of the composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the composition.

[032] Additional embodiments, uses, and advantages of the invention will become apparent to the person skilled in the art upon consideration of the disclosure set forth herein.

INCORPORATION BY REFERENCE

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

BRIEF DESCRIPTION OF THE DRAWINGS

[034] Some embodiments of the invention may be further appreciated upon consideration of the appended drawings, of which:

[035] Figure 1 depicts a 240 hour linear plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

[036] Figure 2 depicts a 240 hour semi-logarithmic plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

[037] Figure 3 depicts a 24 hour linear plot of the arithmetic mean plasma concentration of diazepam after intranasal administration of 10 mg of diazepam as a suspension of Table 11-2, intranasal administration 10 mg of diazepam as a solution of Table 11-1, and 5 mg of diazepam as an intravenous injection.

[038] Figure 4 is a Flow Diagram for one embodiment of a process for the manufacture of a diazepam solution according to the instant invention.

[039] Figure 5 is a Flow Diagram for one embodiment of a process for the manufacture of a diazepam suspension according to the instant invention.

DETAILED DESCRIPTION OF THE INVENTION

[040] Provided herein are pharmaceutical compositions of one or more benzodiazepine drugs and methods of using such pharmaceutical compositions. Such pharmaceutical compositions are administered nasally.

[041] 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 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 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 of microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[042] 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) 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). 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 of microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[043] 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, 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 composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[044] 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, the carrier system includes one or more synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985, which is incorporated herein by reference in its entirety. In particular, it has been found that in some particulate suspensions of benzodiazepines, wherein the benzodiazepine is not dissolved in a tocopherol phase, Vitamin E TPGS can be a desirable excipient for stabilizing the particulate (microparticle, nanoparticle or combination) suspension. In some embodiments, on the other hand, the carrier system specifically excludes synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985, which is incorporated herein by reference in its entirety.

[045] 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 alcohol is ethanol (dehydrated, USP). 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 glycol is propylene glycol USP. 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.

[046] 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.

[047] 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). 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.

[048] 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 55%, about 10% to about 40%, about 10% to about 35%, about 12% to about 55%, about 12% to about 40%, about 12% to about 35%, about 15% to about 55%, about 15% to about 40%, about 15% to about 35%, about 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5% or 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). In some embodiments, the alcohol is ethanol or contains ethanol. 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.

[049] 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).

[050] 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.

[051] In some embodiments, the compositions comprise at least one alkyl glycoside. In some embodiments, the at least one alkyl glycoside is one described in United States Patent No. 5,661,130, which is incorporated by reference herein.

[052] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and an alcohol or glycol, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides. In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides. In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides, wherein the solution is at least substantially free of

water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)

[053] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. Thus, in some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol and an alcohol or glycol, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides. In some embodiments, the composition consists essentially of a benzodiazepine drug that is fully dissolved in a solvent consisting of one or more natural or synthetic tocopherols or tocotrienols, one or more alcohols or glycols, and optionally one or more alkyl glycosides wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.) In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols, one or more alcohols or glycols, and optionally one or more alkyl glycosides. In some embodiments, the composition consists of a benzodiazepine dissolved in a solvent consisting of one or more natural or synthetic tocopherols, one or more alcohols or glycols, and optionally one or more alkyl glycosides, wherein the solution is at least substantially free of water. (In some embodiments, "substantially free of water" indicates that the solution contains less than about 1%, less than about 0.5%, less than about 0.25% or less than about 0.1% water.)

[054] In some embodiments, the composition contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol and one or more alcohols or glycols. In some embodiments, substantially all the benzodiazepine drug is in a particulate form. In some embodiments, at least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. In some embodiments, a carrier system in such a composition includes water. In some embodiments, such a

liquid carrier system contains water and one or more excipients. In some embodiments, one or more excipients are dissolved or suspended in the carrier system. In some embodiments, at least one such excipient stabilizes the suspension of benzodiazepine particulates in the carrier system. In some embodiments, the carrier system may contain varying concentrations of parabens (e.g. methylparaben, propylparaben, etc.), and/or varying amounts of one or more surfactants, such as povidone (polyvinyl pyrrolidinone). In some embodiments, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols, such as polyethylene glycol. In some embodiments, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. In some embodiments, the composition comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. In some embodiments, the composition comprises a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, povidone and water. In some embodiments, the composition comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water. In some embodiments, the composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. In some embodiments, the composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, povidone and water. In some embodiments, the composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water. In some embodiments, the composition consists of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, one or more surfactants and water. In some embodiments, the composition consists of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, povidone and water. In

some embodiments, the composition consists of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, povidone and water.

[055] In some embodiments, the composition contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol, one or more alcohols or glycols, and an alkyl glycoside. In some embodiments, substantially all the benzodiazepine drug is in a particulate form. In some embodiments, at least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. In some embodiments, a carrier system in such a composition includes water. In some embodiments, such a liquid carrier system contains water and one or more excipients. In some embodiments, one or more excipients are dissolved or suspended in the carrier system. In some embodiments, at least one such excipient stabilizes the suspension of benzodiazepine particulates in the carrier system. In some embodiments, the carrier system may contain varying concentrations of parabens (e.g. methylparaben, propylparaben, etc.), and/or varying amounts of one or more surfactants, such as povidone (polyvinyl pyrrolidinone). In some embodiments, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols, such as polyethylene glycol. In some embodiments, benzodiazepine particulate suspensions specifically exclude one or more polymeric glycols having a molecular weight greater than about 200 g/mol. In some embodiments, the composition comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyglycoside and water. In some embodiments, the composition comprises a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, an alkyl glycoside and water. In some embodiments, the composition comprises a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system comprising Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside and water. In some embodiments, the composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyl glycoside, optionally a surfactant, and water. In some embodiments, the composition consists essentially of a benzodiazepine drug in a form including

benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, an alkyl glycoside, optionally a povidone and water. In some embodiments, the composition consists essentially of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting essentially of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside, optionally a povidone, and water. In some embodiments, the composition consists of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of a synthetic tocopherol, one or more parabens, one or more alcohols or glycols, an alkyl glycoside, optionally one or more surfactants, and water. In some embodiments, the composition consists of a benzodiazepine drug in a form including benzodiazepine microparticles or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, one or both of methylparaben and propylparaben, at least one glycol, an alkyl glycoside, optionally a povidone and water. In some embodiments, the composition consists of a benzodiazepine drug in a form including benzodiazepine microparticles and/or nanoparticles suspended in a carrier system consisting of Vitamin E TPGS, methylparaben, propylparaben, propylene glycol, an alkyl glycoside, optionally a povidone and water.

[056] 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% (w/w), 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% (w/w), preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In other embodiments, at least part of the benzodiazepine drug is in a form including microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[057] 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, 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 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.

[058] 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. A synthetic tocopherol may include a tocopherol that has been modified to include a hydrophilic group, such as a polyethylene glycol group, which may be directly covalently bonded to the tocopherol or may be linked to the tocopherol through a covalent linking group, such as a diacid. An exemplary synthetic tocopherol of this type is Vitamin E Polyethylene Glycol Succinate (Vitamin E TPGS), although the person skilled in the art will be able to envision other synthetic tocopherols that have similar diacid and/or hydrophilic groups.

[059] 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, one or more glycols specifically excludes polymeric glycols, such as polyethylene glycol. In some embodiments, one or more glycols specifically excludes a polymeric glycol having a molecular weight of greater than about 200 g/mol.

[060] 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.

[061] 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). In some embodiments, especially where particulate suspensions of a benzodiazepine drug are contemplated, the compositions may include a tocopherol, especially a synthetic tocopherol having a hydrophilic group covalently linked to a tocopherol. In other embodiments, especially where a solution of benzodiazepine drug is contemplated, the tocopherol is substantially or completely free of Vitamin E TPGS.

[062] 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 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). In some embodiments the amount of one or more alcohols or glycols in the carrier system is about 10% to about 55%, about 10% to about 40%, about 10% to about 35%, about 12% to about 55%, about 12% to about 40%, about 12% to about 35%, about 15% to about 55%, about 15% to about 40%, about 15% to about 35%, about 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5% or about 55% (w/w).

[063] 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.

[064] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is an alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130, which is incorporated herein by reference in its entirety. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl

according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

[065] 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.

[066] 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 nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

[067] In some embodiments, the administration of the composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the composition.

Definitions

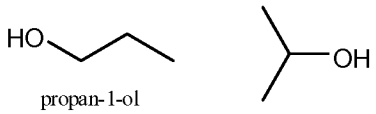
[068] As used herein the phrase "therapeutically effective amount" (or more simply "effective amount") includes an amount sufficient to provide a specific therapeutic response for which the drug is

administered to a patient in need of particular treatment. The skilled clinician will recognize that the therapeutically effective amount of drug will depend upon the patient, the indication and the particular drug administered.

[069] As used herein, the modifier "about" is intended to have its regularly recognized meaning of approximately. In some embodiments, the term may be more precisely interpreted as meaning within a particular percentage of the modified value, e.g. "about" may in some embodiments mean ± 20%, ± 10%, ± 5%, ± 2%, or ± 1% or less.

[070] As used herein, the phrase "analogs or derivatives" includes molecules that differ from one another molecule due to one or more atoms or functional groups having been replaced with a different atom or functional group. This may result in molecules with similar chemical formulas but different chemical and/or biological properties.

[071] As used herein, the term, "isomer" includes molecules with identical chemical formulas, but between which the arrangement of the molecules may vary. These varying arrangements may result in molecules with identical chemical formulas but different chemical properties. By way of non-limiting example, propanol has the chemical formula C_3H_7OH. It may be found as propan-1-ol, wherein the –OH is found attached to an end carbon. Alternatively, it may be found as propan-2-ol, wherein the –OH is found attached to the second carbon.



propan-1-ol propan-2-ol

[072] As used herein, the term "seizure" includes commonly recognized types of seizures, including absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, and atonic seizures. Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura that will be familiar to the patient or those familiar with the patient. Each patient will generally experience a different type of aura, which is unique to the patient; however auras may be classified as audible, visual, olfactory or tactile sensations that usually, or at least often, precedes a patient's experiencing a seizure. (Not all patients who suffer seizures experience aura; however aura are not uncommon amongst those who suffer the worst type of seizures, especially tonic-clonic seizures.)

[073] As used herein, the term "prevention" refers to a forestalling, including temporary forestalling, of the onset of a disorder. In the case of seizures, this can occur either with or without the benefit of a warning aura.

[074] As used herein, the term "treatment" refers to a reduction in the intensity and/or duration of a disorder, or similar effects. The term also encompasses the side-effects of such a "treatment."

[075] As used herein, unless otherwise qualified, "a" and "an" can mean one or more.

[076] As used herein, the term "comprising" in all its variants, is a transitional phrase used in a claim to indicate that the invention includes or contains, but is not limited to, the specifically recited claim elements.

[077] As used herein, the phrase "consisting essentially of" is a transitional phrase used in a claim to indicate that the a following list of ingredients, parts or process steps must be present in the claimed composition, machine or process, but that the claim is open to unlisted ingredients, parts or process steps that do not materially affect the basic and novel properties of the invention.

[078] As used herein, the term "consisting of" is a transitional phrase used in a claim to indicate that the claimed invention includes only those elements set forth in the claim.

Benzodiazepine Drugs

[079] In the context of the present invention, the term "benzodiazepine drug" includes any therapeutically effective benzodiazepine compound, or pharmaceutically acceptable salt, or combinations thereof. In some embodiments, benzodiazepine comprises a member of the group consisting of alprazolam, diazepam, flurazepam, lorazepam, medazepam, mexazolam, midazolam, temazepam and pharmaceutically acceptable salts and combinations thereof.

[080] It should be recognized by those of skill in the art that additional benzodiazepine compounds that have heretofore been considered to have marginal or little therapeutic benefit, either because of low bioavailability, poor pharmacokinetic properties or poor pharmacodynamic properties, may find use through the present invention, which can provide for improved bioavailability of benzodiazepine drugs, delivery of higher concentrations of benzodiazepine drugs via the nasal route, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein and concomitant avoidance of first pass effects and/or faster presentation of benzodiazepine drug to the brain.

[081] For example, most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. By use of the present carrier system, which in some embodiments, provides an improved ability to dissolve benzodiazepine drugs, the present invention allows benzodiazepine drugs to be administered to one or more mucosal membranes, including to nasal mucosal membranes. This can allow one to administer the drug without hospitalization or unnecessary discomfort. Additionally, in

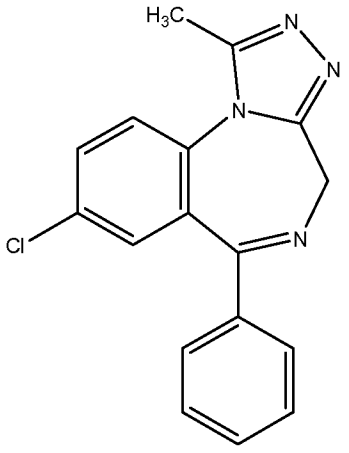
some embodiments of the present invention, such as nasal administration, the digestive system largely may be bypassed. This latter improvement can yield improved bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

[082] Nasal administration of the composition can result in faster presentation of the one or more benzodiazepine drugs to the brain due to the close proximity of the membranes and the brain. A seizing patient, for example, suffers from rigid muscles and uncontrollable movement. This can make oral and/or intravenous administration difficult or inconvenient. However, the nasal passageways remain open and easily accessible, and therefore is a useful route of administration for of the present invention.

[083] In some embodiments, the pharmaceutical composition is used to treat a patient suffering from a disorder that is amenable to treatment or prevention with an effective amount of the one or more benzodiazepine drugs. By way of non-limiting example such disorders can include: insomnia, anxiety, seizures, muscle spasms and rigidity, and the symptoms of drug withdrawal.

[084] In some embodiments, the one or more benzodiazepine drugs, are used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure.

[085] **Alprazolam** (8-chloro-6-phenyl-1-methyl-4H-1,2,4-triazolo[4,3-a][1,4]benzodiazepine).



[086] Alprazolam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic. Alprazolam has also been shown to be useful in the treatment of panic disorder. The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose,

from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

[087] In some embodiments, alprazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

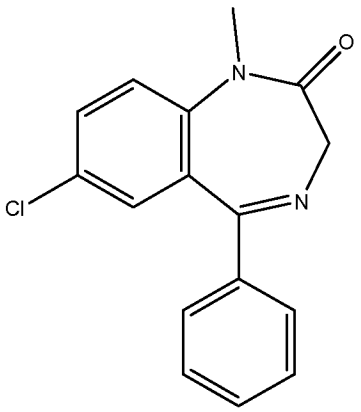
[088] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of alprazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of alprazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or *status epilepticus*, administration of alprazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with alprazolam to provide an anticonvulsant or synergistic anticonvulsant effect.

[089] Alprazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the alprazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The alprazolam formulations of the invention, and in particular nasal formulations, also

provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[090] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[091] **Diazepam** (7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[092] Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085; 3,109,843; 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

[093] In some embodiments, diazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

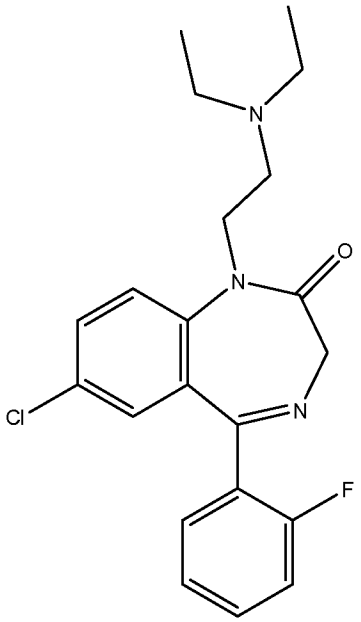
[094] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of diazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of diazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of diazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with diazepam to provide a synergistic anticonvulsant effect.

[095] Diazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the diazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The diazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[096] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of

benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[097] Flurazepam (7-chloro-5-(2-flurophenyl)-2,3-dihydro-1-(2-(diethylamino)ethyl)-1H-1,4-benzodiazepin-2-one)



[098] Flurazepam is a benzodiazepine drug having sedative (especially soporific and hypnotic), anxiolytic, anticonvulsant and muscle relaxing properties. It is classified as an sedative, hypnotic. Flurazepam has been shown to be useful in the treatment of insomnia. The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053, each of which is incorporated herein by reference in its entirety.

[099] In some embodiments, flurazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[0100] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam

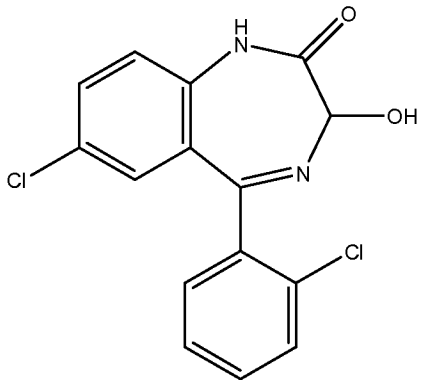
may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of flurazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of flurazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of flurazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with flurazepam to provide a synergistic anticonvulsant effect.

[0101] Flurazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the flurazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The flurazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0102] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention

of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0103] Lorazepam (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0104] Lorazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Lorazepam has also been shown to be useful in the treatment of nausea. The dosage of lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249, which is incorporated herein by reference in its entirety.

[0105] In some embodiments, lorazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

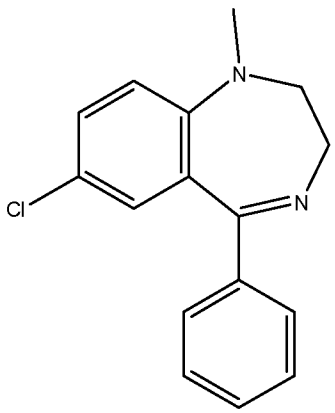
[0106] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of lorazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of lorazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of lorazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam),

other anti-convulsant drugs may be combined with lorazepam to provide a synergistic anticonvulsant effect.

[0107] Lorazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the lorazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The lorazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0108] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0109] Medazepam ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



[0110] Medazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Medazepam has also been shown to be useful in the treatment of nausea. The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427, which is incorporated herein by reference in its entirety.

[0111] In some embodiments, medazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

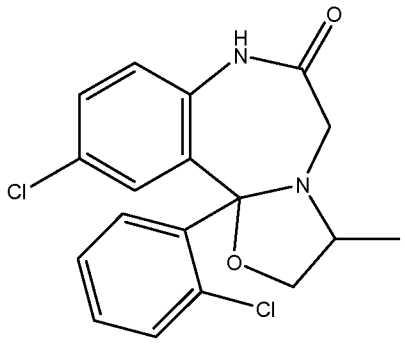
[0112] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of medazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of medazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of medazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with medazepam to provide a synergistic anticonvulsant effect.

[0113] Medazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure.

Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the medazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The medazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0114] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0115] Mexazolam (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methyloxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



[0116] Mexazolam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Mexazolam has also been shown to be useful in the treatment of nausea. The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371, which is incorporated herein by reference in its entirety.

[0117] In some embodiments, mexazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

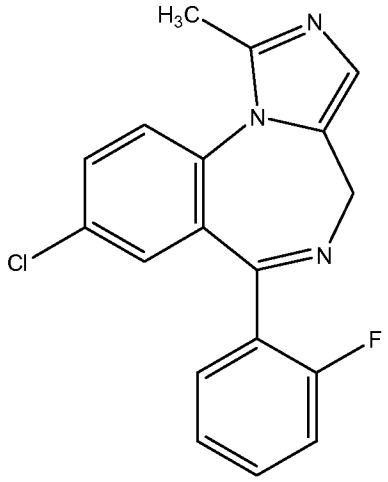
[0118] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of mexazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of mexazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of mexazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with mexazolam to provide a synergistic anticonvulsant effect.

[0119] Mexazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the mexazolam formulations of the invention, and in

particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The mexazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0120] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0121] Midazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



[0122] Midazolam is a tricyclic benzodiazepine having anxiolytic, amnesic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. Midazolam is considered soluble in water at a pH lower than about 4, but is relatively insoluble in most aqueous solutions at neutral pH (e.g. about 6 to 8). Thus it is desirable in some embodiments for aqueous nasal preparations of midazolam to have a pH above about 5.5, preferably above about 6.0, or above about 6.5. In some preferred embodiments, the pH is between about 6 and 9, between about 6 and 8. It is considered that preparations of midazolam are particularly suitable for nasal administration as the lipid-soluble (at approximately neutral pH)

midazolam is rapidly absorbed across nasal mucosa, leading to efficient uptake of midazolam. It is further considered that midazolam may be formulated in a non-aqueous delivery vehicle, such as is known in the aerosol administration art, such as hydrofluorocarbon propellants, hydrocarbon propellants, etc.

[0123] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

[0124] In some embodiments, midazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

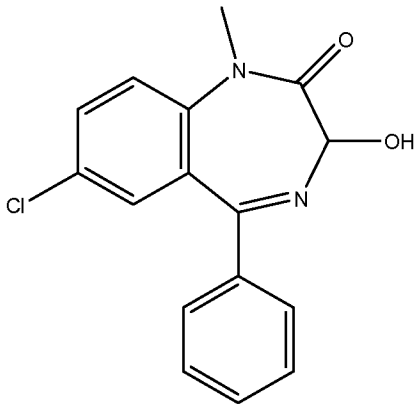
[0125] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of midazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of midazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of midazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with midazolam to provide a synergistic anticonvulsant effect.

[0126] Midazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction

in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the midazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The midazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0127] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

[0128] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0129] Temazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Temazepam has also been shown to be useful in the treatment of nausea. The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per

day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

[0130] In some embodiments, temazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

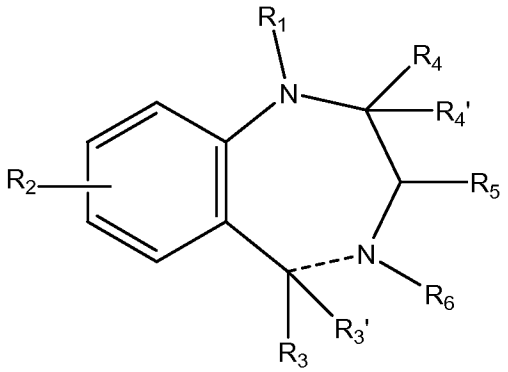
[0131] In some embodiments, temazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Temazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of temazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of temazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of temazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with temazepam to provide a synergistic anticonvulsant effect.

[0132] Temazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the temazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The temazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0133] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

Pharmaceutically Acceptable Salts

[0134] Benzodiazepines have the generally basic structure of formula I:



Formula I

wherein R_1-R_5 are substituents. In particular embodiments, R_1 is an optionally substituted alkyl or forms a ring with R_4, R_2 is a halogen (e.g. Cl, Br), R_3 is optionally substituted aryl (e.g. 2-Chloro or 2-Fluorophenyl), R_5 is H or OH, R_4 and R_4' together form a carbonyl (C=O) with the carbon to which they are attached or R_4 and R_1 form an optionally substituted heterocyclic ring with the diazepam ring atoms to which they are respectively attached; R_3' and R_6 together form a double bond or may be combined to form an optionally substituted heterocyclic ring along with the diazepam ring atoms to which they are respectively attached. Such basic compounds may form acid addition salts with pharmaceutically acceptable acids, such as pharmaceutically acceptable mineral acids and pharmaceutically acceptable organic acids.

[0135] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4, H_2SO_3, H_3PO_4, H_3PO_3, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. Thus, in some embodiments, the pharmaceutically acceptable acid may be selected from the group consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acidascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acidfumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (- L), malonic acid, mandelic acid (DL), methanesulfonic acid, benzenesulfonic acid (besylic acid), naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid (- L), salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (p) and undecylenic acid. Other pharmaceutically acceptable acids may be pharmaceutically acceptable acidic (anionic) polymers or pharmaceutically acceptable amphoteric polymers. One skilled in the art will recognize that other basic active pharmaceutical ingredients may be combined with the foregoing acids to produce acid addition salts. Likewise the person skilled in the art will recognize that in some embodiments it may be advantageous that some or all of the added acid be an active pharmaceutical ingredient in its own right.

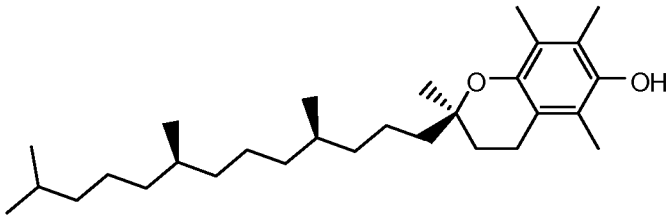
[0136] In some embodiments, the invention provides nasal compositions comprising one or more acidic pharmaceutically active ingredients. It is considered well within the ordinary skill in the art to determine which of the compounds set for the above are acidic. Such compounds may be prepared as base addition salts, e.g. by the addition of one or more mineral bases (e.g. NaOH, KOH, $NaHCO_3$, Na_2CO_3, NH_3) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

[0137] Known benzodiazepine compounds have anxiolytic, anticonvulsant, sedative and/or skeletal muscle relaxant effect. The term "anticonvulsant" includes treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure. In this regard, treatment of seizure includes cessation of an ongoing seizure, reduction in the severity of an ongoing seizure,

reduction in the duration of an ongoing seizure. Protection against seizure includes forestalling an oncoming seizure.

Carrier System

[0138] Vitamin E is a class of fat soluble methylated phenols. There are at least eight naturally-occurring compounds that comprise this class: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, and δ- tocotrienol, all of which may be used in the compositions and methods of the present invention. There are multiple isomers of each of these compounds, all of which may be used in the compositions and methods of the present invention. There are also multiple esters of each of these compounds, including tocophersolan, all of which may be used in the compositions and methods of the present invention. As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.



α-tocopherol

[0139] The compounds that comprise Vitamin E are antioxidants. There is also evidence that they can prevent, delay the onset of, or ameliorate the symptoms of heart disease, cancer, cataracts, macular degeneration, glaucoma, Alzheimer's, and Parkinson's disease.

[0140] The inventors have found that Vitamin E can provide an effective carrier for benzodiazepine drugs. In some embodiments, benzodiazepines are soluble, or partially soluble, in Vitamin E. In some embodiments, Vitamin E may be present as microparticles, nanoparticles, or any combination thereof. Furthermore, use of Vitamin E can have the added benefit of either avoiding irritation of sensitive mucosal membranes and/or soothing irritated mucosal membranes.

[0141] Vitamin E is generally classified as hydrophobic, and when used as a carrier may be limited to formulations as an emulsion. However, emulsions can have several drawbacks. For instance, they may be difficult to create and can be highly unstable. Additionally, they can leave an oily film on the surface of the skin. Thus, to avoid the drawbacks of emulsions, some embodiments of the present invention comprise solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols or one or more lower alkyl glycols, or any combinations thereof.

[0142] Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof can be used.

[0143] Lower alkyl glycols are those with six or fewer carbon atoms. Thus, any of ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, or any combinations thereof can be used.

Additional Excipients

[0144] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is at least one alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130, which is incorporated herein by reference in its entirety. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Specific excipients that may be employed in a nasal composition according to the invention include alkylsaccharide is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof. Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail® by Aegis Therapeutics, LLC, San Diego, CA. Other alkyl glycosides may be selected from those having a hydrophile-lipophile balance (HLB) number of from about 10-20, especially about 11-15. The HLB number may be determined as set forth in the publication US2009/0047347, published on 19 February 2009, the entirety of which, and especially paragraphs [0075]-[0079], is incorporated herein by reference. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a

benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

[0145] The term "penetration enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[0146] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% (w/v).

[0147] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

[0148] Thus, in some embodiments, the invention provides 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); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount

from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

[0149] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, which benzodiazepine drug comprises microparticles, nanoparticles or both, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

Mucosal Membrane Preparations

[0150] Mucosal membrane preparations are generally administered in metered sprays having volumes of less than 250 μL, preferably less than 150 μL, and ideally from 25 to 100 μL. Although not prohibited in this invention, administration of volumes larger than about 300 μL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost.

[0151] The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed.

Alprazolam

[0152] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

[0153] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays

Diazepam

[0154] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

[0155] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Flurazepam

[0156] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053, each of which is incorporated herein by reference in its entirety.

[0157] As a nasal formulation, flurazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Lorazepam

[0158] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249, which is incorporated herein by reference in its entirety.

[0159] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Medazepam

[0160] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427, which is incorporated herein by reference in its entirety.

[0161] As a nasal formulation, medazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Mexazolam

[0162] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371, which is incorporated herein by reference in its entirety.

[0163] As a nasal formulation, mexazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Midazolam

[0164] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam

may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

[0165] As a nasal formulation, midazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Temazepam

[0166] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

[0167] As a nasal formulation, temazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Formulation

[0168] Some embodiments comprise administering to one or more mucosal membranes of a patient a therapeutically effective amount of one or more benzodiazepine drugs, or pharmaceutically-acceptable salts thereof. Some embodiments of the composition disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration up to about 600 mg/mL. Other compositions disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 10 mg/mL up to about 250 mg/mL. Further, some embodiments disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 20 mg/mL up to about 50 mg/mL.

[0169] Some embodiments disclose a carrier system that is about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol or lower alkyl glycol, or any combinations thereof. Some embodiments disclose a carrier system that is about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof. Further, some embodiments disclose a carrier system that is about 70% (w/w) Vitamin E and about 30% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof.

[0170] Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of

the desired result. Other dosage levels disclose a dosage level of about 2.0 mg to about 15.0 mg until the desired result is achieved. Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.

[0171] In some embodiments of the method, the dosage volume ranges from about 10 μL to about 200 μL. In some embodiments, the dosage volume ranges from about 20 μL to about 180 μL. Further, some embodiments disclose a dosage volume of about 50 μL to about 140 μL. In some embodiments, the dosage volume is 50 μL, 75 μL or 100 μL per nostril.

Formulation Process

[0172] In some embodiments, the composition for nasal administration is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is made by slowly warming or heating the Vitamin E until it is liquefied. Next, the one or more benzodiazepine drugs are added. The mixture is stirred and heated until the one or more benzodiazepine drugs dissolve or are substantially dissolved. Next, the one or more alcohols or glycols, or any combinations thereof, are added to the composition. This composition is stirred until a less viscous composition is achieved.

[0173] The formulation process may be adjusted to take into consideration variations in the formulation. For example, as depicted in Figure 4, formulations comprising both benzyl alcohol and ethanol may be formulated by first combining Vitamin E, benzyl alcohol and ethanol (*e.g.*, dehydrated alcohol, USP), mixing until the ingredients are homogenous, heating the mixture to about 45°C (±2°C), adding alkyl glocoside and mixing until the alkyl glycoside is dissolved and the solution is homogenous, adding benzodiazepine (*e.g,* diazepam) while maintaining the mixture at about 45 °C, cooling the solution to about 25°C (±2°C) and adding ethanol (Q.S.) to achieve the final target weight of solution, mixing well to assure homogeneity. Solutions manufactured according to this process may be formulated in different concentrations of diazepam. For example, some embodiments of the invention include diazepam formulations summarized in the following table. While diazepam is used as an illustration in Figure 4 and the following table, any benzodiazepines may also be used, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam,

prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

[0174] NRL-1 Quantitative Composition. In some embodiments, the formulations are for nasal administration.

Component	Solution Concentration		
	50mg/mL	**75 mg/mL**	**100 mg/mL**
Vitamin E	56.47 mg	56.47 mg	56.47 mg
Benzyl alcohol	10.50 mg	10.50 mg	10.50 mg
Diazepam	5.00 mg	7.50 mg	10.00 mg
Intravail A3®	0.25 mg	0.25 mg	0.25 mg
Dehydrated ethanol	q.s. to 100µL	q.s. to 100µL	q.s. to 100µL

[0175] In some embodiments, the aforementioned formulations are sterile solutions with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent. In some embodiments, the solutions are self-preserving, self-sterile or both.

[0176] In some embodiments, the benzodiazepine drug is formulated as a microparticulate and/or nanoparticulate suspension of the benzodiazepine. Preparation of microparticulate and nanoparticulate benzodiazepine may be accomplished by methods such as milling, etc. Such methods are known to those skilled in the art.

[0177] Figure 5 depicts one embodiment of a process of manufacturing a suspension of benzodiazepine according to the instant invention. First, the benzodiazepine (*e.g.,* diazepam) is sieved to produce a micronized benzodiazepine (*e.g.,* diazepam). The micronized benzodiazepine (*e.g.*, diazepam) is then split into two intermediates products - Diazepam A (high pressure) is a small particle size (mean particle size < 2000 nm) and Diazepam B (low pressure) is a large particle size (mean particle diameter > 2000 nm). After in-process testing, the two intermediate products are combined with one or more excipients in correct proportions to produce a bimodal particle suspension having a pre-selected mean particle diameter, which in some embodiments is greater than 2000 nm. In some embodiments, the excipients are prepared according to the second column in Figure 5, *e.g.* by first combining propylene glycol, water and vitamin E polyethylene glycol succinate to form a mixture and heating the mixture until the ingredients are dissolved, then adding methylparaben, propyl paraben and Intravail™ (alkyl glycoside) to the mixture and mixing until the newly added ingredients are dissolved, and finally cooling the mixture, *e.g.* to 25°C ± 2°C. The excipients can then be combined with Micronized Diazepam A and

Micronized Diazepam B and mixed vigorously to disperse the micronized Diazepam to form the suspension. Next, povidone is added to the mixture, which is mixed until the povidone is fully dissolved. Finally, the suspension is brought to its final target weight with purified water and mixed well to achieve homogeneity. The final product can then be filled into suitable containers. In some embodiments, 3 mL may be filled into 4 mL amber glass vials with PTFE lined phenolic closures, though other containers are of course possible and contemplated within the scope of the invention. As diazepam is depicted in Figure 5 as an exemplary benzodiazepine, any benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof may also be employed.

[0178] In some embodiments, the aforementioned formulations are sterile suspensions with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent. In some embodiments, the suspensions are self-preserving, self-sterile or both.

[0179] In some embodiments, the benzodiazepine drug is formulated as a solution. It is considered an aspect of the invention that employment of microparticulate and/or nanoparticulate benzodiazepine drug during the process of preparing the formulation, can improve the overall solubility of the benzodiazepine drug in the solvent system.

Additional Active and Inactive Ingredients

[0180] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from active ingredients. By way of non-limiting example, such active ingredients include insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof, enkephalins, LHRH and analogues (Nafarelin, Buserelin, Zolidex), GHRH (growth hormone releasing hormone), nifedipin, THF (thymic humoral factor), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, antibiotics, metoclopramide, ergotamine, Pizotizin, nasal vaccines (particularly HIV vaccines, measles, rhinovirus Type 13 and respiratory syncitial virus), pentamidine, CCK (Cholecystikinine), DDVAP, Interferons, growth hormone (solatotropir polypeptides or their derivatives (preferably with a molecular weight from 1000 to 300000), secretin, bradykinin antagonists, GRF (Growth releasing factor), THF, TRH (Thyrotropin releasing hormone), ACTH analogues, IGF (Insulin like growth factors), CGRP (Calcitorin gene related peptide) Atrial Natriuretic peptide, Vasopressin and analogues (DDAVP, Lypressin),

Metoclopramide, Migraine treatment (Dihydroergotamine, Ergometrine, Ergotamine, Pizotizin), Nasal Vaccines (Particularly AIDS vaccines) FACTOR VIII, Colony Stimulating factors, G-CSF (granulocyte-colony stimulating factor), EPO (Erythropoitin) PTH (Parathyroid hormone) or pharmaceutically acceptable salts or combinations thereof.

[0181] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: paraldehyde; aromatic allylic alcohols (such as stiripentol); barbiturates (e.g. phenobarbitol, primidone, methylphenobarbital, metharbital and barbexaclone); bromides (such as potassium bromide); carbamates (such as felbamate); carboxamides (such as carbamazepine and oxcarbazepine); fatty acids (such as valproic acid, sodium valproate, and divalproex sodium, vigabatrin, progabide, tiagabine); fructose, topiramate, Gaba analogs (e.g. gabapentin and pregabalin); hydantoins (e.g. ethotoin, phenytoin, mephenytoin and fosphenytoin); oxazolidinediones (such as paramethadione, trimethadione, ethadione); propionates (e.g. beclamide), pyrimidinediones (e.g. primidone); pyrrolidines (e.g. brivaracetam, levetiracetam and seletracetam); succinimides (e.g. ethosuximide, phensuximide and mesuximide); sulfonamides (e.g. acetazolamide, sulthiame, methazolamide and zonisamide); triazines (such as lamotrigine); ureas (such as pheneturide, phenacemide); valproylamides (such as valpromide and valnoctamide); as well as other anticonvulsants or pharmaceutically acceptable salts or combinations thereof.

[0182] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, gentamicin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and ethacridine; enzymes such as lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, active vitamin D and vitamin C; sex hormones; hypotensives; sedatives; anti-tumor agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen,

diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

[0183] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional inactive ingredient in the composition. By way of non-limiting example, minor amounts of ingredients such as stabilizers, coloring agents, pH adjusters, buffering agents, preservatives such as agents which may prevent degradation, wetting agents, and flavoring agents may also be present. Examples of coloring agents include β-carotene, Red No. 2 and Blue No. 1. Examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid. Examples of corrigents include menthol and citrus perfume.

[0184] In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer. The term "enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[0185] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% (w/v).

[0186] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are

appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

[0187] In some embodiments, the invention takes advantage of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, bestatin, chloroacetyl-HOLeu-Ala-Gly-NH.sub.2, diprotin A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin, kallikrein, chymostatin, benzamidine, chymotrypsin and trypsin. Suitable concentrations are from 0.01 to 10% (w/v). The person skilled in the art will readily be able to determine whether an enhancer should be included.

Administration

[0188] In some embodiments, the administration of the composition comprises administering at least a portion of the therapeutically effective amount of the composition onto at least one mucosal membrane. 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 nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

Alprazolam

[0189] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

[0190] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL,

metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Diazepam

[0191] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

[0192] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Flurazepam

[0193] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053, each of which is incorporated herein by reference in its entirety.

[0194] As a nasal formulation, flurazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Lorazepam

[0195] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249, which is incorporated herein by reference in its entirety.

[0196] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications

of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Medazepam

[0197] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427, which is incorporated herein by reference in its entirety.

[0198] As a nasal formulation, medazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Mexazolam

[0199] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371, which is incorporated herein by reference in its entirety.

[0200] As a nasal formulation, mexazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μL, especially about 100 μL,

metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Midazolam

[0201] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

[0202] As a nasal formulation, midazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Temazepam

[0203] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

[0204] As a nasal formulation, temazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

[0205] Those skilled in the art will be aware that a systematic, therapeutically effective amount of benzodiazepine drugs for treating the aforementioned disorders will vary with age, size, weight, and general physical condition of the patient as well as the severity of the disease. Frequency of administration will likewise vary with the formulation of the composition and it can be adjusted so that any suitable number of doses per day may be used.

Examples

[0206] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

[0207] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in adults. Treatment is administered either before or after a seizure has begun. If the

patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 5.0 mg/puff (5.0 mg/0.1 mL and 0.1 mL/puff)) every 5 minutes until cessation of the seizure. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 2.5 mg/puff (5.0 mg/0.1 mL and 0.05 mL/puff)) every 5 minutes until cessation of the seizure. The composition according to this example is set forth in the following table.

Table 1-1

5.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 2

[0208] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in children. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 2.0 mg/puff (2.0 mg/0.1 mL and 0.1 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 1.0 mg/puff (2.0 mg/0.1 mL and 0.05 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. The composition according to this example is set forth in the following table.

Table 2-1

2.0 mg/0.1mL	Diazepam
70.0 mg	α-tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 3 – Formulation of Diazepam Solutions

[0209] In general, benzodiazepine solutions may be formulated by combining one or more natural or synthetic tocopherols or tocotrienols and one or more lower alcohols or glycols and mixing until a homogeneous mixture is formed, adding the benzodiazepine drug to the homogeneous mixture, heating and mixing the ingredients until the benzodiazepine is fully dissolved in the homogeneous mixture, cooling the mixture, and bringing the mixture to its final mass or volume with lower alcohol or glycol.

[0210] Two different diazepam solutions were formulated by the foregoing process. Vitamin E USP and dehydrated ethanol USP were combined in the amounts set forth in the following table and mixed to form a homogeneous mixture. Diazepam in the amounts set forth in the following table was then added to the homogeneous mixture. The ingredients were heated to 40-45°C with mixing until the diazepam was fully dissolved, thereby forming a solution. The solution was cooled to 20-25°C, whereupon the solution was brought to its final target weight with dehydrated ethanol USP and the solution was mixed thoroughly to assure homogeneity. The solution was then sampled for in-process testing and packaged in 3 mL amber glass vials.

Table 3-1: Diazepam Solutions – 70 mg/mL

Component	Solution 00 (65% Vitamin E) Concentration (mg/mL)	Solution 02 (80% Vitamin E) Concentration (mg/mL)
Diazepam USP	70.0	70.0
Vitamin E USP	650.0	800.0
Dehydrated Ethanol USP	q.s. to 1 mL	q.s. to 1 mL

[0211] Additional solutions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and the relative amounts of Vitamin E and ethanol. Other benzodiazepine solutions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process (e.g. before or concurrently with the addition of benzodiazepine).

Example 4 -- Formulation of Diazepam Suspensions

[0212] In general, benzodiazepine suspensions are formulated by micronizing benzodiazepine and combining the benzodiazepine with a carrier. The carrier is prepared by combining one or more lower alcohols or glycols with water, adding a natural or synthetic tocopherol or tocotrienol, heating the mixture until the tocopherol or tocotrienol is dissolved, adding one or more parabens and mixing until the parabens are dissolved and cooling the carrier. Once the benzodiazepine is added to the carrier,

additional excipients, such as surfactants, can optionally be added and dissolved in the carrier. The suspension is then brought up to its final mass or volume with water.

[0213] Two different diazepam suspensions were formulated by the foregoing general process. Two different diazepam particle sizes were prepared – A: a small particle size by prepared by high pressure micronization, and B: a large particle size prepared by low pressure micronization. The carrier was prepared by combining propylene glycol USP and purified water USP, then adding Vitamin E Polyethylene Glycols Succinate NF, then mixing and heating the combined ingredients to about 45°C. Mixing was continued until the Vitamin E Polyethylene Glycol Succinate was fully dissolved. The carrier was then cooled to 20-25°C. The micronized diazepam (A and B) was then added to the carrier with vigorous mixing until the diazepam was fully dispersed in the carrier. Polyvinylpyrrolidone Povidone USP/NF was then added to the mixture and mixed until fully dissolved. The suspension was then brought up to weight with purified water USP. The suspension was then mixed until homogeneous, sampled for in-process testing, and packaged in 3 mL amber glass bottles.

Table 4-1: Diazepam Suspension Formulations

Component	Suspension 03 (200 mg/mL Diazepam) Concentration (mg/mL)	Suspension 01 (100 mg/mL Diazepam) Concentration (mg/mL)
Diazepam USP	200.00	100.00
Vitamin E Polyethylene Glycol Succinate NF	100.0	100.0
Methylparaben NF	2.0	2.0
Propylparaben NF	0.5	0.5
Propylene Glycol USP	100.0	100.0
Povidone USP/NF	25.0	25.0
Purified Water USP/EP	q.s. to 1 mL	q.s. to 1 mL

[0214] Additional suspensions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and optionally other excipients. Other benzodiazepine suspensions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process. For example, an alkylglycoside may be added to the carrier during compounding of the carrier, or may be added to the suspension mixture concurrently with or after addition of the povidone.

Example 5 -- Stability of Diazepam Solutions and Suspensions

[0215] Solutions 00 and 02 (Example 3) and Suspensions 01 and 03 (Example 4) were set up on stability at 25°C / 60% RH, 30°C / 65% RH and 40°C / 75% RH. One batch each of four different formulations, packaged in 3-ml vials with screw-top closures, along with corresponding actuators, were set up at three storage conditions. They are listed in Table 1 with their corresponding Particle Sciences initial sample control numbers.

Table 5-1: Summary of PSI sample control numbers

Formulation #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00 – 70 mg/ml solution, 65% Vitamin E	083101.01	083101.02	083101.02
Solution 02 – 70 mg/ml solution, 80% vitamin E	083102.01	083102.02	083102.03
Suspension 01 - 100 mg/mi suspension	083103.01	083103.02	083103.03
Suspension 03 - 200 mg/ml suspension	083104.01	083104.02	083104.03

[0216] Samples were tested for spray content uniformity, spray volume, diazepam content, diazepam related substances, and methylparaben and propylparaben assay (suspension samples only). Unit weights were determined as per USP <755>.

[0217] Summaries of the average assay values and all other results are given in Tables 5-4, 5-5, 5-6 and 5-7. The results for the initial, 1-month and 3-month time points are also shown for comparison. Individual spray content uniformity results are given in Tables 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, and 5-15.

[0218] In general, all of the assays and the other results are similar to the initial data, with the exceptions of diazepam related compounds A and B.

[0219] Related compound A did not meet the specification of not more than (NMT) 0.01% for some samples (see Table 2). Related compound A has increased with time and temperature.

Table 5-2: Summary of related compound A T6M results

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	0.058%	0.051%
Solution 02	Meets specification	Meets specification	Meets specification
Suspension 01	0.038%	0.046%	0.157%
Suspension 03	0.019%	0.029%	0.081%

[0220] Related compound B is also increasing with time and temperature, and now fails specification of NMT 0.1% at 40°C condition for both suspension and one solution formulation. Only formulation 2602 meets all impurity specifications.

Table 5-3: Summary of related compound B T6M results

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	Meets specification	0.398%
Solution 02	Meets specification	Meets specification	Meets specification
Suspension 01	Meets specification	Meets specification	0.289%
Suspension 03	Meets specification	Meets specification	0.123%

Table 5-4: Summary of Solution 00 results

Solution 00, 70mg/mL, 65% Vitamin E	Specifications	Initial	1 month 25°C/60 %RH	1 month 30°C/65 %RH	1 month 40°C/75 %RH	3 month 25°C/60 %RH	3 month 30°C/65 %RH	3 month 40°C/75 %RH	6 month 25°C/60 %RH	6 month 30°C/65 %RH	6 month 40°C/75 %RH
Description	Yellow to orange solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution

Identification – UV	Conforms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.1	100.3	93.9	98.8	96.3	96.9	101.2	97.5	94.6	100.6
Impurities (%) [1]											
Nordazepam	NMT 0.3%	0.005	0.01	0.014	0.019	0.013	0.013	0.013	0.013	0.013	0.013
Related Compound B	NMT 0.1%	ND	0.002	0.007	0.03	0.008	0.016	0.089	0.024	0.098	0.398
Related Compound A	NMT 0.01%	0.002	0.002	0.004	0.011	0.002	0.002	0.01	0.005	0.058	0.051
Unknown	NMT 0.1%	0.011	0.012	0.014	0.02	0.037	0.039	0.047	0.035	0.066	0.055
Total	NMT 1.0%	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.1	0.2	0.5
Microbial Limits	Meets USP {61}	pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.108	1.105	1.111	1.112	1.109	1.109	1.113	1.103	1.111	1.109
Fill volume (ml)	report results	1.192	1.189	1.195	1.196	1.193	1.193	1.198	1.187	1.195	1.193
Spray delivered (µl)	report results	133.9	140.7	146.8	140.5	149.1	143.5	139.6	131.4	not tested	136.4
Average Spray Content (%)	report results	95.0	101.2	100.4	99.4	99.7	94.6	99.4	95.7	not tested	108.7
Viscosity (Pa*s)	report results	0.14	0.086	0.12	0.12	0.096	0.14	0.12	0.12	0.11	0.11

[1] LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-5: Summary of Solution 02 results

Solution 02, 70mg/mI, 65% Vitamin E	**Specifica -tions**	**Initial**	**1 month 25°C/ 60 %RH**	**1 month 30°C/ 65 %RH**	**1 month 40°C/ 75 %RH**	**3 month 25°C/ 60 %RH**	**3 month 30°C/ 65 %RH**	**3 month 40°C/ 75 %RH**	**6 month 25°C/ 60 %RH**	**6 month 30°C/ 65 %RH**	**6 month 40°C/ 75 %RH**
Description	Yellow to orange sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n	Amber sol'n

Identification – UV	Con-forms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.5	94.9	96.2	103.3	98.0	97.2	99.6	97.0	94.3	100.3
Impurities (%) [1]											
Nordazepam	NMT 0.3%	0.003	0.004	0.005	0.006	0.005	0.005	0.006	0.005	0.004	0.005
Related Compound B	NMT 0.1%	ND	0.002	0.003	0.006	0.003	0.005	0.032	0.007	0.020	0.058
Related Compound A	NMT 0.01%	0.003	0.002	0.002	0.003	0.002	0.002	0.004	0.003	0.009	0.007
Unknown	NMT 0.1%	0.01	0.012	0.014	0.018	0.019	0.025	0.032	0.014	0.020	0.018
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1
Microbial Limits	Meets USP {61}	pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.135	1.117	1.128	1.123	1.116	1.133	1.137	1.124	1.133	1.127
Fill volume (ml)	report results	1.184	1.165	1.177	1.172	1.164	1.182	1.186	1.172	1.183	1.176
Spray delivered (µl)	report results	115.0	137.5	137.6	133.1	143.9	136.3	143.8	129.3	not tested	124.2
Average Spray Content (%)	report results	98.6	97.6	97.7	100.7	98.7	94.7	100.5	95.8	not tested	97.1
Viscosity (Pa*s)	report results	0.69	0.68	0.64	0.68	0.63	0.65	0.64	0.61	0.55	0.56

(1) LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-6: Summary of Suspension 01 results

Suspension 01, 100 mg/ml	**Specifi-cations**	**Initial**	**1 month 25°C/60 %RH**	**1 month 30°C/65 %RH**	**1 month 40°C/75 %RH**	**3 month 25°C/60 %RH**	**3 month 30°C/65 %RH**	**3 month 40°C/75 %RH**	**6 month 25°C/60 %RH**	**6 month 30°C/65 %RH**	**6 month 40°C/75 %RH**
Description	Cloudy to white	White dispersion	White dispersio	White dispersio	White dispersio	White dispersio	White dispersio	White dispersio	White dispersio	pale yellow	yellow dispersio

	solution		n	n	n	n	n	n	n	dispersion	n
Identification – UV	Conforms to reference std. UV and RT	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	102.8	102.6	100.9	104.3	101.3	101.8	103.6	100.7	104.3	99.4
Impurities (%) [(1)]											
Nordazepam	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Related Compound B	NMT 0.1%	ND	ND	ND	0.004	ND	0.004	0.053	0.005	0.013	0.289
Related Compound A	NMT 0.01%	ND	0.01	0.02	0.034	0.026	0.036	0.08	0.038	0.046	0.157
Unknown	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.007	0.007	0.008	0.007	0.018
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5
Methylparaben (%)	80.0%-115.%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
Propylparaben (%)	80.0% 115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235
Fill volume (ml)	report results	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
Spray delivered (µl)	report results	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	not tested	137.6
Average Spray Content (%)	report results	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	not tested	95.94
Viscosity (Pa*s)	report results	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

(1) LOQ is approximately 0006%, LOD is approximatelyo.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-7: Summary of Suspension 03 results

Suspension 03, 200mg/mL	**Specifications**	**Initial**	**1 month 25°C/60 %RH**	**1 month 30°C/65 %RH**	**1 month 40°C/75 %RH**	**3 month 25°C/60 %RH**	**3 month 30°C/65 %RH**	**3 month 40°C/75 %RH**	**6 month 25°C/60 %RH**	**6 month 30°C/65 %RH**	**6 month 40°C/75 %RH**
Description	Cloudy to white dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	pale yellow dispersion	yellow dispersion
Identification – UV	Conforms to reference std. UV and RT	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	100.7	101.2	98.9	101.6	102.6	103.6	103.1	100.5	98.9	100.1
Impurities (%) [(1)]											
Nordazepam	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Related Compound B	NMT 0.1%	ND	ND	ND	ND	0.002	ND	0.023	0.002	0.008	0.123
Related Compound A	NMT 0.01%	ND	0.005	0.01	0.017	0.017	0.012	0.039	0.019	0.029	0.081
Unknown	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.007	0.008
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2
Methylparaben (%)	80.0%-115.%	93.4	101.1	93.8	99.7	101.5	101.6	101.2	103.5	97.2	102.1
Propylparaben (%)	80.0% 115.0%	95.6	100.2	94	98.4	100.1	101.3	99.2	97.1	91.9	95.9
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.276	1.28	1.259	1.272	1.279	1.279	1.276	1.280	1.262	1.260
Fill volume (ml)	report results	1.186	1.19	1.171	1.183	1.19	1.19	1.187	1.190	1.173	1.172
Spray delivered (µl)	report results	112.4	137.4	134.3	119.9	138.9	139.3	134.3	149.4	not tested	138.0
Average Spray Content (%)	report results	82.8	99.3	97.3	86.7	98.6	102.3	96.2	98.2	not tested	98.7

Viscosity (Pa*s)	report results	0.021	0.017	0.017	0.019	0.016	0.016	0.018	0.014	0.013	0.015

(1) LOQ is approximately 0.006%, LOD is approximately 0.002%. Results below LOQ are reported in this table for trending purposes.

Table 5-8: Solution 00 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
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
Average	0.13135	0.13716	9.380	95.72
St. Dev.	0.0070	0.0071	0.4309	4.3970
% RSD	5.35	5.20	4.59	4.59

Table 5-9: Solution 00 40°C/75% RH spray content uniformity results

Sample	**Weight Collected, g**	**Weight Actuated, g**	**Diazepam Recovered, mg**	**% Diazepam Recovered**
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
Average	0.13635	0.14131	10.653	108.70
St. Dev.	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

Table 5-10: Solution 02 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
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
Average	0.12931	0.13178	9.394	95.85
St. Dev.	0.0058	0.0056	0.3303	3.3701
% RSD	4.52	4.25	3.52	3.52

Table 5-11: Solution 02 40°C/75% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
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
Average	0.12423	0.12649	9.517	97.11
St. Dev.	0.0254	0.0260	0.3148	3.2119
% RSD	20.45	20.57	3.31	3.31

Table 5-12: Suspension 01 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
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
Average	0.13995	0.14190	14.252	101.80
St. Dev.	0.0070	0.0074	0.6602	4.7154
% RSD	5.03	5.18	4.63	4.63

Table 5-13: Suspension 01 40°C/75% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
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
Average	0.13755	0.14015	13.431	95.94
St. Dev.	0.0073	0.0073	0.5223	3.7310
% RSD	5.28	5.19	3.89	3.89

Table 5-14: Suspension 03 25°C/60% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
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
Average	0.14941	0.15125	27.490	98.18
St. Dev.	0.0057	0.0053	1.5812	5.6472
% RSD	3.79	3.50	5.75	5.75

Table 5-15: Suspension 03 40°C/75% RH spray content uniformity results

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered

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
Average	0.13796	0.14002	27.631	98.68
St. Dev.	0.0073	0.0076	0.7642	2.7294
% RSD	5.28	5.43	2.77	2.77

Example 6

[0221] All of the solutions and suspensions described in Examples 3 and 4 are formulated as described in Examples 3 and 4, with the addition of a suitable amount of an alkyl glycoside, as described herein, such as dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof, or marketed as Intravail® by Aegis Therapeutics, San Diego, CA. The solutions and suspensions with added alkyl glycoside may then be put up on stability as described in Example 5, *mutatis mutandis*.

Example 7

[0222] The solutions and suspensions of Examples 3, 4 and 6 are evaluated for pharmacokinetics in a suitable animal model, such as in mice, rats, rabbits or dogs. First each animal (e.g. rabbit) is administered an amount of a benzodiazepine drug intravenously. The amount of intravenously dosed benzodiazepine drug is selected to be less, e.g. roughly half, of what is considered an effective dose administered nasally. For example, the intravenous dose of diazepam administered to rabbits is about 0.05 to about 0.2 mg/kg, e.g. about 0.1 mg/kg. Blood is collected immediately before administration and at specific time points post-administration. Plasma blood levels of the drug are assayed for each of the blood samples. After at least a one day washout period, each animal is administered, intranasally, an amount of a solution or suspension as described in Examples 3, 4 and 6. Blood is collected immediately before administration and at substantially the same specific time points as the IV dose post-

administration. Pharmacokinetic curves (blood plasma concentration of drug versus time) are constructed for the intravenous route of administration and for each of the solutions and suspensions administered by the intranasal administration route.

[0223] Toxicity is assessed by known means. In particular, histological samples are collected from the nasal mucosal tissues of the test animals. Other toxological methods are optionally employed as well.

Example 8

[0224] The solutions and suspensions of Examples 3, 4 and 6 are evaluated for their ability to deliver drug across the blood brain barrier in a suitable animal model, such as in mice, rats, rabbits or dogs. Each animal is administered, intranasally, an amount of a solution or suspension as described in Examples 3, 4 and 6, with the solution or suspension optionally containing an imaging agent, such as a dye, that may be used as a proxy for determining the ability of the drug to cross the blood brain barrier. The drug or imaging agent is detected at selected time points after administration of the suspension or solution to determine how well the drug or imaging agent crosses the blood brain barrier. These results may be compared with analogous result obtained with an intravenous solution containing the drug or imaging agent.

Example 9

[0225] The above-described solutions and/or suspensions can be evaluated for pharmacokinetics in humans. Normal, healthy human test subjects are administered an amount of the drug intravenously. The amount chosen for intravenous administration may be any amount, but is conveniently a dose that is considered effective in treating seizure in humans. For example, an IV dose of diazepam administered to humans may be in the range of 1 to 15 mg, e.g. about 7.5 mg. Blood is collected immediately before administration and at selected time points after administration. Plasma blood levels of the drug are assayed for each of the blood samples. After at least a one day washout period, each subject is administered, intranasally, an amount of a solution or suspension as described herein. Blood is collected immediately before administration and at substantially the same time points after administration as the intravenous time points. Pharmacokinetic curves (blood plasma concentration of drug versus time) are constructed for the intravenous and intranasal administration routes.

Example 10

[0226] The above-described solutions and/or suspensions can be evaluated for efficacy in a suitable animal model. Briefly, for each dose of suspension or solution to be tested, a test animal is stimulated with a seizure inducing stimulus. The stimulus may be light, sound, chemical or other stimulus effective to induce seizure in the model animal. Once the animal has begun to seize, a solution or suspension as described herein is administered intranasally to the animal. The efficacy of the dose of the solution and/or suspension is evaluated based upon the animal's response to the test dose. This procedure is repeated through sufficient iterations, and at sufficient numbers of doses, to identify a dose that is considered effective to treat seizure by intranasal administration of the drug.

Example 11

[0227] A pharmaceutical composition comprising diazepam was prepared as a composition formulated as a solution to be delivered via a nasal delivery device. The solution was prepared according to the procedure outlined in the flow diagram of Figure 4. The ingredients used in the 100 mg/mL diazepam solution are set forth in Table 11-1, below:

Table 11-1

Ingredient	Concentration (% (w/v))
Diazepam	10.00 % (w/v)
α-tocopherol*	56.47 % (w/v)
Ethanol (dehydrated)	q.s. ((~18.07) % (w/v))
Intravail A3**	0.25 % (w/v)
Benzyl alcohol	10.50 % (w/v)

*Vitamin E, **Dodecyl maltoside

[0228] A batch of solution of Table 11-1 was prepared and subjected to stability testing at 25°C/60% R.H. for 12 months. The following table provides stability determinations for this batch at initial, 3 month, 6 month and 12 month time points.

Test Parameter	**Initial % Label Claim (100 mg/mL)**	**1 Month**	**3 Month**	**6 Month**
Appearance	Pale amber to amber solution	Amber solution	Amber solution	Amber solution
Diazepam % Label Claim	103.3	99.5	99.2	99.1

[0229] A batch of solution of Table 11-1 was prepared and subjected to stability testing at 30°C/65% R.H. (accelerated conditions) for 12 months. The following table provides stability determinations for this batch at initial, 1 month and 12 month time points.

Test Parameter	**Initial % Label Claim (100 mg/mL)**	**1 Month**	**6 Month**
Appearance	Pale amber to amber solution	Amber solution	Amber solution
Diazepam % Label Claim	103.3	97.8	99.7

[0230] A batch of solution of Table 11-1 was prepared and subjected to stability testing at 40°C/75% R.H. (accelerated conditions) for 12 months. The following table provides stability determinations for this batch at initial, 3 month, 6 month and 12 month time points.

Test Parameter	**Initial % Label Claim (100 mg/mL)**	**1 Month**	**3 Month**	**6 Month**
Appearance	Pale amber to amber solution	Amber solution	Amber solution	Amber solution
Diazepam % Label Claim	103.3	97.9	100.0	99.4

[0231] The suspension formulation is set forth in Table 11-2, below

Component	Function	Concentration (mg/mL)
Diazepam	Active	100.0
Methyl Paraben	Preservative	2.0
Propyl Paraben	Preservative	0.5
Intravail A3	Absorption aid	2.5
Vitamin E TPGS	Dispersant	10.0
Propylene Glycol	Dispersant	100.0
Povidone	Suspending agent	5.0
Water	Carrier	q.s. to 1.0 mL

[0232] A batch of suspension of Table 11-2 was prepared and subjected to stability testing at 25°C/60% R.H. for 3 months. The following table provides stability determinations for this batch at initial and 3 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	3 Month
Appearance	Opaque white liquid	Opaque white liquid
Diazepam % Label Claim	104.4	102.1

[0233] A batch of suspension of Table 11-2 was prepared and subjected to stability testing at 30°C/65% R.H. (accelerated conditions) for 1 month. The following table provides stability determinations for this batch at initial and 1 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month
Appearance	Opaque white liquid	Opaque white liquid
Diazepam % Label Claim	104.4	102.9

[0234] A batch of suspension of Table 11-2 was prepared and subjected to stability testing at 40°C/75% R.H. (accelerated conditions) for 3 months. The following table provides stability determinations for this batch at initial, 1 month and 3 month time points.

Test Parameter	Initial % Label Claim (100 mg/mL)	1 Month	3 Month
Appearance	Opaque white liquid	Opaque white liquid	White liquid
Diazepam % Label Claim	104.4	102.7	108.7

[0235] A three-period, three-treatment, six-sequence, randomized cross-over study was conducted in healthy volunteers. For each dose, each volunteer was domiciled for at least 12 hours prior to each dose and until after a 24 hour pharmacokinetic sample was collected. Single doses of 100 μL of the pharmaceutical compositions described in Tables 11-1 and 11-2 were administered to each volunteer as one spray to the left nostril of 100 μL per spray. Pharmacokinetic samples were collected at 22 time points over 10 days. (PK time points: 2.5, 5, 10, 15, 20, 30 and 45 minutes, 1, 1.5, 2, 4, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours after each dose.) No serious adverse events were noted. PK data were compared with those obtained with 5 mg of diazepam administered intravenously. The PK data are summarized in Table 11-3 and Figures 1-3.

[0236] The solution of Table 11-1 and the suspension of Table 11-2 were found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% of i.v.) The intranasal formulation of

Table 11-1 exhibited a Tmax of 1.5 hours, a Cmax of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diastat®).

[0237] Solutions similar to those set forth in Table 11-1 can be prepared consisting of: diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); or diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

[0238] Solutions similar to those set forth in Table 11-1 achieve bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously, *e.g.* bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously or about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously. Such solutions may be used in methods of treating a patient with a disorder which may be treatable with a benzodiazepine drug, such as seizure, epileptic seizure and/or breakthrough seizure. In some embodiments, solutions described herein may be used to treat a disorder such as is treated with Diastat® diazepam gel.

[0239] A summary of pharmacokinetic data obtained for the solution and a suspension form of diazepam is shown below in Table 11-3:

Table 11-3

Summary of Pharmacokinetic Parameters for Intranasal (10 mg) and IV (5 mg) Diazepam

	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
Parameter [a]	n	Mean (SD) [a]	n	Mean (SD) [a]	n	Mean (SD) [a]
C_{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T_{max} (h) [b]	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC_{0-t} (h*ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h*ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λ_z (h^{-1})	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0058)
$t_{1/2}$ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

a: Mean values are presented as arithmetic means.
b: Median (min, max) reported for T_{max}

[0240] The data collected in the study are further illustrated in Figures 1-3. Figure 1 is a linear scale plot of the arithmetic mean of the plasma concentration of diazepam after intranasal (IN) administration of

10 mg of diazepam as the suspension of Table 11-2 and after IN administration of 10 mg of diazepam as a solution of Table 11-1 compared to intravenous (IV) administration of 5 mg of diazepam. Figure 2 is a semi-logarithmic scale plot of the same data shown in Figure 1. Figure 3 shows the first 24 hours of data from Figure 1 on a linear scale.

[0241] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

(b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);

(c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and

(d) an alkyl glycoside,

in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient.

2. The pharmaceutical solution of claim 1, 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).

3. The pharmaceutical solution of claim 2, 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, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

4. The pharmaceutical solution of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

5. The pharmaceutical solution of claim 1, containing about 1 to about 20 % (w/v) of benzodiazepine.

6. The pharmaceutical solution of claim 5, containing about 1 to about 20 % (w/v) of diazepam.

7. The pharmaceutical solution of claim 1, 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.

8. The pharmaceutical solution of claim 1, wherein the 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.

9. The pharmaceutical solution of claim 1, containing two or more alcohols.

10. The pharmaceutical solution of claim 1, containing ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).

11. The pharmaceutical solution of claim 1, containing ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

12. The pharmaceutical solution of claim 11, wherein the benzodiazepine is present in the pharmaceutical solution in a concentration from about 20 mg/mL to about 200 mg/mL.

13. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w).

14. The pharmaceutical solution of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w).

15. The pharmaceutical solution of claim 1, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w).

16. The pharmaceutical solution of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 25% to about 40% (w/w).

17. The solution of claim 1, consisting of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

18. The solution of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

19. The solution of claim 18, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside.

20. The solution of claim 1, consisting essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

21. The solution of claim 20, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

22. The solution of claim 21, consisting of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

23. A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of 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); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside.

24. The method of claim 23, 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).

25. The method of claim 24, wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E.

26. The method of claim 23, 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, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

27. The method of claim 26, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

28. The method of claim 23, wherein the solution contains about 1 to about 20 % (w/v) of benzodiazepine.

29. The method of claim 28, wherein the solution contains about 1 to about 20 % (w/v) of diazepam.

30. The method of claim 23, 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.

31. The method of claim 23, 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.

32. The method of claim 23, wherein the solution contains two or more alcohols.

33. The method of claim 23, wherein the solution contains ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).

34. The method of claim 33, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

35. The method of claim 34, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

36. The method of claim 23, 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).

37. The method claim 36, 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).

38. The method of claim 23, 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).

39. The method of claim 38, 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).

40. The method of claim 23, wherein the solution contains ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

41. The method of claim 23, wherein the solution is in a pharmaceutically-acceptable spray formulation.

42. The method of claim 41, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

43. The method of claim 42, wherein said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

44. The method of claim 43, 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.

45. The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

46. The method of claim 45, 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.

47. The method of claim 46, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

48. The method of claim 46, 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 solution.

49. The method of claim 23, wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside.

50. The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

51. The method of claim 50, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.

52. The method of claim 23, wherein the solution consists essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

53. The method of claim 23, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

54. The method of claim 23, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

55. The method of one of claims 23-54, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.

56. The method of one of claims 23-54, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

57. The solution of claim 17, consisting of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

58. The solution of claim 17, consisting of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

59. The solution of claim 17, consisting of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

60. The method of claim 23, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

61. The method of claim 23, wherein the solution consists of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

62. The method of claim 23, wherein the solution consists of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

63. The method of one of claims 23-56 or 60-62, wherein said treatment achieves bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously.

64. The method of claim 63, wherein said treatment achieves bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously.

65. The method of claim 64, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

ABSTRACT

The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Linda Anders
Attorney Docket Number:	35401-716.301

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	2051	1	70	70
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**800**

Electronic Acknowledgement Receipt

EFS ID:	20554884
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	29-OCT-2014
Filing Date:	
Time Stamp:	19:02:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$800
RAM confirmation Number	5476
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	35401-716-301-transmittal.pdf	276721 8b28a54b0925fd4efb3fddf82c2d9c2b06b773cc	no	2
Warnings:					
Information:					
2	Application Data Sheet	35401-716-301-ADS.pdf	1566872 8049dda8c0527a4f3ddab3952eeedd63cfb07b1c	no	11
Warnings:					
Information:					
3	Drawings-only black and white line drawings	35401-716-301-figures.pdf	212775 660c3e1d168b0a29d55b93b7c68020be9c4e94bb	no	5
Warnings:					
Information:					
4		35401-716-301-continuation1.pdf	624943 d2b815f926860ea4126e7c6d09078cd6fd0d601a	yes	87

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	79
	Claims	80	86
	Abstract	87	87

Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	36718 312208bee06c1bcb85c3cff6ffa5527ac3550302	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2718029	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/527,613	10/29/2014	Steve Cartt	35401-716.301

CONFIRMATION NO. 2149

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

FORMALITIES LETTER

Date Mailed: 11/24/2014

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing.

Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- Additional claim fees of $ **4670** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **4280** for **107** total claims over 20.
- $ **390** for multiple dependent claim surcharge.
- $(**0**) previous unapplied payment amount.
- $ **4670** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Steve Cartt
  David Medeiros

Garry Thomas Gwozdz
Andrew Loxley
Mark Mitchnick
David Hale
Edward T. Maggio

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/nhassani/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
14527613	

Applicant(s) Steve Cartt

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
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Total Indep	2		0		0	
Total Depend	125	↵	0	↵	0	↵
Total Claims	127		0		0	

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	Indep	Depend	Indep	Depend	Indep	Depend
51		1				
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54		1				
55		32				
56		32				
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58		1				
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61		1				
62		1				
63		(1)				
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/527,613	10/29/2014	1629	800	35401-716.301	65	2

CONFIRMATION NO. 2149

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

FILING RECEIPT

OC00000071968384

Date Mailed: 11/24/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Steve Cartt, Union City, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Residence Not Provided;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

Applicant(s)

Hale Biopharma Ventures, Encinitas, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/495,942 06/13/2012 PAT 8895546
which is a CIP of 12/413,439 03/27/2009
which claims benefit of 61/040,558 03/28/2008
and said 13/495,942 06/13/2012
claims benefit of 61/497,017 06/14/2011
and claims benefit of 61/570,110 12/13/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 11/20/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/527,613**

Projected Publication Date: 03/05/2015

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/527,613

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	127 minus 20 =	* 107	x 40 =	4280	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				390			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	5400		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

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

AMENDMENT B

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
Sheet	1	of	14	Attorney Docket Number	35401-716.301

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-2001-0042932	11/22/2001	Mathiowitz et al.	
	2.	US-2002-0110524 A1	8/15/2002	Cowan, et al.	
	3.	US-2002-0127278	09/12/2002	Kipp	
	4.	US-2002-0141971 A1	10/3/2002	Frey	
	5.	US-2002-0168402	11/14/2002	Kipp	
	6.	US-2003-0017203 A1	1/23/2003	Crotts et al.	
	7.	US-2003-0031719	02/13/2003	Kipp	
	8.	US-2003-0040497 A1	2/27/2003	Teng et al.	
	9.	US-2003-0087820 A1	5/1/2003	Young et al.	
	10.	US-2003-0100755 A1	5/29/2003	Sham et al.	
	11.	US-2003-0118547 A1	6/26/2003	Vandenberg	
	12.	US-2003-0118594 A1	6/26/2003	Nag et al.	
	13.	US-2003-0158206 A1	8/21/2003	Billotte et al.	
	14.	US-2003-0170206 A1	9/11/2003	Rasmussen et al.	
	15.	US-2003-0181411	9/25/2003	Bosch et al.	
	16.	US-2004-0115135 A1	6/17/2004	Quay	
	17.	US-2004-0126358 A1	7/1/2004	Warne et al.	
	18.	US-2004-0147473 A1	7/29/2004	Warriell, Jr.	
	19.	US-2004-0258663 A1	12/23/2004	Quay & El-Shafy	
	20.	US-2004-141923 A1	07/22/2004	Dugger et al.	
	21.	US-2005-0130260 A1	6/16/2005	Linden et al.	
	22.	US-2005-0234101 A1	10/20/2005	Stenkamp et al.	
	23.	US-2006-0045869 A1	03/02/2006	Meezan et al.	
	24.	US-2006-0046962	3/2/2006	Meezan et al.	
	25.	US-2006-0046969 A1	3/2/2006	Maggio	
	26.	US-2006-0106227 A1	5/18/2006	Reddy et al.	
	27.	US-2006-0147386 A1	07-062006	Wermling, D. P.	

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				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
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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
	28.	US-2006-0198896	09/07/2006	Liversidge et al.	
	29.	US-2007-0298010 A1	12/27/2007	Maggio	
	30.	US-2007-0059254 A1	3/15/2007	Singh	
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	32.	US-2008-0200418	08/21/2008	Maggio	
	33.	US-2008-0248123	10/09/2008	Swanson et al.	
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	38.	US-2009-0047347	2/19/2009	Maggio	
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	41.	US-2009-0297619	12/03/2009	Swanson et al.	
	42.	US-2009-0304801	12/10/2009	Liversidge et al.	
	43.	US-2009-258865	10/15/2009	Cartt	
	44.	US-2010-0068209 A1	3/18/2010	Maggio, E. T.	
	45.	US-2010-0203119 A1	8/12/2010	Leane et al.	
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	47.	US-2011-0172211	07/14/2011	Back et al.	
	48.	US-2011-0257096	10/20/2011	Maggio	
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	51.	US-2014-0128479 A1	05/08/2014	Maggio	
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	55.	US-3,136,815	6/9/1964	Reeder et al.	

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				First Named Inventor	Steve Cartt
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	56.	US-3,243,427	3/29/1966	Reeder et al.	
	57.	US-3,296,249	1/13/1967	Bell	
	58.	US-3,299,053	1/17/1967	Archer et al.	
	59.	US-3,340,253	9/5/1967	Reeder et al.	
	60.	US-3,371,085	2/27/1968	Reeder et al.	
	61.	US-3,374,225	3/19/1968	Reeder et al.	
	62.	US-3,547,828	12/15/1970	Mansfield et al.	
	63.	US-3,567,710	3/2/1971	Fryer et al.	
	64.	US-3,609,145	9/28/1971	Moffett	
	65.	US-3,722,371	3/27/1973	Boyle	
	66.	US-3,849,341	11/19/1974	Lambeiti	
	67.	US-3,987,052	10/19/1976	Hester, Jr.	
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	71.	US-4,748,158	5/31/1988	Biermann et al.	
	72.	US-4,826,689	5/2/1989	Violanto et al.	
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	77.	US-5,091,188	2/25/1992	Haynes	
	78.	US-5,100,591	3/31/1992	Leclef et al.	
	79.	US-5,118,528	6/2/1992	Fessi et al.	
	80.	US-5,145,684	9/8/1992	Liversidge et al.	
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	82.	US-5,188,837	2/23/1993	Domb	
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	84.	US-5,236,707	8/17/1993	Stewart	
	85.	US-5,268,461	12/7/1993	Shoji et al.	
	86.	US-5,308,531	5/3/1994	Urfer et al.	
	87.	US-5,317,010	5/31/1994	Pang et al.	
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	97.	US-5,738,845	4/14/1998	Imakawa	
	98.	US-5,780,062	7/14/1998	Frank et al.	
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	103.	US-5,831,089	11/3/1998	Huber	
	104.	US-5,849,884 (withdrawn)		Woiszwillo et al.	
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	113.	US-6,193,985	02/27/2001	Sonne	
	114.	US-6,235,224	05/22/2001	Mathiowitz et al.	
	115.	US-6,254,854	7/3/2001	Edwards, et al.	
	116.	US-6,268,053	7/31/2001	Woiszwillo et al.	
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	124.	US-6,482,834	11/19/2002	Spada, et al.	
	125.	US-6,495,498	12/17/2002	Niemiec et al.	
	126.	US-6,524,557	2/25/2003	Backstrom et al.	
	127.	US-6,607,784	8/19/2003	Kipp et al.	
	128.	US-6,610,271	08/26/2003	Wermeling	
	129.	US-6,616,914	09/09/2003	Ward et al.	
	130.	US-6,627,211	09/30/2003	Choi et al.	
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	134.	US-6,908,626	06/21/2005	Cooper et al.	
	135.	US-6,932,962	8/23/2005	Backstrom et al.	
	136.	US-6,991,785	1/31/2006	Frey	
	137.	US-7,008,920	3/7/2006	Kimura et al.	
	138.	US-7,037,528	5/2/2006	Kipp	
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	140.	US-7,434,579	10/14/2008	Young et al.	
	141.	US-8,530,463	09/10/2013	Cartt	
	142.	US-8,895,546	11/25/2014	Cartt	

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	143.	U.S. Prov. Appl. No. 60/148,464	08/12/1999	Noe	

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	144.	EP-00780386	6/25/1997	Hoffman-La Roche AG		
	145.	EP-0396777 A1	11/14/1990	OTSUKA PHARMA CO LTD		
	146.	EP-0818442	1/14/1998	Pfizer Inc.		
	147.	EP-0945485	9/29/1999	Morton Int'l., Inc.		
	148.	EP-1004578	5/31/2000	Pfizer Products Inc.		
	149.	EP-1417972 A1	5/12/2004	ELI LILLY & COMPANY		
	150.	EP-606046	7/13/1994	CIBA-GEIGY AG		
	151.	EP-931788	7/28/1999	Pfizer Limited		
	152.	JP1-151528 (English Abstract and Claims)	6/14/1989	TAIHO YAKUHN KOGYO KK		X
	153.	JP-2003-505403 (Corresponding English equivalent WO01/06987 A2)	2/12/2003	SK Corporation (US)		X
	154.	JP-2005-508939	4/7/2005	Cooper, Eugene R.		X

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		(Corresponding English equivalent WO03/030872 A2)				
	155.	JP-2007-510722 (Corresponding English equivalent WO2005-044234 A2)	4/26/2007	Elan Pharma International Ltd.		X
	156.	WO-1990-05719	5/31/1990	British Bio-Technology Ltd.		
	157.	WO-1991-019481	12/26/1991	ALLERGAN, INC.		
	158.	WO-1994-05262 A1	3/17/1994	F.H. FAUDLING & CO. LTD.		
	159.	WO-1995-000151 A1	1/5/1995	UAB RESEARCH FOUNDATION		
	160.	WO-1995-31217 A1	11/23/1995	Dumex Ltd.		
	161.	WO-1996-27583	9/12/1996	Pfizer Inc.		
	162.	WO-1996-33172	10/24/1996	Pfizer Inc.		
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	165.	WO-1998-07697	2/26/1998	Pfizer Inc.		
	166.	WO-1998-30566	7/16/1998	Pfizer Inc.		
	167.	WO-1998-33768	8/6/1998	Pfizer Products Inc.		
	168.	WO-1998-34915	8/13/1998	Pfizer Inc.		
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	170.	WO-1999-007675	2/18/1999	Pfizer Products Inc.		
	171.	WO-1999-29667	6/19/1999	Pfizer Limited		
	172.	WO-1999-52889	10/21/1999	Pfizer Inc.		
	173.	WO-1999-52910	10/21/1999	Pfizer Products Inc.		
	174.	WO-2000-001390 A1	01/13/2000	RECORDATI S.A. CHEMICAL AND		

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				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
				PHARMACEUTICAL COMPANY ET AL.		
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	181.	WO-2006-025882 A2	3/9/2006	The UAB Research Foundation et al.		
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	188.	WO-2009-120933 A2	10/01/2009	Particle Sciences Inc.		

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**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.

Electronic Acknowledgement Receipt

EFS ID:	20803033
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	25-NOV-2014
Filing Date:	29-OCT-2014
Time Stamp:	18:47:53
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		NEURELIS_IDS_35401_716_301_NOV2014.pdf	403252 6b0bb73955e83aa82cddc51a1baaf834019fb85d	yes	18

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	18	
Warnings:					
Information:					
2	Non Patent Literature	US13495942_OA_1Oct2013.pdf	546105 dede09f83a1dd271f69e618ed8f26b9d798323ad	no	10
Warnings:					
Information:					
		Total Files Size (in bytes):	949357		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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: 1629
Serial Number: 14/527,613	Examiner: N/A
Filing Date: October 29, 2014	**CONFIRMATION NO: 2149**
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 A1ong 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).* A1though 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 A1lowance 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 $180.00 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).* A1though 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 A1lowance 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: 13/495,942

Information Disclosure Statement(s) filed on: All references cited in IDSs filed on 4/15/2013, 9/13/2013, 4/9/2014, and 10/16/2014 in the parent case, with the exception of Cite Nos. 51-52 and 272

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. 35401-716.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: 11/21/2014

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

650 Page Mill Road
Palo A1to, CA 94304-1050
(650) 493-9300
Customer No. 021971

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/527,613	10/29/2014	Steve Cartt	35401-716.301

CONFIRMATION NO. 2149

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

PUBLICATION NOTICE

OC000000073786980

Title:ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Publication No.US-2015-0065491-A1
Publication Date:03/05/2015

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	1	of	1	Attorney Docket Number	35401-716.301

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

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]
	1.	CA 2,723,470 Office Action dated February 19, 2015	
	2.	CN 201280039077.9 Office Action dated 12/26/2014	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.

Attorney Docket No.

Electronic Acknowledgement Receipt

EFS ID:	21798591
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	17-MAR-2015
Filing Date:	29-OCT-2014
Time Stamp:	18:15:45
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		Neurelis35401_716301_IDS_17 Mar2015.pdf	183499 0afa9c005f58452341ddcc882350cc3f90dd12b1	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	4
	Information Disclosure Statement (IDS) Form (SB08)	5	5

Warnings:					
Information:					
2	Non Patent Literature	CA2756690_OA_19FEB2015.pdf	344037 e83113dc801db90e0ec6b90bcaf630e5d9be018c	no	5
Warnings:					
Information:					
3	Non Patent Literature	ChineseOA_26Dec2014_translation.pdf	178717 8efe832241aa7c30d382d09e36530d3f30bb2d34	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	706253		

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	Group Art Unit: 1629
Serial Number: 14/527,613	Examiner: Not Yet Assigned
Filing Date: October 29, 2014	**CONFIRMATION NO: 2149**
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

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 $180.00 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 $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.301).

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Steve Cartt, et al. Serial No.: 14/527,613 Filing Date: October 29, 2014 Title: **Administration of Benzodiazepine Compositions**	Group Art Unit: 1629 Confirmation No.: 2149 Examiner: To be assigned Customer No.: 21971 Certificate of Electronic Filing I hereby certify that the attached **Preliminary Amendment** and all marked attachments are being deposited by Electronic Filing on May 27, 2015 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/

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Dear Madam:

This paper responds to the Notification of Missing Requirements mailed November 24, 2014, setting an initial deadline of January 24, 2015. Accordingly, Applicants petition for a five-month extension of time, and submit the appropriate fee. Applicants respectfully request entry of the proposed amendments prior to examination and allowance of the pending claims.

Amendments to the Claims begin on page **2**.

Remarks begin on page **7**.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in this application.

1-22. (Canceled)

23. (Currently Amended) A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of 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); ~~one or more alcohols or glycols, or any combinations thereof, in an~~ ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.

24. (Canceled).

25. (Currently Amended) The method of claim ~~24~~23, wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E.

26. (Previously Presented) The method of claim 23, 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, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

27. (Previously Presented) The method of claim 26, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

28. (Previously Presented) The method of claim 23, wherein the solution contains about 1 to about 20 % (w/v) of benzodiazepine.

29. (Previously Presented) The method of claim 28, wherein the solution contains about 1 to about 20 % (w/v) of diazepam.

30. (Previously Presented) The method of claim 23, 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.

31. (Canceled).

32. (Canceled).

33. (Previously Presented) The method of claim 23, wherein the solution contains ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).

34. (Previously Presented) The method of claim 33, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

35. (Previously Presented) The method of claim 34, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

36. (Previously Presented) The method of claim 23, 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).

37. (Previously Presented) The method claim 36, 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).

38. (Currently Amended) The method of claim 23, wherein the pharmaceutical solution comprises ~~one or more alcohols or glycols, or any combinations thereof, in an~~ ethanol and benzyl alcohol in a combined amount from about 15% to about 55% (w/w).

39. (Currently Amended) The method of claim 38, wherein the pharmaceutical solution comprises ~~one or more alcohols or glycols, or any combinations thereof, in an~~ ethanol and benzyl alcohol in a combined amount from about 25% to about 40% (w/w).

40. (Currently Amended) The method of claim 23, wherein the solution ~~contains~~ comprises ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

41. (Previously Presented) The method of claim 23, wherein the solution is in a pharmaceutically-acceptable spray formulation.

42. (Previously Presented) The method of claim 41, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

43. (Previously Presented) The method of claim 42, wherein said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

44. (Previously Presented) The method of claim 43, 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.

45. (Previously Presented) The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

46. (Previously Presented) The method of claim 45, 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.

47. (Previously Presented) The method of claim 46, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

48. (Previously Presented) The method of claim 46, 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 solution.

49. (Previously Presented) The method of claim 23, wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside.

50. (Previously Presented) The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

51. (Previously Presented) The method of claim 50, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.

52. (Previously Presented) The method of claim 23, wherein the solution consists essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

53. (Previously Presented) The method of claim 23, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

54. (Previously Presented) The method of claim 23, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

55. (Currently Amended) The method of ~~one of claims 23-54~~claim 23, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.

56. (Currently Amended) The method of ~~one of claims 23-54~~claim 23, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

57. (Canceled).

58 (Canceled).

59. (Canceled).

60. (Previously Presented) The method of claim 23, wherein the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).

61. (Previously Presented) The method of claim 23, wherein the solution consists of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).

62. (Previously Presented) The method of claim 23, wherein the solution consists of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

63. (Currently Amended) The method of ~~one of claims 23-56 or 60-62~~claim 23, wherein said treatment achieves bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously.

64. (Previously Presented) The method of claim 63, wherein said treatment achieves bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously.

65. (Previously Presented) The method of claim 64, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.

REMARKS

The claims have been amended prior to calculation of filing fees. Claims 23-30, 33-56 and 60-65 are pending and presented for examination. Favorable action is respectfully requested.

Applicants note that the parent application, 13/495,942 was subject to a restriction requirement on May 8, 2013. Applicants submit that the claims remaining in the instant application were those withdrawn from consideration during prosecution of 13/495,942, which is now U.S. Patent No. 8,895,546.

CONCLUSION

This Preliminary Amendment is submitted prior to the examination of this application on the merits. Since the present amendment does not introduce new matter, its entry prior to examination of the present application is respectfully requested.

Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned attorney at (858) 350-2332. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415, referencing Attorney Docket No. 35401-716.301.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: May 27, 2015

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

650 Page Mill Road
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Electronic Patent Application Fee Transmittal

Application Number:	14527613
Filing Date:	29-Oct-2014
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Linda Anders
Attorney Docket Number:	35401-716.301

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:				
Claims in excess of 20	2202	17	40	680
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 5 months with $0 paid	2255	1	1500	1500
Miscellaneous:				
			Total in USD ($)	**2180**

Electronic Acknowledgement Receipt

EFS ID:	22460022
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	27-MAY-2015
Filing Date:	29-OCT-2014
Time Stamp:	15:20:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2180
RAM confirmation Number	1783
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 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		35401-716-301-preliminaryamend.pdf	140620 5b52a5f30cfb931e2f02a61b2b84dc0166bf34b9	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	32793 c24a9ab77e831124959c4372938f7a30158c6394	no	2

Warnings:

Information:

Total Files Size (in bytes):	173413

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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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/527,613	Filing Date 10/29/2014	☐ 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 **05/27/2015**

	(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))	* 37	Minus	** 37	= 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
/eugenia v. hardy/

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/527,613	10/29/2014	1629	1480	35401-716.301	37	1

CONFIRMATION NO. 2149

UPDATED FILING RECEIPT

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

OC000000075496781

Date Mailed: 06/03/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Steve Cartt, Union City, CA;
David Medeiros, South San Francisco, CA;
Garry Thomas Gwozdz, Jim Thorpe, PA;
Andrew Loxley, Residence Not Provided;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

Applicant(s)

Hale Biopharma Ventures, Encinitas, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/495,942 06/13/2012 PAT 8895546
which is a CIP of 12/413,439 03/27/2009
which claims benefit of 61/040,558 03/28/2008
and said 13/495,942 06/13/2012
claims benefit of 61/497,017 06/14/2011
and claims benefit of 61/570,110 12/13/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 11/20/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/527,613**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/527,613	10/29/2014	Steve Cartt	35401-716.301

CONFIRMATION NO. 2149

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

INFORMAL NOTICE

OC00000075496762

Date Mailed: 06/03/2015

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Steve Cartt
  David Medeiros
  Garry Thomas Gwozdz
  Andrew Loxley
  Mark Mitchnick
  David Hale
  Edward T. Maggio

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/dgela/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/527,613

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	37 minus 20 =	* 17	x 40 =	680	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1410		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/527,613	10/29/2014	Steve Cartt	35401-716.301	2149

21971 7590 07/14/2016

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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. 14/527,613	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 _____.

☐ 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) *23, 25-30, 33-56 and 60-65* 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) *23, 25-30, 33-56 and 60-65* 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 *11/25/14, 3/17/15*.

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

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25-30, 33-56 and 60-65 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for disorders which are treatable with a benzodiazepine drug, does not reasonably provide enablement for all disorders which may be treatable by a benzodiazepine drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Specifically, if the drug is not treatable with a benzodiazepine drug, there is no expectation that the instantly claimed method will succeed. The phrase “may be treated" includes diseases which cannot be treated with benzodiazepines as well as those which can be treated with benzodiazepines. Examiner suggests replacing “may be" with “are” in line 1 of claim 23.

Claim Rejections – 35 U.S.C. § 112 - 2nd Paragraph

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33, 40, 56 and 60-62 are rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The claims include values in parenthesis. It is not clear whether the values in parentheses are part of the claimed invention. If Applicants intend the values to be limiting on the respective claims, Examiner suggests removing the values from the parentheses.

Claim Rejections - 35 USC § 112 – 4th Paragraph

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], 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 36-40 and 52 are rejected under 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 23 recites a solution “consisting of” while dependent claims 36-40 recite the term “comprising” when referencing the solution and claim 52 recites the term “consisting essentially of” when referring to the

solution. Thus, dependent claims 36-40 and 52 incorporate subject matter not included in the claim from which they depend. Applicant may cancel the claims, amend the claims to place them in proper dependent form, rewrite the claims in independent form, or present a sufficient showing that the dependent claims comply with the statutory requirements.

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 23, 25-30, 33-56 and 60-65 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,895,546. Although the claims at issue are not identical, they are not patentably distinct from each other because it is obvious to administer a composition "for nasal administration" to the nasal mucosal membranes. see MPEP 804.01(E)

Claims 23, 25-30, 33-56 and 60-65 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 20, 22-24, 27-36, 38, 40-45 and 48-54 of copending Application No. 12/413,439 (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.

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)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	1	of	1	Attorney Docket Number	35401-716.301

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

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]
	1.	CA 2,723,470 Office Action dated February 19, 2015	
	2.	CN 201280039077.9 Office Action dated 12/26/2014	X

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	07/11/2016

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Attorney Docket No.

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	1.	US-2001-0042932	11/22/2001	Mathiowitz et al.	
	2.	US-2002-0110524 A1	8/15/2002	Cowan, et al.	
	3.	US-2002-0127278	09/12/2002	Kipp	
	4.	US-2002-0141971 A1	10/3/2002	Frey	
	5.	US-2002-0168402	11/14/2002	Kipp	
	6.	US-2003-0017203 A1	1/23/2003	Crotts et al.	
	7.	US-2003-0031719	02/13/2003	Kipp	
	8.	US-2003-0040497 A1	2/27/2003	Teng et al.	
	9.	US-2003-0087820 A1	5/1/2003	Young et al.	
	10.	US-2003-0100755 A1	5/29/2003	Sham et al.	
	11.	US-2003-0118547 A1	6/26/2003	Vandenberg	
	12.	US-2003-0118594 A1	6/26/2003	Nag et al.	
	13.	US-2003-0158206 A1	8/21/2003	Billotte et al.	
	14.	US-2003-0170206 A1	9/11/2003	Rasmussen et al.	
	15.	US-2003-0181411	9/25/2003	Bosch et al.	
	16.	US-2004-0115135 A1	6/17/2004	Quay	
	17.	US-2004-0126358 A1	7/1/2004	Warne et al.	
	18.	US-2004-0147473 A1	7/29/2004	Warriell, Jr.	
	19.	US-2004-0258663 A1	12/23/2004	Quay & El-Shafy	
	20.	US-2004-141923 A1	07/22/2004	Dugger et al.	
	21.	US-2005-0130260 A1	6/16/2005	Linden et al.	
	22.	US-2005-0234101 A1	10/20/2005	Stenkamp et al.	
	23.	US-2006-0045869 A1	03/02/2006	Meezan et al.	
	24.	US-2006-0046962	3/2/2006	Meezan et al.	
	25.	US-2006-0046969 A1	3/2/2006	Maggio	
	26.	US-2006-0106227 A1	5/18/2006	Reddy et al.	
	27.	US-2006-0147386 A1	07-062006	Wermling, D. P.	

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Sheet	2	of	14	Attorney Docket Number	35401-716.301

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	28.	US-2006-0198896	09/07/2006	Liversidge et al.	
	29.	US-2007-0298010 A1	12/27/2007	Maggio	
	30.	US-2007-0059254 A1	3/15/2007	Singh	
	31.	US-2007-0098805 A1	5/3/2007	Liversidge	
	32.	US-2008-0200418	08/21/2008	Maggio	
	33.	US-2008-0248123	10/09/2008	Swanson et al.	
	34.	US-2008-0268032 A1	10/30/2008	Maggio	
	35.	US-2008-0279784	11/13/2008	Cartt	
	36.	US-2008-0299079 A1	12/4/2008	Meezan et al.	
	37.	US-2009-0258865 A1	10/15/2009	Cartt et al.	
	38.	US-2009-0047347	2/19/2009	Maggio	
	39.	US-2009-0130216	5/21/2009	Cartt	
	40.	US-2009-0163447	06/25/2009	Maggio	
	41.	US-2009-0297619	12/03/2009	Swanson et al.	
	42.	US-2009-0304801	12/10/2009	Liversidge et al.	
	43.	US-2009-258865	10/15/2009	Cartt	
	44.	US-2010-0068209 A1	3/18/2010	Maggio, E. T.	
	45.	US-2010-0203119 A1	8/12/2010	Leane et al.	
	46.	US-2010-0209485 A1	8/19/2010	Maggio	
	47.	US-2011-0172211	07/14/2011	Back et al.	
	48.	US-2011-0257096	10/20/2011	Maggio	
	49.	US-2012-0196941	08/02/2012	Maggio	
	50.	US-2013-0065886	03/14/2013	Cartt	
	51.	US-2014-0128479 A1	05/08/2014	Maggio	
	52.	US 2014-0170220 A1	06/19/2014	Cartt	
	53.	US-3,102,116	8/27/1963	Chase et al.	
	54.	US-3,109,843	11/5/1963	Reeder et al.	
	55.	US-3,136,815	6/9/1964	Reeder et al.	

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	56.	US-3,243,427	3/29/1966	Reeder et al.	
	57.	US-3,296,249	1/13/1967	Bell	
	58.	US-3,299,053	1/17/1967	Archer et al.	
	59.	US-3,340,253	9/5/1967	Reeder et al.	
	60.	US-3,371,085	2/27/1968	Reeder et al.	
	61.	US-3,374,225	3/19/1968	Reeder et al.	
	62.	US-3,547,828	12/15/1970	Mansfield et al.	
	63.	US-3,567,710	3/2/1971	Fryer et al.	
	64.	US-3,609,145	9/28/1971	Moffett	
	65.	US-3,722,371	3/27/1973	Boyle	
	66.	US-3,849,341	11/19/1974	Lambeiti	
	67.	US-3,987,052	10/19/1976	Hester, Jr.	
	68.	US-4,280,957	7/28/1981	Walser et al.	
	69.	US-4,397,951	8/9/1983	Taki et al.	
	70.	US-4,608,278	8/26/1986	Frank et al.	
	71.	US-4,748,158	5/31/1988	Biermann et al.	
	72.	US-4,826,689	5/2/1989	Violanto et al.	
	73.	US-4,868,289	9/1/1989	Magnusson et al.	
	74.	US-4,921,838	5/1/1990	Catsimpoolas et al.	
	75.	US-4,973,465	11/27/1990	Baurain et al.	
	76.	US-4,997,454	3/5/1991	Violanto et al.	
	77.	US-5,091,188	2/25/1992	Haynes	
	78.	US-5,100,591	3/31/1992	Leclef et al.	
	79.	US-5,118,528	6/2/1992	Fessi et al.	
	80.	US-5,145,684	9/8/1992	Liversidge et al.	
	81.	US-5,182,258	1/1/1993	Chiou	
	82.	US-5,188,837	2/23/1993	Domb	
	83.	US-5,192,528	3/3/1993	Radhakrishnan et al.	

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	07/11/2016

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Sheet	4	of	14	Attorney Docket Number	35401-716.301

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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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	85.	US-5,268,461	12/7/1993	Shoji et al.	
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	98.	US-5,780,062	7/14/1998	Frank et al.	
	99.	US-5,789,375	8/4/1998	Mukae et al.	
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	105.	US-5,861,510	01/19/1999	Piscipio et al.	
	106.	US-5,863,949	01/26/1999	Robinson et al.	
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	108.	US-5,981,719	11/9/1999	Woiszwillo et al.	
	109.	US-6,004,574	12/21/1999	Backstrom et al.	
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	111.	US-6,143,211	11/07/2000	Mathiowitz et al.	

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				Application Number	14/527,613
				Filing Date	October 29, 2014
				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
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	139.	US-7,132,112	11/07/2006	Choi et al.	

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				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
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	141.	US-8,530,463	09/10/2013	Cartt	
	142.	US-8,895,546	11/25/2014	Cartt	

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	143.	U.S. Prov. Appl. No. 60/148,464	08/12/1999	Noe	

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	144.	EP-00780386	6/25/1997	Hoffman-La Roche AG		
	145.	EP-0396777 A1	11/14/1990	OTSUKA PHARMA CO LTD		
	146.	EP-0818442	1/14/1998	Pfizer Inc.		
	147.	EP-0945485	9/29/1999	Morton Int'l., Inc.		
	148.	EP-1004578	5/31/2000	Pfizer Products Inc.		
	149.	EP-1417972 A1	5/12/2004	ELI LILLY & COMPANY		
	150.	EP-606046	7/13/1994	CIBA-GEIGY AG		
	151.	EP-931788	7/28/1999	Pfizer Limited		
	152.	JP1-151528 (English Abstract and Claims)	6/14/1989	TAIHO YAKUHN KOGYO KK		X
	153.	JP-2003-505403 (Corresponding English equivalent WO01/06987 A2)	2/12/2003	SK Corporation (US)		X
	154.	JP-2005-508939	4/7/2005	Cooper, Eugene R.		X

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	155.	JP-2007-510722 (Corresponding English equivalent WO2005-044234 A2)	4/26/2007	Elan Pharma International Ltd.		X
	156.	WO-1990-05719	5/31/1990	British Bio-Technology Ltd.		
	157.	WO-1991-019481	12/26/1991	ALLERGAN, INC.		
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	162.	WO-1996-33172	10/24/1996	Pfizer Inc.		
	163.	WO-1997-14407 A1	4/24/1997	Research Triangle Pharmaceuticals Board of Regents, U. Tx. System		
	164.	WO-1998-03516	1/29/1998	Pfizer Inc.		
	165.	WO-1998-07697	2/26/1998	Pfizer Inc.		
	166.	WO-1998-30566	7/16/1998	Pfizer Inc.		
	167.	WO-1998-33768	8/6/1998	Pfizer Products Inc.		
	168.	WO-1998-34915	8/13/1998	Pfizer Inc.		
	169.	WO-1998-34918	8/13/1998	Pfizer Inc.		
	170.	WO-1999-007675	2/18/1999	Pfizer Products Inc.		
	171.	WO-1999-29667	6/19/1999	Pfizer Limited		
	172.	WO-1999-52889	10/21/1999	Pfizer Inc.		
	173.	WO-1999-52910	10/21/1999	Pfizer Products Inc.		
	174.	WO-2000-001390 A1	01/13/2000	RECORDATI S.A. CHEMICAL AND		

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	175.	WO-2000-74681	12/14/2000	Pfizer Limited		
	176.	WO-2003-055464	07/10/2003	BESINS INTERNATIONAL BELGIQUE ET AL.		
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	183.	WO-2006-088894	8/24/2006	Elan Pharma International Ltd.		
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	186.	WO-2007-144081 A1	12/21/2007	LTS Lohmann Therapie-System		
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NON PATENT LITERATURE DOCUMENTS			
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				First Named Inventor	Steve Cartt
				Art Unit	1629
				Examiner Name	N/A
Sheet	11	of	14	Attorney Docket Number	35401-716.301

NON PATENT LITERATURE DOCUMENTS			
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventors: Steve Cartt, et al. Serial No.: 14/527,613 Filing Date: October 29, 2014 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Confirmation No.: 2149 Examiner: Adam C. Milligan Customer No.: 21971 Certificate of Electronic Filing I hereby certify that the attached Response and all marked attachments are 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**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Dear Commissioner:

This Amendment is submitted in response to the Non-Final Office Action mailed July 14, 2016. This Amendment is being submitted along with extension of time fees. The Commissioner is authorized to charge any additional fees which may be required to Deposit Account No. 23-2415 (Docket No. 35401-716.301).

Amendments to the Claims begin on page **2**.

Remarks begin on page 7.

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:

1-22. (Canceled)

23. (Currently Amended) A method of treating a patient with a disorder which ~~may be~~ is treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of 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); ethanol and benzyl alcohol in a combined amount from about 10% to about 70% (w/w); and an alkyl glycoside.

24. (Canceled).

25. (Previously Presented) The method of claim 23, wherein the natural or synthetic tocopherols or tocotrienols is Vitamin E.

26. (Previously Presented) The method of claim 23, 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, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

27. (Previously Presented) The method of claim 26, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.

28. (Previously Presented) The method of claim 23, wherein the solution contains about 1 to about 20 % (w/v) of benzodiazepine.

29. (Previously Presented) The method of claim 28, wherein the solution contains about 1 to about 20 % (w/v) of diazepam.

30. (Previously Presented) The method of claim 23, 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.

31. (Canceled).

32. (Canceled).

33. (Currently Amended) The method of claim 23, wherein the solution contains ethanol from 1 to 25% (w/v) ~~(1-25 % (w/v))~~ and benzyl alcohol from 1 to 25% (w/v) ~~(1-25 % (w/v))~~.

34. (Previously Presented) The method of claim 33, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.

35. (Previously Presented) The method of claim 34, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.

36. (Currently Amended) The method of claim 23, wherein the ~~pharmaceutical solution comprises~~ one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w).

37. (Currently Amended) The method claim 36, wherein the ~~pharmaceutical solution comprises~~ one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w).

38. (Currently Amended) The method of claim 23, wherein the ~~pharmaceutical solution comprises~~ ethanol and benzyl alcohol is in a combined amount from about 15% to about 55% (w/w).

39. (Currently Amended) The method of claim 38, wherein the ~~pharmaceutical solution comprises~~ ethanol and benzyl alcohol is in a combined amount from about 25% to about 40% (w/w).

40. (Currently Amended) The method of claim 23, wherein the solution comprises ethanol [[(]] from 10[[-]] to 22.5 % (w/v)[[)]] and benzyl alcohol from [[(]]7.5[[-]] to 12.5 % (w/v)[[)]].

41. (Previously Presented) The method of claim 23, wherein the solution is in a pharmaceutically-acceptable spray formulation.

42. (Previously Presented) The method of claim 41, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

43. (Previously Presented) The method of claim 42, wherein said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

44. (Previously Presented) The method of claim 43, 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.

45. (Previously Presented) The method of claim 43, wherein the administration of the pharmaceutical solution comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril.

46. (Previously Presented) The method of claim 45, 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.

47. (Previously Presented) The method of claim 46, further comprising, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical solution to the second nostril.

48. (Previously Presented) The method of claim 46, 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 solution.

49. (Previously Presented) The method of claim 23, wherein the solution contains at least about 0.01% (w/w) of an alkyl glycoside.

50. (Previously Presented) The method of claim 24, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

51. (Previously Presented) The method of claim 50, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.

52. (Cancelled)

53. (Previously Presented) The method of claim 23, wherein the solution consists of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.

54. (Previously Presented) The method of claim 23, wherein the solution consists of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

55. (Previously Presented) The method of claim 23, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.

56. (Currently Amended) The method of claim 23, wherein the solution consists of diazepam ~~(5-15 % (w/v))~~ from 5 to 15% (w/v), dodecyl maltoside from about 0.01 to 1% (w/v) ~~(0.01-1 % (w/v))~~, vitamin E from 45 to 65% (w/v) ~~(45-65 % (w/v))~~, ethanol from 10 to 25% (w/v) ~~(10-25 % (w/v))~~ and benzyl alcohol from 5 to 15% (w/v) ~~(5-15 % (w/v))~~.

57. (Canceled).

58 (Canceled).

59. (Canceled).

60. (Currently Amended) The method of claim 23, wherein the solution consists of diazepam from 5 to 15% (w/v) ~~(5-15 % (w/v))~~, dodecyl maltoside from 0.01 to 1% (w/v) ~~(0.01-1 % (w/v))~~, vitamin E from 45 to 65% (w/v) ~~(45-65 % (w/v))~~, ethanol from 10 to 25% (w/v) ~~(10-25 % (w/v))~~ and benzyl alcohol from 5 to 15% (w/v) ~~(5-15 % (w/v))~~.

61. (Currently Amended) The method of claim 23, wherein the solution consists of diazepam from 9 to 11% (w/v) ~~(9-11 % (w/v))~~, dodecyl maltoside from 0.1 to 0.5% (w/v) ~~(0.1-0.5 % (w/v))~~, vitamin E from 50 6o 60% (w/v) ~~(50-60 % (w/v))~~, ethanol from 15 to 22.5% (w/v) ~~(15-22.5 % (w/v))~~ and benzyl alcohol from 7.5 to 12.5% (w/v) ~~(7.5-12.5 % (w/v))~~.

62. (Currently Amended) The method of claim 23, wherein the solution consists of diazepam [[(]]10 % (w/v)[[)]], dodecyl maltoside from 0.15 to 0.3% (w/v) ~~(0.15-0.3 % (w/v))~~, vitamin E from 50 to 60% (w/v) ~~(50-60 % (w/v))~~, ethanol from 17 to 20% (w/v) ~~(17-20 % (w/v))~~ and benzyl alcohol from 10 to 12% (w/v) ~~(10-12 % (w/v))~~.

63. (Currently Amended) The method of claim 23, wherein said treatment achieves bioavailability that is from about 80[[-]] to 125% of that achieved with the same benzodiazepine administered intravenously.

64. (Currently Amended) The method of claim 63, wherein said treatment achieves bioavailability that is from about 90[[-]] to 110% of that achieved with the same benzodiazepine administered intravenously.

65. (Previously Presented) The method of claim 64, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.

REMARKS

This Amendment is in response to the Non-Final Office Action dated July 14, 2016. Claims 23, 25-30, 33-51, 53-56, and 60-65 are currently pending. Claims 23, 33, 36-40, 56, and 60-64 are currently amended. Claim 52 is cancelled. 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.

No new matter is added by any amendment made herein. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112 (pre-AIA), First Paragraph

The Office rejected claims 23, 25-30, 33-56, and 60-65 under 35 U.S.C. § 112 (pre-AIA), first paragraph, as allegedly lacking enablement in the specification for "all disorders which may be treatable by a benzodiazepine drug." Office Action dated July 14, 2016, page 2.

Without agreeing with the office and solely in the interest of compact and expeditious prosecution, Applicants herein amend claim 23 replace "may be" with "is." Applicants believe the rejection is moot.

Rejections under 35 U.S.C. § 112 (pre-AIA), Second Paragraph

The Office rejected claims 33, 40, 56 and 60-62 under 35 U.S.C. § 112 (pre-AIA), second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." Office Action dated July 14, 2016, page 3. Specifically, the Examiner points to the use of parentheses containing values in the claims stating that "It is not clear whether the values in parentheses are part of the claimed invention. If Applicants intend the values to be limiting on the respective claims, Examiner suggests removing the values from the parentheses." Office Action dated July 14, 2016, page 3.

Without agreeing with the office and solely in the interest of compact and expeditious prosecution, Applicants herein amend claims 33, 40, 56 and 60-62 to remove the parentheses as suggested by the Examiner, rendering the rejection moot.

Rejections under 35 U.S.C. § 112 (pre-AIA), Fourth Paragraph

The Office rejected claims 36-40 and 52 under 35 U.S.C. § 112 (pre-AIA), fourth paragraph, as allegedly being of improper dependent form. Office Action dated July 14, 2016, page 3. Specifically, the Examiner states that "independent claim 23 recites a solution 'consisting of' while dependent claims 36-40 recite the term 'comprising' when referencing the solution and claim 52 recites the term 'consisting essentially of' when referring to the solution." Office Action dated July 14, 2016, page 3.

Without agreeing with the office and solely in the interest of compact and expeditious prosecution, Applicants herein cancel claim 52 and amend claims 36-40 to place them in proper dependent form as suggested by the Examiner, rendering this rejection moot.

Nonstatutory Double Patenting Rejection

The Examiner rejected claims 23, 25-30, 33-56 and 60-65 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 of U.S. Patent No. 8,895,546. Office Action dated July 14, 2016, page 4.

The Examiner provisionally rejected claims 23, 25-30, 33-56 and 60-65 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 20, 22-24, 27-36, 38, 40-45 and 48-54 of co-pending Application No. 12/413,439. Office Action dated July 14, 2016, page 5.

Without conceding the basis for rejection, Applicant will consider filing terminal disclaimers over U.S. Patent No. 8,895,546 and 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.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Attorney Docket No. 35401-716.301).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Date: January 10, 2017

By: /Matthew V. Grumbling/
Matthew V. Grumbling.
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Customer No. 021971

Electronic Patent Application Fee Transmittal

Application Number:	14527613
Filing Date:	29-Oct-2014
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/Erin Allen
Attorney Docket Number:	35401-716.301

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Miscellaneous:				
			Total in USD ($)	**1400**

Electronic Acknowledgement Receipt

EFS ID:	28025984
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	10-JAN-2017
Filing Date:	29-OCT-2014
Time Stamp:	16:57:07
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		35401-716-301-NF-RESPONSE.pdf	514106 a0962dac345835fd63f2d31f43371fbd243b366a	yes	9

	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	9

Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30892 1efc73643f2b04a45bdc5077cc4a2bb99a35f85a	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	544998	

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.

Electronic Patent Application Fee Transmittal

Application Number:	14527613
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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:	28026101
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	10-JAN-2017
Filing Date:	29-OCT-2014
Time Stamp:	17:03:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$700
RAM confirmation Number	011117INTEFSW00003599232415
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.)
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Warnings:

Information:

Total Files Size (in bytes):	30844

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/527,613	Filing Date 10/29/2014	☐ 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 **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))	* 36	Minus	** 37	= 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
MARY HOLMES

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	14527613
Filing Date	10-29-2014
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam
Attorney Docket Number	35401-716.301

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
	001	US-20040101482	05-27-2004	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]
	001	CN-1303674-A	07-18-2001	INST OF MEDICAL INDUSTRY SHAND [CN]	English abstract provided	☒
	002	EP-1208863-A2	05-29-2002	UNISIA JECS CORP [JP]		☐
	003	JP-2011516425-A	05-26-2011	HALE BIOPHARMA VENTURES LLC [US], et al.	See WO-2009121039-A2 for English	☒
	004	WO-03004015-A1	01-16-2003	WEST PHARM SERV DRUG RES LTD [GB], et al.		☐
	005	WO-2009121039-A2	10-01-2009	HALE BIOPHARMA VENTURES LLC [US], et al.		☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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	14527613
Filing Date	10-29-2014
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam
Attorney Docket Number	35401-716.301

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	Canadian Patent Application No. 2756690 Examiner's Report dated October 20, 2015	☐
	002	Chinese Patent Application No. 201280039077.9 Office Action dated November 21, 2016.	☒
	003	Chinese Patent Application No. 2012800390779 Second Office Action dated August 11, 2015	☒
	004	Chinese Patent Application No. 201280039077.9 Third Office Action dated March 17, 2016.	☒
	005	European Patent Application No. 12801372.9 Extended EP Search Report dated March 26, 2015.	☐
	006	European Patent Application No. 12801372.9 Communication dated July 5, 2016.	☐
	007	Japanese Patent Application No. 2014-515967 Office Action dated March 30, 2016.	☒
	008	Japanese Patent Application No. 2014-515967 Office Action dated November 28, 2016.	☒
	009	Newman. Aerosol deposition consideration in inhalation therapy. Chest 152S-160S (1985).	☐
	010	U.S. Patent Application No. 12/413,439 Office Action dated July 14, 2016.	☐
	011	U.S. Patent Application No. 12/413,439 Office Action dated October 5, 2015	☐
	012	U.S. Patent Application No. 14/948,081 Office Action dated October 31, 2016.	☐
	013	U.S. Patent Application No. 12/116,842 Office Action mailed July 8, 2015.	☐
	014	U.S. Patent Application No. 14/021,988 Office Action mailed May 22, 2015.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Electronic Patent Application Fee Transmittal

Application Number:	14527613
Filing Date:	29-Oct-2014
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Matthew Virgil Grumbling/diane garcia
Attorney Docket Number:	35401-716.301

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:	28036815
Application Number:	14527613
International Application Number:	
Confirmation Number:	2149
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:	35401-716.301
Receipt Date:	11-JAN-2017
Filing Date:	29-OCT-2014
Time Stamp:	17:01:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$90
RAM confirmation Number	011217INTEFSW00003718232415
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	CN1303674A_trans_18Jul2001.pdf	2021264 8559852ac40805a838c6f607878097130ece5b57	no	39
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Information:					
2	Foreign Reference	EP1208863.pdf	988370 5b3b462da4acf1cf851da58a4d920716f3b46616	no	15
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Information:					

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Information:					
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Information:					
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Warnings:					
Information:					
		Total Files Size (in bytes):	18954577		

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New International Application Filed with the USPTO as a Receiving Office

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Alprazolam nasal spray

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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.

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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[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

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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(54) Inhalator

(57) An inhalator including an inhalator body including a powder receiving chamber for receiving a powder, an air-powder mixture reservoir for temporarily storing an air-powder mixture flowing from the powder receiving chamber, and a diluent air passage for introducing a diluent air into the air-powder mixture reservoir. The air-powder mixture is formed within the powder receiving chamber when an air is introduced into the powder receiving chamber. The air-powder mixture within the air-powder mixture reservoir is admixed with a diluent air introduced thereinto through the diluent air passage. The diluted air-powder mixture is discharged from an air-powder mixture outlet into a user's oral or nasal cavity. A powder composition for inhalators includes at least two kinds of fine particles different in particle diameter.

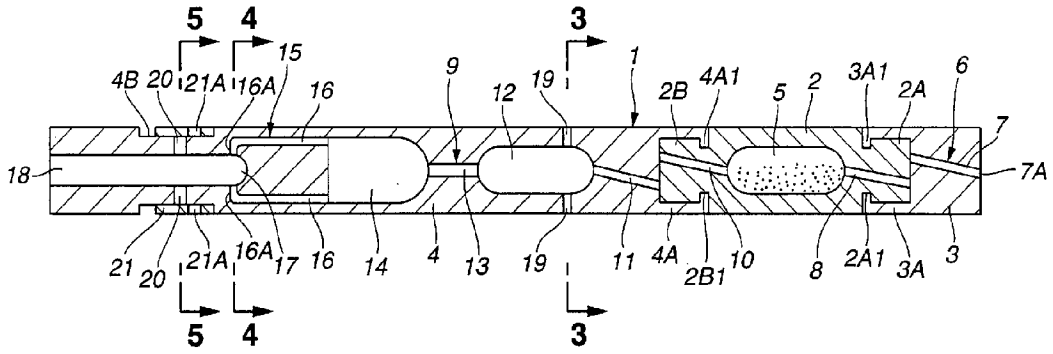

FIG.2

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Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to an inhalator suitable for administering a powder or powder composition, and a powder composition containing powders different in particle diameter from each other and a process for administering the powder composition using inhalators.

[0002] Generally, a powder inhalator is used for inhaling a powder or powder composition such as a powdered medicine into a human body through the oral or nasal cavity. The inhalator includes an inhalator body having an air intake path for introducing an ambient air and a suction opening through which an air-powder mixture within the inhalator body is sucked into the oral or nasal cavity. A powder receiving chamber for receiving the powder is disposed within the inhalator body and communicated with the outside of the inhalator body via the air intake path. An air-powder mixture path extends from the powder receiving chamber to the suction opening. The air-powder mixture is formed when the air is introduced into the powder receiving chamber through the air intake path. The air-powder mixture is then transmitted from the powder receiving chamber to the suction opening via the air-powder mixture path.

[0003] There are several types of powders different in aerodynamic mean particle diameter as follows: a powder having the aerodynamic mean particle diameter of not less than 7 μm and depositing in an oral cavity or hypoglottis, a powder having the aerodynamic mean particle diameter of 5-7 μm and depositing in a throat, a powder having the aerodynamic mean particle diameter of 3-5 μm and depositing in a trachea, a powder having the aerodynamic mean particle diameter of 1-3 μm and depositing in bronchi, and a powder having the aerodynamic mean particle diameter of not more than 1 μm and depositing into alveoli, and the like. The powder having the aerodynamic mean particle diameter of not more than 3 μm is required to surely reach affected areas of the human body. Also, the powder such as an acrid powder is preferably dosed in several parts upon being inhaled.

[0004] In addition, there has been proposed powder tobacco for use with the inhalator. The powder tobacco can be substituted for a usual smoking tobacco because the powder tobacco provides a smoking feeling upon being inhaled. When the powder tobacco is used, one dose of the powder tobacco is dispensed in parts from the inhalator upon each inhalation.

[0005] The human bronchi and alveoli exist in deeper portions of the human body. Therefore, in order to ensure stable deposit of the powder having the particle diameter of not more than 3 μm in the bronchi and alveoli, it is preferable to dose the powder in parts, i.e., dispense a small amount of the powder each inhalation.

[0006] However, in the earlier technique, the whole amount of the powder received within the powder receiving chamber of the inhalator is dispensed from the inhalator by the inhalation substantially at one time. If a dose of the powder having the particle diameter of not more than 3 μm is inhaled through the inhalator upon inhalation, a large amount of the powder dosed will be deposited in the oral cavity or trachea before being deposited in the bronchi and alveoli.

[0007] Further, there is known a process for administering a particulate medicament having a specific mean particle diameter into a patient's lungs upon the patient breathing. International Publication No. WO97/36574 discloses a process and device for inhalation of particulate medicament. The process includes (i) providing an inhalator which contains at least one dose of medicament particles comprising spherical hollow particulates of respirable particle size suitable for deposition in a human lungs, and (ii) removing the spherical hollow particulates from the inhalator. In the earlier technique, the particulate medicament having the specific particle diameter is used with the inhalator, but there is not described inhalation on multi-purpose prescription, for instance, one-time inhalation of multiple particulate medicaments for the purpose of simultaneous deposition in different portions such as the trachea and the alveoli of the patient's body. In order to follow the multi-purpose prescription, it is required that the patient repeatedly inhales separate doses of particulate medicaments for different prescriptions, takes a specific particulate medicament formulated for the multi-purpose prescription, or is treated with the combination of various prescriptions including peroral medicament, injection, application of fomentation, and the like.

SUMMARY OF THE INVENTION

[0008] It is an object of the present invention to provide an inhalator capable of dispensing one dose of a powder or powder composition in parts therefrom.

[0009] It is another object of the present invention to provide a powder composition containing powders different in particle diameter from each other and a process for administering the powder composition using inhalators, which are suitable for simultaneous deposition in different portions of the human body by one-time inhalation.

[0010] According to one aspect of the present invention, there is provided an inhalator for administering an air-powder mixture, comprising:

an inhalator body including an air intake path for introducing air into the inhalator body, and an air-powder mixture outlet for discharging the air-powder mixture from the inhalator body;

a powder receiving chamber adapted to receive a powder, the powder receiving chamber being disposed within the inhalator body and communicated with an outside of the inhalator body through the air

intake path;
an air-powder mixture path adapted to transmit the air-powder mixture flowing from the powder receiving chamber to the air-powder mixture outlet;
an air-powder mixture reservoir adapted to temporarily store the air-powder mixture flowing from the powder receiving chamber, the air-powder mixture reservoir being disposed within the air-powder mixture path; and
a diluent air passage adapted to introduce a diluent air into the air-powder mixture reservoir, the diluent air passage communicating the air-powder mixture reservoir with the outside of the inhalator body.

[0011] According to a further aspect of the present invention, there is provided an inhalator for administering an air-powder mixture, comprising:

a casing including an air intake inlet for introducing air into the casing, and an air-powder mixture outlet for discharging the air-powder mixture from the casing;
powder receiving means for receiving a powder within the casing and permitting the powder to be admixed with the air introduced from the air intake inlet;
air-powder mixture storing means for temporarily storing the air-powder mixture passing through the powder receiving means;
diluent air passage means for permitting a diluent air to flow into the air-powder mixture storing means; and
air-powder mixture path means for permitting the air-powder mixture to flow from the powder receiving means to the air-powder mixture outlet via the air-powder mixture storing means.

[0012] According to another aspect of the present invention, there is provided a powder composition for use with an inhalator, comprising:

at least two kinds of fine particles selected from a first kind of fine particles having an aerodynamic mean particle diameter of not less than 7 μm, a second kind of fine particles having an aerodynamic mean particle diameter of 5-7 μm, a third kind of fine particles having an aerodynamic mean particle diameter of 3-5 μm, a fourth kind of fine particles having an aerodynamic mean particle diameter of 1-3 μm, and a fifth kind of fine particles having an aerodynamic mean particle diameter of not more than 1 μm.

[0013] According to a further aspect of the present invention, there is provided a process for administering a powder composition using an inhalator, comprising:

preparing the powder composition containing at least two kinds of fine particles selected from a first kind of fine particles having an aerodynamic mean particle diameter of not less than 7 μm, a second kind of fine particles having an aerodynamic mean particle diameter of 5-7 μm, a third kind of fine particles having an aerodynamic mean particle diameter of 3-5 μm, a fourth kind of fine particles having an aerodynamic mean particle diameter of 1-3 μm, and a fifth kind of fine particles having an aerodynamic mean particle diameter of not more than 1 μm;
supplying the powder composition to the inhalator; and
discharging the powder composition from the inhalator.

[0014] The other objects and features of this invention will become understood from the following description with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015]

Fig. 1 is an elevation of an inhalator of a preferred embodiment, according to the present invention;
Fig. 2 is a longitudinal section of the inhalator, taken along the line 2-2 of Fig. 1, showing a rest position of the inhalator;
Fig. 3 is an enlarged section of the inhalator, taken along the line 3-3 of Fig. 2;
Fig. 4 is an enlarged section of the inhalator, taken along the line 4-4 of Fig. 2;
Fig. 5 is an enlarged section of the inhalator, taken along the line 5-5 of Fig. 2; and
Fig. 6 is a view similar to Fig. 2, but showing a use position of the inhalator.

DETAILED DESCRIPTION OF THE INVENTION

[0016] Referring to Figs. 1-6, an inhalator, according to the present invention, of a preferred embodiment is explained.

[0017] As illustrated in Fig. 1, the inhalator includes an inhalator body 1 as a casing which is formed into a cylindrical shape. Inhalator body 1 is made of a suitable resin material such as polypropylene, polystyrene, ABS resin and the like. Inhalator body 1 is constituted of cap 3, suction body 4 and capsule body 2 interposed between cap 3 and suction body 4. Cap 3 has air intake inlet 7A shown in Fig. 2, through which an ambient air is introduced into cap 3 and flows toward capsule body 2 and suction body 4 as explained later. Cap 3 has a length shorter than that of capsule body 2 and is rotatably connected with an upstream side of capsule body 2. Suction body 4 has air-powder mixture outlet 18 shown in Fig. 2, from which an air-powder mixture formed in inhalator body 1 is discharged into a user's

oral cavity. Suction body 4 has a length longer than that of capsule body 2 and is rotatably connected with a downstream side of capsule body 2.

[0018] As illustrated in Fig. 2, capsule body 2 has engaging projection 2A and engaging groove 2A1 on the upstream end portion. Engaging projection 2A and engaging groove 2A1 axially adjacent thereto are engaged with engaging tube portion 3A and engaging projection 3A1 of cap 3, respectively. Capsule body 2 is coupled with cap 3 by the engagement of engaging projection 2A and engaging groove 2A1 with engaging tube portion 3A and engaging projection 3A1, respectively. Capsule body 2 also has at the downstream end portion, engaging projection 2B and engaging groove 2B1 axially adjacent thereto. Engaging projection 2B and engaging groove 2B1 are engaged with engaging tube portion 4A and engaging projection 4A1 of suction body 4, respectively. Capsule body 2 is coupled with suction body 4 by the engagement of engaging projection 2B and engaging groove 2B1 with engaging tube portion 4A and engaging projection 4A1, respectively.

[0019] Cocoon-shaped powder receiving chamber 5 is substantially coaxially disposed within capsule body 2. Powder receiving chamber 5 is provided for receiving a dose of a powder or powder composition such as particulate medicament, powder tobacco or the like. Powder receiving chamber 5 is in communication with the outside of inhalator body 1 through air intake path 6, when the inhalator is in a use position as explained later by referring to Fig. 6. The air-powder mixture is formed within powder receiving chamber 5 when the air flows into powder receiving chamber 5 via air intake path 6 in the use position of the inhalator.

[0020] Air intake path 6 is provided for introducing the air into powder receiving chamber 5. Air intake path 6 includes upstream intake passage 7 formed in cap 3 and downstream intake passage 8 formed in capsule body 2. Upstream intake passage 7 has an upstream end opening as air intake inlet 7A which is open to a generally central portion of an axial end face of cap 3. Upstream intake passage 7 has a downstream end opening that is open to a bottom of engaging tube portion 3A which mates with an axial end face of engaging projection 2A, in an offset position relative to the center axis of cap 3. Downstream intake passage 8 has an upstream end opening that is open to the axial end face of engaging projection 2A in an offset position relative to the center axis of capsule body 2. Downstream intake passage 8 has a downstream end opening that is open to an upstream end portion of powder receiving chamber 5 and in substantially alignment with the center axis of capsule body 2.

[0021] Capsule body 2 and cap 3 are relatively rotatable to be placed in a non-communication position shown in Fig. 2 and a communication position shown in Fig. 6. In the non-communication position, the downstream end opening of upstream intake passage 7 and the upstream end opening of downstream intake passage 8 are out of alignment with each other. Fluid communication between upstream intake passage 7 and downstream intake passage 8 is blocked so that powder receiving chamber 5 is prevented from being fluidly communicated with the outside of the inhalator. On the other hand, in the communication position, the downstream end opening of upstream intake passage 7 and the upstream end opening of downstream intake passage 8 are in alignment with each other. The fluid communication between upstream intake passage 7 and downstream intake passage 8 is established so that powder receiving chamber 5 is fluidly communicated with the outside of the inhalator. The opening area at the connection of upstream intake passage 7 and downstream intake passage 8 may be desirably regulated by adjusting the alignment of intake passages 7 and 8 to thereby control a flow amount of the air introduced into powder receiving chamber 5 and therefore control an amount of the powder in the air-powder mixture flowing from powder receiving chamber 5 toward air-powder mixture outlet 18.

[0022] Air-powder mixture path 9 extends between powder receiving chamber 5 and air-powder mixture outlet 18. Air-powder mixture path 9 permits the air-powder mixture to flow from powder receiving chamber 5 to air-powder mixture outlet 18 when the inhalator is in the use position.

[0023] First air-powder mixture reservoir 12 is disposed within air-powder mixture path 9. Air-powder mixture reservoir 12 is disposed in substantially coaxial with suction body 4. Air-powder mixture reservoir 12 is adapted to be communicated with powder receiving chamber 5 through discharge passage 10 and connecting passage 11 of air-powder mixture path 9. Air-powder mixture reservoir 12 has a cocoon shape having a volumetric capacity greater than a volumetric capacity of connecting passage 11. Air-powder mixture reservoir 12 having the greater volumetric capacity allows the air-powder mixture flowing thereinto through connecting passage 11 to be temporarily stored.

[0024] Discharge passage 10 is formed in capsule body 2 so as to be open to powder receiving chamber 5 at the upstream end and to engaging projection 2B at the downstream end. An upstream end opening of discharge passage 10 is open to a downstream end portion of powder receiving chamber 5 and in substantially alignment with the center axis of capsule body 2. A downstream end opening of discharge passage 10 is open to an axial end face of engaging projection 2B in an offset position relative to the center axis of capsule body 2. Connecting passage 11 is formed in suction body 4 so as to be open to engaging tube portion 4A at the upstream end and to air-powder mixture reservoir 12 at the downstream end. An upstream end opening of connecting passage 11 is open to a bottom of engaging tube portion 4A which mates with the axial end face of engaging projection 2B, in an offset position relative to the center axis of suction body 4. A downstream end

opening of connecting passage 11 is open to an upstream end portion of air-powder mixture reservoir 12 and in substantially alignment with the center axis of suction body 4. Capsule body 2 and suction body 4 are relatively rotatable so as to be placed in a non-communication position shown in Fig. 2 and a communication position shown in Fig. 6. In the non-communication position, the downstream end opening of discharge passage 10 and the upstream end opening of connecting passage 11 are out of alignment with each other so that fluid communication between discharge passage 10 and connecting passage 11 is blocked. Powder receiving chamber 5 is prevented from being fluidly communicated with air-powder mixture reservoir 12. On the contrary, in the communication position, the downstream end opening of discharge passage 10 and the upstream end opening of connecting passage 11 are in alignment with each other. The fluid communication between discharge passage 10 and connecting passage 11 is established so that powder receiving chamber 5 is fluidly communicated with the air-powder mixture reservoir 12. The opening area at the connection of discharge passage 10 and connecting passage 11 may be desirably regulated by adjusting the alignment of discharge passage 10 and connecting passage 11 to thereby control an amount of the air-powder mixture flowing from powder receiving chamber 5 into air-powder mixture reservoir 12.

[0025] First diluent air passage 19 is formed in suction body 4 and communicated with air-powder mixture reservoir 12. Diluent air passage 19 introduces a diluent air into air-powder mixture reservoir 12 when the air-powder mixture flows from powder receiving chamber 5 into air-powder mixture reservoir 12. The diluent air introduced is merged in the air-powder mixture within air-powder mixture reservoir 12 to thereby dilute the air-powder mixture. The diluted air-powder mixture flowing from air-powder mixture reservoir 12 has a reduced flow rate and a decreased mixing ratio of the powder relative to the air which are present in the diluted air-powder mixture. Diluent air passage 19 is constituted of four passages arranged in crossed manner in lateral section in this embodiment as shown in Fig. 3. As illustrated in Fig. 3, each of four diluent air passages 19 has an inlet open to an outer circumferential surface of suction body 4 and an outlet open to a circumferential surface of air-powder mixture reservoir 12.

[0026] Second air-powder mixture reservoir 14 is disposed within air-powder mixture path 9 downstream of first air-powder mixture reservoir 12. Air-powder mixture reservoir 14 is disposed in substantially coaxial relation to suction body 4. Air-powder mixture reservoir 14 is communicated with air-powder mixture reservoir 12 through communication passage 13 of connecting passage 11 which extends in the axial direction of suction body 4. Air-powder mixture reservoir 14 has a bell shape having a volumetric capacity greater than a volumetric capacity of communication passage 13 when viewed in axial cross-section. Air-powder mixture reservoir 14 with the greater volumetric capacity allows the air-powder mixture flowing thereinto through communication passage 13 to be temporarily stored.

[0027] Dispersion part 15 is disposed within air-powder mixture path 9 downstream of second air-powder mixture reservoir 14. Dispersion part 15 is adapted to prevent the powder in the air-powder mixture flowing from second air-powder mixture reservoir 14 from aggregating together and intimately mix the powder and the air to form a uniform air-powder mixture. Dispersion part 15 includes dispersion chamber 17 and a plurality of dispersion passages 16 connected with dispersion chamber 17. Dispersion passages 16, four passages in this embodiment, connect dispersion chamber 17 with air-powder mixture reservoir 14. Each of dispersion passages 16 has an inlet open to air-powder mixture reservoir 14 and an outlet open to dispersion chamber 17. Specifically, dispersion passage 16 includes an inlet passage portion extending from an outer peripheral portion of air-powder mixture reservoir 14 in the axial direction of suction body 4. Dispersion passage 16 also includes outlet passage portion 16A that radially inwardly extends from a downstream side of the inlet passage portion and is open to an upstream end portion of dispersion chamber 17. As illustrated in Fig. 4, dispersion chamber 17 has a generally circular-shaped section and outlet passage portion 16A extends in a tangential direction of dispersion chamber 17. The air-powder mixture flowing into dispersion chamber 17 through dispersion passages 16 forms a swirl flow within dispersion chamber 17. The swirl flow of the air-powder mixture prevents the powder in the air-powder mixture from forming an aggregated mass of the powder.

[0028] Second diluent air passage 20 is formed within suction body 4 in communication with dispersion chamber 17. As seen from Figs. 2 and 5, four diluent air passages 20 radially extend from grooved portion 4B on an outer surface of suction body 4 to dispersion chamber 17. Grooved portion 4B extends along the entire circumference of the outer surface of suction body 4. Diluent air passages 20 introduce the ambient air as a diluent air into dispersion chamber 17 when the air-powder mixture within dispersion chamber 17 is directed toward outlet 18 by the user's suction.

[0029] Regulator 21 for variably controlling a flow amount of the diluent air introduced into dispersion chamber 17 via diluent air passages 20 is axially moveably disposed on grooved portion 4B of suction body 4. Regulator 21 is in the form of a ring in this embodiment. Regulator 21 has four regulator holes 21A coming into alignment with diluent air passages 20 by the axial movement of the regulator 21. Regulator 21 variably regulates an opening area of each of diluent air passages 20 to thereby variably control the flow amount of the diluent air which is merged in the air-powder mixture within dispersion chamber 17.

[0030] The air-powder mixture passing through dis-

persion passages 16 and dispersion chamber 17 flows to air-powder mixture outlet 18 from which the air-powder mixture is dispensed into the user's oral cavity. Air-powder mixture outlet 18 is communicated with dispersion chamber 17 and open to one axial end surface of suction body 4. Air-powder mixture outlet 18 is disposed substantially coaxially with the center axis of suction body 4.

[0031] Referring back to Fig. 1, counter or registration marks 22, 22, 22 are formed on the upstream and downstream end portions of the outer circumferential surface of capsule body 2, downstream engaging tube portion 3A of cap 3, and upstream engaging tube portion 4A of suction body 4, respectively. When counter mark 22 on the upstream-end side of capsule body 2 is aligned with counter mark 22 on the downstream-end side of cap 3, upstream and downstream intake passages 7 and 8 of air intake path 6 are communicated with each other. When counter mark 22 on the downstream-end side of capsule body 2 is aligned with counter mark 22 on the upstream-end side of suction body 4, discharge passage 10 and connecting passage 11 of air-powder mixture path 9 are communicated with each other.

[0032] An operation of the thus-constructed inhalator of the present invention will be explained hereinafter.

[0033] When the inhalator is in a rest or nonuse position shown in Fig. 2, upstream and downstream intake passages 7 and 8 of air intake path 6 are fluidly disconnected from each other and discharge passage 10 and connecting passage 11 of air-powder mixture path 9 are fluidly disconnected from each other. In this state, powder receiving chamber 5 is prevented from being fluidly communicated with the outside of inhalator body 1 and air-powder mixture reservoir 12. Thus, if the inhalator is in the rest position, the powder received within powder receiving chamber 5 can be restrained from flowing therefrom and inhalator body 1 when the user carries the inhalator.

[0034] Next, upon using the inhalator, cap 3 and suction body 4 are rotated relative to capsule body 2 to align respective counter marks 22 with each other. Regulator 21 is axially moved in grooved portion 4B so as to desirably adjust the opening area of second diluent air passage 20. The inhalator is thus placed in a use position shown in Fig. 6. In the use position, upstream and downstream intake passages 7 and 8 of air intake path 6 are fluidly connected with each other and discharge passage 10 and connecting passage 11 of air-powder mixture path 9 are fluidly connected with each other. Powder receiving chamber 5 is allowed to be in fluid communication with the outside of inhalator body 1 and air-powder mixture reservoir 12. In this state, air-powder mixture outlet 18 of inhalator body 1 is put into the user's oral cavity and the ambient air is sucked by the user. The air is introduced into air intake path 6 through air intake inlet 7A. The air then flows into powder receiving chamber 5 as indicated by arrows in Fig. 6. The introduced air is admixed with the dose of the powder within powder receiving chamber 5, forming the air-powder mixture. The air-powder mixture flows into first air-powder mixture reservoir 12 via discharge passage 10 and connecting passage 11 of air-powder mixture path 9. The air-powder mixture is temporarily stored within air-powder mixture reservoir 12 and admixed with the diluent air introduced through diluent air passage 19. The thus diluted air-powder mixture has a decreased flow rate flowing into communication passage 13, and a reduced mixing ratio of the powder in the diluted air-powder mixture to the air in the diluted air-powder mixture.

[0035] The diluted air-powder mixture within first air-powder mixture reservoir 12 flows into second air-powder mixture reservoir 14 via communication passage 13 and then enters into dispersion chamber 17 via dispersion passages 16. There occurs a swirl flow of the diluted air-powder mixture within dispersion chamber 17. The swirl flow atomizes an aggregated mass of the powder which remains in dispersion chamber 17, to thereby assure the air-powder mixture containing fine particles of the powder in a suitably dispersed state. The air-powder mixture within dispersion chamber 17 is diluted by the diluent air introduced thereinto through second diluent air passage 20 and regulator holes 21A of regulator 21. The thus diluted air-powder mixture then is discharged from air-powder mixture outlet 18 into the user's oral cavity.

[0036] As be appreciated from the above explanation, the air-powder mixture flowing from powder receiving chamber 5 is diluted within air-powder mixture reservoir 12 by the diluent air introduced into air-powder mixture reservoir 12 through diluent air passage 19. A flow rate of the air-powder mixture is reduced within air-powder mixture reservoir 12 by the introduction of the diluent air. As a result, a part of the dose of the powder received within powder receiving chamber 5 is sucked by one-time inhalation by the user. Therefore, the dose of the powder received within powder receiving chamber 5 can be divided into a plurality of dose parts each being sucked by the user. Thus, the user can suck a small amount of the powder that forms each dose part, by one-time inhalation. If it is required to deposit fine particulate medicament having a small particle diameter in the bronchi or alveoli of a patient, a dose of the medicament can be dispensed in parts which are inhaled by multiple-time inhalation of the user through the inhalator of the invention. The fine particulate medicament can be prevented from being deposited in the trachea and be stably deposited in the bronchi or alveoli by multiple-time inhalation of the dose parts. The inhalator of the invention can be effectively used for dispensing a dose of a powder or powder composition such as particulate medicament and powder tobacco, in parts by multiple-time inhalation.

[0037] Further, with the arrangement of second diluent air passage 20 and regulator 21 for regulating the opening area of diluent air passage 20, an amount of the diluent air introduced into dispersion chamber 17

can be desirably regulated by axially moving regulator 21. A mixing ratio between the powder and the air present in the air-powder mixture within dispersion chamber 17 can be readily controlled by the regulation of the diluent air to be introduced. Accordingly, an amount of the powder which is sucked by one-time inhalation by the user, can be desirably controlled using regulator 21 depending on the user's liking, kinds of particulate medicaments, or the like. This can improve a performance of the inhalator. The amount of the powder for one-time inhalation may be controlled by regulating the opening area at the connection of upstream and downstream intake passages 7 and 8 of air intake path 6 or the opening area at the connection of discharge passage 10 and connecting passage 11 of air-powder mixture path 9.

[0038] Furthermore, with the arrangement of dispersion passages 16 and dispersion chamber 17 at dispersion part 15, the swirl flow of the air-powder mixture can be produced within dispersion chamber 17,-which atomizes an aggregated mass of the powder remaining in dispersion chamber 17 and forms the air-powder mixture containing the powder particles in a good dispersed state. This can improve a dispersion efficiency of the inhalator.

[0039] Further, upstream and downstream intake passages 7 and 8 of air intake path 6 is arranged to establish and block the fluid communication between powder receiving chamber 5 and the outside of inhalator body 1. When the inhalator is in the nonuse position, upstream and downstream intake passages 7 and 8 are disconnected from each other so that the fluid communication between powder receiving chamber 5 and the outside of inhalator body 1 is blocked. In addition, discharge passage 10 and connecting passage 11 of air-powder mixture path 9 is arranged to allow and block the fluid communication between powder receiving chamber 5 and first air-powder mixture reservoir 12. In the nonuse position of the inhalator, discharge passage 10 and connecting passage 11 are disconnected from each other so that the fluid communication between powder receiving chamber 5 and first air-powder mixture reservoir 12 is blocked. With this arrangement of intake passages 7 and 8 and discharge passage 10 and connecting passage 11, the powder received within powder receiving chamber 5 can be prevented from flowing therefrom toward both air intake inlet 7A and air-powder mixture reservoir 12 upon the user carrying the inhalator. This can improve reliability of the inhalator. Further, when intake passages 7 and 8 are communicated with each other upon using the inhalator, the opening area of the connection of intake passages 7 and 8 can be regulated to control the flow amount of the air flowing into powder receiving chamber 5. Therefore, the amount of the powder present in the air-powder mixture produced within powder receiving chamber 5 can be adjusted. Similarly, upon communication of discharge passage 10 and connecting passage 11, the opening area of the connection thereof can be regulated to control the flow amount of the air-powder mixture flowing from powder receiving chamber 5 into air-powder mixture reservoir 12. The amount of the powder in the air-powder mixture flowing from air-powder mixture reservoir 12 toward air-powder mixture outlet 18 can be adjusted, and therefore, the amount of the powder to be sucked can be adjusted.

[0040] Although two air-powder mixture reservoirs 12 and 14 are provided within suction body 4 in this embodiment, a single air-powder mixture reservoir or three or more air-powder mixture reservoirs may be provided.

[0041] In addition, a capsule chamber for storing a capsule having a dose of the powder may be substituted for powder receiving chamber 5. In this case, the capsule within the capsule chamber may be pierced using a piercing device upon inhalation.

[0042] Further, a shutter member may be provided for blocking and allowing the fluid communication between powder receiving chamber 5 and the outside of inhalator body 1 and air-powder mixture reservoir 12, instead of the arrangement of upstream and downstream intake passages 7 and 8 of air intake path 6 and discharge passage 10 and connecting passage 11 of air-powder mixture path 9. The shutter member may be rotatably or slidably disposed within air intake path 6 extending between powder receiving chamber 5 and air intake inlet 7A and the portion of air-powder mixture path 9 which extends between powder receiving chamber 5 and air-powder mixture reservoir 12.

[0043] Furthermore, either one of the upstream end portion of capsule body 2 and engaging tube portion 3A of cap 3 may have on the outer circumferential surface a groove circumferentially extending within a predetermined angular region. The other may have on the outer circumferential surface a projection engageable with the groove such that both capsule body 2 and cap 3 are rotatably moveable to each other in the predetermined angular region. A similar circumferentially extending groove may be formed on either one of the outer circumferential surface of the downstream end portion of capsule body 2 and the outer circumferential surface of engaging tube portion 4A of suction body 4, and a similar projection may be formed on the other thereof. If the projections reach the respective ends of the grooves, the communication between upstream and downstream intake passages 7 and 8 and the communication between discharge passage 10 and connecting passage 11 will be established. In this case, counter marks 22 can be omitted.

[0044] Next, a powder composition for use with inhalators and a process for administering the powder composition using inhalators, according to the present invention, will be explained hereinafter.

[0045] The powder composition is suitable to be administered from an oral or nasal cavity for deposition in inside parts of the human body. The powder composition includes at least two kinds of fine particles selected

from a group consisting of a first kind of fine particle having an aerodynamic mean particle diameter of not less than 7 μm, a second kind of fine particle having an aerodynamic mean particle diameter of 5-7 μm, a third kind of fine particle having an aerodynamic mean particle diameter of 3-5 μm, a fourth kind of fine particle having an aerodynamic mean particle diameter of 1-3 μm, and a fifth kind of fine particle having an aerodynamic mean particle diameter of not more than 1 μm. The first kind of fine particle having the aerodynamic mean particle diameter of not less than 7 μm is deposited in an oral cavity or hypoglottis of a human body. The second kind of fine particle having the aerodynamic mean particle diameter of 5-7 μm is deposited in a throat of a human body. The third kind of fine particle having the aerodynamic mean particle diameter of 3-5 μm is deposited in a trachea of a human body. The fourth kind of fine particle having the aerodynamic mean particle diameter of 1-3 μm is deposited in bronchi of a human body. The fifth kind of fine particle having the aerodynamic mean particle diameter of not more than 1 μm is deposited in alveoli of a human body.

[0046] Preferably, the fine particles of the powder composition of the present invention have a significantly narrow particle size distribution. More preferably, the fine particles have the particle size distribution consistent with a predetermined range of an aerodynamic mean particle diameter which is required for deposition in the respective parts of the human body.

[0047] The powder composition may be powder tobacco and particulate medicament. The powder tobacco contains at least two kinds of fine particles selected from the first, third and fifth kinds of fine particles as described above. For instance, the powder tobacco may contain fine particles as a gustatory component which have the aerodynamic mean particle diameter of 45-55 μm for deposition in the oral cavity or hypoglottis, fine particles as a stimulatory component which have the aerodynamic mean particle diameter of 3-5 μm for deposition in the trachea or throat, and fine particles as an agent which have the aerodynamic mean particle diameter of 0.5-2 μm for deposition in the alveoli or bronchi. A coffee extract powder may be used for the fine particles as a gustatory component having the aerodynamic mean particle diameter of 45-55 μm. A menthol extract powder may be used for the fine particles as a stimulatory component having the aerodynamic mean particle diameter of 3-5 μm. A nicotine extract powder may be used for the fine particles as an agent having the aerodynamic mean particle diameter of 0.5-2 μm. If the powder tobacco is inhaled with the inhalator, the same taste, stimulus and nicotinic effect as those obtained by smoking can be obtained.

[0048] The particulate medicament as the powder composition of the present invention contains at least two kinds of fine particles selected from the first through fifth kinds of fine particles as described above. The particulate medicament may contain fine particles as a gustatory component which have the aerodynamic mean particle diameter of 60-80 μm for deposition in the oral cavity or hypoglottis, fine particles as an antiphlogistic agent which have the aerodynamic mean particle diameter of 4-6 μm for deposition in the trachea or throat, and fine particles as an agent which have the aerodynamic mean particle diameter of 1-3 μm for deposition in the alveoli or bronchi. A powdered troche or candy may be used for the fine particles as a gustatory component having the aerodynamic mean particle diameter of 60-80 μm. An antiphlogistic powder may be used for the fine particles as an antiphlogistic agent having the aerodynamic mean particle diameter of 4-6 μm. An antibiotic powder may be used for the fine particles as an agent having the aerodynamic mean particle diameter of 1-3 μm.

[0049] In addition, the particulate medicament as the powder composition of the present invention may be selected from an analgesic agent, an anginal preparation, an antiallergic agent, an anti-infective agent, an antihistaminic agent, an anti-inflammatory agent, an antitussive agent, a bronchodilator agent, a diuretic agent, an anticholinergic agent, and the like, depending on cure purposes. These powder agents may have various aerodynamic mean particle diameters suitable for deposition in different target parts of the human body.

[0050] If required, the particulate medicament as the powder composition of the present invention may be used together with a known excipient acceptable for inhalation into the human body. The composition of the particulate medicament is prepared in accordance with the doctor's prescription given on the basis of the patient's symptom.

[0051] In the administration process of the present invention, first the powder composition is prepared so as to contain at least two kinds of fine particles selected from the first to fifth kinds of fine particles as described above. The at least two kinds of fine particles of the powder composition may be blended together. The thus prepared powder composition is supplied to an inhalator suitable for dispensing a powder into the human body. The powder composition may be capsulated and then accommodated in the inhalator. Subsequently, the powder composition supplied is discharged from the inhalator. If the above-described inhalator of the present invention is used, the powder composition may be dispersed within the inhalator and then discharged therefrom without aggregation of the fine particles of the powder composition.

[0052] The powder composition and administration process of the present invention can be suitably used for cure of multiple diseases using the particulate medicaments which have effects on the multiple diseases, respectively. Specially, the powder composition and administration process of the present invention is suitable for providing analgesia and curing inflammation in the oral cavity and/or throat, asthma, bronchitis, COPD (chronic obstructive pulmonary disease), respiratory

disease such as thoracho-infection, and allergosis.

[0053] The inhalators useable in this embodiment are described in Japanese Patent Applications First Publication Nos. 62-41668 and 9-47509, Japanese Patent Application Second Publication No. 63-6024, and United States Patent No. 5,996,577.

EXAMPLES

[0054] The present invention is described in more detail by way of examples. However, these examples are only illustrative and not intended to limit a scope of the present invention thereto.

Example 1

[0055] A dose of a powder tobacco was prepared by blending 5 mg of coffee extract particulates having an aerodynamic mean particle diameter of 50 μm, 10 mg of menthol extract particulates having an aerodynamic mean particle diameter of 4 μm, and 1 mg of nicotine extract particulates having an aerodynamic mean particle diameter of 0.5-2 μm together. The thus prepared dose of a powder tobacco was supplied to a suitable inhalator as described above and then discharged from the inhalator.

Example 2

[0056] A dose of a particulate medicament mixture was prepared by blending candy particles having an aerodynamic mean particle diameter of 70 μm, antiphlogistic agent particles having an aerodynamic mean particle diameter of 5 μm, antibiotic agent particles having an aerodynamic mean particle diameter of 2 μm together in accordance with a doctor's prescription. The thus prepared dose of a particulate medicament mixture was filled in a capsule. The thus capsulated dose of a particulate medicament mixture was accommodated in a suitable inhalator as described above and then discharged from the inhalator.

[0057] Using the powder composition and the administration process of the present invention, a dose of the powder composition containing the at least two kinds of fine particulates different in mean particle diameter from each other can be selected depending on the target parts of the human body in which the powder composition is required to be deposited, and can be deposited in the target parts by one-time inhalation using the inhalator. Namely, multi-purpose dosage of particulate medicaments, for instance, deposition of the particulate medicaments in both of the trachea and the alveoli or all of the throat, the bronchi and the alveoli, can be achieved during the one-time inhalation.

[0058] Further, using the powder composition and the administration process of the present invention, the patient can dispense with multiple times of inhalation for dosing a plurality of particulate medicaments required in different prescriptions. Also, any specific compound of particulate medicaments may not be required for multi-purpose prescription.

[0059] Furthermore, in a case where the capsulated powder composition of particulate medicaments having different mean particle diameters is used, the patient can dispense with adjusting the amount of the powder composition required for each inhalation and the mixing ratio of the different kinds of particulate medicaments.

[0060] The entire contents of basic Japanese Patent Applications Nos. 2000-363636 filed on November 29, 2000, and 2000-359822 filed on November 27, 2000, inclusive of the specification, claims and drawings, are herein incorporated by reference.

[0061] Although the invention has been described above by reference to certain embodiments of the invention, the invention is not limited to the embodiments described above. Modifications and variations of the embodiment described above will occur to those skilled in the art, in light of the above teachings. The scope of the invention is defined with reference to the following claims.

Claims

1. An inhalator for administering an air-powder mixture, comprising:

   an inhalator body including an air intake path for introducing an air into the inhalator body, and an air-powder mixture outlet for discharging the air-powder mixture from the inhalator body;

   a powder receiving chamber adapted to receive a powder, the powder receiving chamber being disposed within the inhalator body and communicated with an outside of the inhalator body through the air intake path;

   an air-powder mixture path adapted to transmit the air-powder mixture flowing from the powder receiving chamber to the air-powder mixture outlet;

   an air-powder mixture reservoir adapted to temporarily store the air-powder mixture flowing from the powder receiving chamber, the air-powder mixture reservoir being disposed within the air-powder mixture path; and

   a diluent air passage adapted to introduce a diluent air into the air-powder mixture reservoir, the diluent air passage communicating the air-powder mixture reservoir with the outside of the inhalator body.

2. The inhalator as claimed in claim 1, further comprising a second diluent air passage adapted to introduce a diluent air into the air-powder mixture path downstream of the air-powder mixture reservoir up-

on the air-powder mixture flowing from the air-powder mixture reservoir, and a regulator variably controlling an opening area of the second diluent air passage.

3. The inhalator as claimed in claim 1, further comprising a dispersion part adapted to disperse the powder in the air-powder mixture passing through the air-powder mixture path downstream of the air-powder mixture reservoir.

4. The inhalator as claimed in claim 3, wherein the dispersion part comprises a plurality of dispersion passages branched from the air-powder mixture path downstream of the air-powder mixture reservoir, and a dispersion chamber disposed within the air-powder mixture path downstream of the dispersion passages, each of the dispersion passages having an outlet passage portion that is open into the dispersion chamber and arranged to form a swirl flow of the air-powder mixture.

5. The inhalator as claimed in claim 4, wherein the dispersion chamber has a generally circular-shaped section and the outlet passage portion of each of the dispersion passages extends in a tangential direction of the dispersion chamber.

6. The inhalator as claimed in claim 1, wherein the air intake path is arranged to allow and block fluid communication between the powder receiving chamber and the outside of the inhalator body.

7. The inhalator as claimed in claim 6, wherein the air intake path comprises at least two passages having an alignment position where the at least two passages are in alignment with each other and an offset position where the at least two passages are out of alignment with each other.

8. The inhalator as claimed in claim 1, wherein the air-powder mixture path is arranged to allow and block fluid communication between the powder receiving chamber and the air-powder mixture reservoir.

9. The inhalator as claimed in claim 8, wherein the air-powder mixture path comprises at least two passages disposed between the powder receiving chamber and the air-powder mixture reservoir, the plurality of passages having an alignment position where the at least two passages are aligned with each other and an offset position where the at least two passages are offset from each other.

10. The inhalator as claimed in claim 4, further comprising a second air-powder mixture adapted to temporarily store the air-powder mixture flowing from the first air-powder mixture reservoir toward the dispersion passages of the dispersion part.

11. The inhalator as claimed in claim 10, wherein each of the dispersion passages comprises an inlet open into the second air-powder mixture reservoir.

12. An inhalator for administering an air-powder mixture, comprising:

a casing including an air intake inlet for introducing an air into the casing, and an air-powder mixture outlet for discharging the air-powder mixture from the casing;
powder receiving means for receiving a powder within the casing and permitting the powder to be admixed with the air introduced from the air intake inlet;
air-powder mixture storing means for temporarily storing the air-powder mixture passing through the powder receiving means;
diluent air passage means for permitting a diluent air to flow into the air-powder mixture storing means; and
air-powder mixture path means for permitting the air-powder mixture to flow from the powder receiving means to the air-powder mixture outlet via the air-powder mixture storing means.

13. The inhalator as claimed in claim 12, further comprising air intake path means for permitting the air to flow from the air intake inlet into the powder receiving means.

14. The inhalator as claimed in claim 12, wherein the air-powder mixture path means allows and blocks fluid communication between the powder receiving means and the air-powder mixture storing means.

15. The inhalator as claimed in claim 12, further comprising a second diluent air passage means for permitting a diluent air to flow into the air-powder mixture path means downstream of the air-powder mixture storing means upon the air-powder mixture flowing from the air-powder mixture storing means.

16. The inhalator as claimed in claim 15, further comprising a regulator variably controlling an opening area of the second diluent air passage means.

17. The inhalator as claimed in claim 12, further comprising dispersion means for preventing the powder in the air-powder mixture from being aggregated together.

18. The inhalator as claimed in claim 17, wherein the dispersion means comprises passages means for forming a swirl flow of the air-powder mixture and chamber means for receiving the swirl flow of the

air-powder mixture.

19. The inhalator as claimed in claim 18, wherein the chamber means has a generally circular-shaped section and the passage means extends in a tangential direction of the chamber means.

20. A powder composition for use with an inhalator, comprising:

at least two kinds of fine particles selected from a first kind of fine particles having an aerodynamic mean particle diameter of not less than 7 μm, a second kind of fine particles having an aerodynamic mean particle diameter of 5-7 μm, a third kind of fine particles having an aerodynamic mean particle diameter of 3-5 μm, a fourth kind of fine particles having an aerodynamic mean particle diameter of 1-3 μm, and a fifth kind of fine particles having an aerodynamic mean particle diameter of not more than 1 μm.

21. The powder composition as claimed in claim 20, wherein the powder composition comprises powder tobacco.

22. The powder composition as claimed in claim 20, wherein the powder composition comprises particulate medicament.

23. A process for administering a powder composition using an inhalator, comprising:

preparing the powder composition containing at least two kinds of fine particles selected from a first kind of fine particles having an aerodynamic mean particle diameter of not less than 7 μm, a second kind of fine particles having an aerodynamic mean particle diameter of 5-7 μm, a third kind of fine particles having an aerodynamic mean particle diameter of 3-5 μm, a fourth kind of fine particles having an aerodynamic mean particle diameter of 1-3 μm, and a fifth kind of fine particles having an aerodynamic mean particle diameter of not more than 1 μm;
supplying the powder composition to the inhalator; and
discharging the powder composition from the inhalator.

24. The process as claimed in claim 23, wherein the discharging comprises dispersing the powder composition within the inhalator.

25. The process as claimed in claim 23, further comprising capsulating the powder composition.

26. The process as claimed in claim 23, wherein the powder composition comprises powder tobacco.

27. The process as claimed in claim 23, wherein the powder composition comprises particulate medicament.

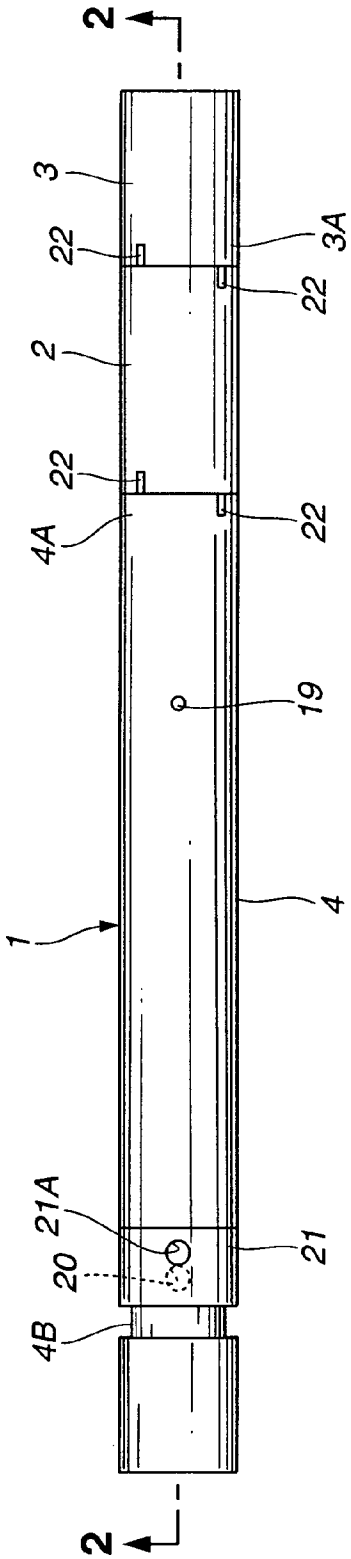


FIG.1

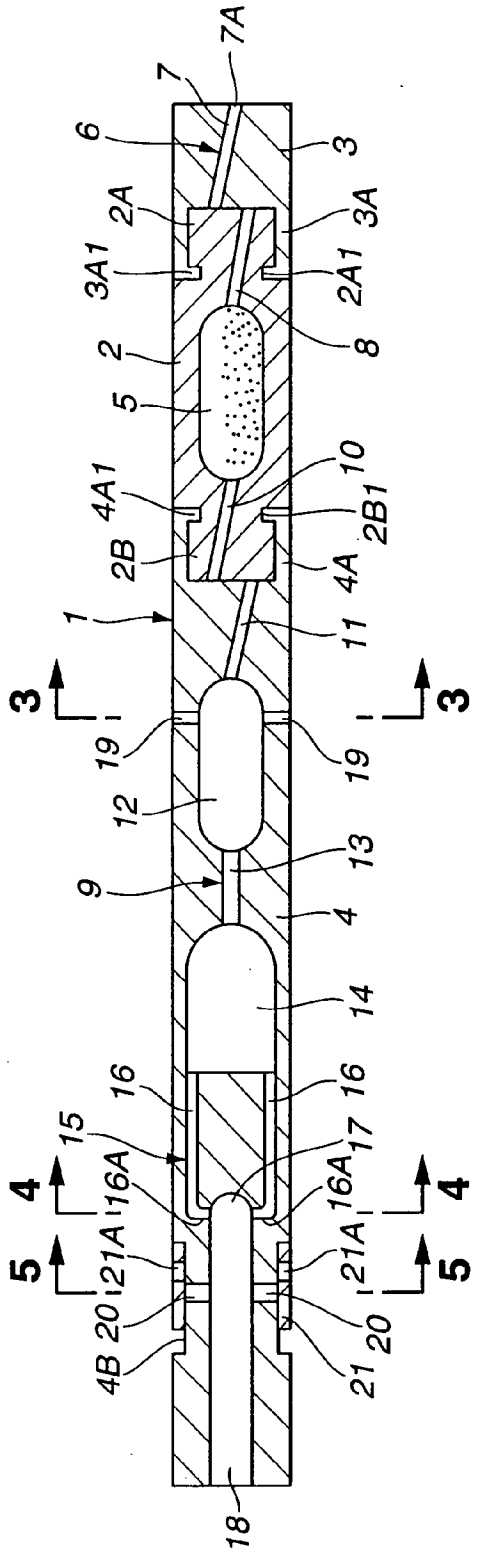


FIG.2

FIG.3

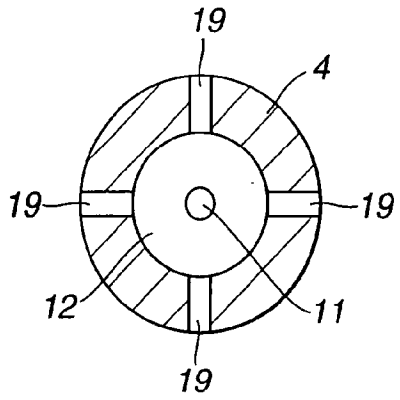


FIG.4

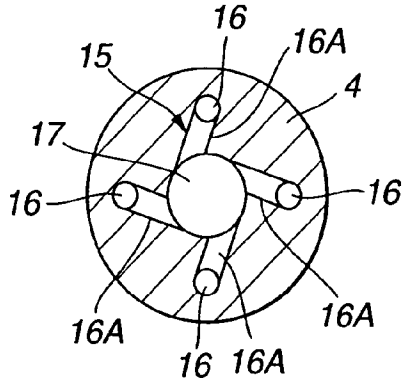
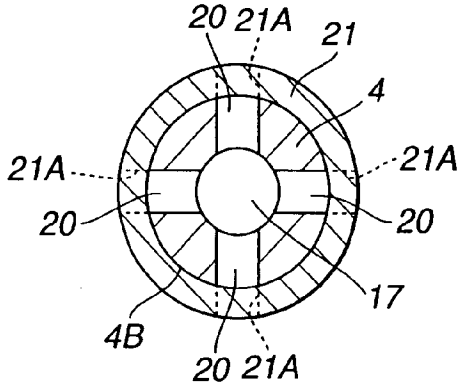


FIG.5



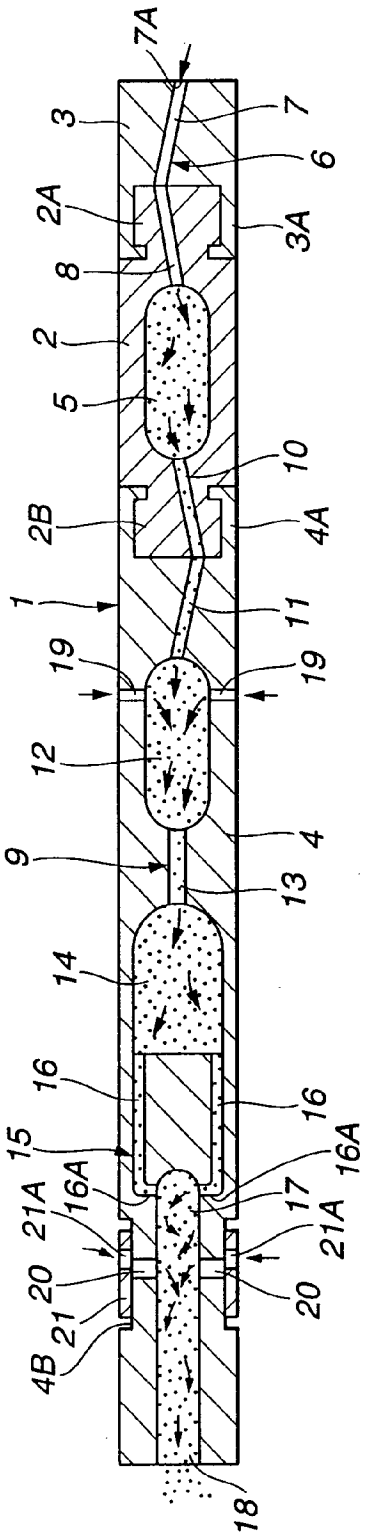


FIG.6

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(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