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UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	35401-716.201
First Inventor	Steve Cartt
Title	Administration of Benzodiazepine Compositions
Electronically filed on.	03/27/2009

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☒ **Specification** *[Total Pages 65]*
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☐ **Drawing(s)** (35 U.S.C. 113) *[Total Sheets ___]*
5. ☐ **Oath or Declaration** *[Total Sheets ___]*
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☒ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-Rom or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape table on CD
8. **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
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ACCOMPANYING APPLICATION PARTS

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

18. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: _____

Prior application information: *Examiner* _____ *Art Unit:* _____

19. CORRESPONDENCE ADDRESS

☒ *The address associated with Customer Number:* 021971 *OR* ☐ Correspondence address below

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Signature	/Peter R. Munson/	*Date*	03/27/2009
Name (Print/Type)	Peter R. Munson	*Registration No. (Attorney/Agent)*	43,821

WSGR Docket No. 35401-716.201

PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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I hereby certify that the attached Nonprovisional Application and all marked attachments are being deposited by Electronic Filing on March 27, 2009 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
Linda Anders

Date: March 27, 2009

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

[001] This application claims priority under 35 U.S.C. § 119(e) from United States provisional patent application number 61/040,558, which was filed on March 28, 2008, and which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[002] This application relates to the nasal administration of benzodiazepine drugs and combinations thereof.

BACKGROUND OF THE INVENTION

[003] By way of non-limiting example, the benzodiazepine family consists of drugs such as diazepam, lorazepam, and medazepam. The drugs in this family have been observed as possessing sedative, tranquilizing and muscle relaxing properties. They are frequently classified as an anxiolytic and skeletal muscle relaxants. They are thought to be useful in preventing, treating, or ameliorating the symptoms of anxiety, insomnia, agitation, seizures (such as those caused by epilepsy), muscle spasms and rigidity (which can be caused by tetanus), the symptoms of drug withdrawal associated with the continuous abuse of central nervous system depressants, and exposure to nerve agents.

[004] Benzodiazepines are thought to act by binding to the $GABA_A$ receptor of a neuron, possibly causing the receptor to change shape and making it more accessible to gama-aminobutyric acid (GABA).

[005] GABA is an inhibitory neurotransmitter that, when bound to the $GABA_A$ receptor, facilitates Cl^- ions flooding into the neuron to which the receptor is bound. The increase in Cl^- ions hyperpolarizes the membrane of the neuron. This completely or substantially reduces the ability of the neuron to carry an action potential. Targeting this receptor is particularly useful in treating many disorders, such as tetanus and epilepsy, which may result from too many action potentials proceeding through the nervous system.

[006] Current formulations of benzodiazepine drugs can be administered orally, rectally, or parenterally. The ability to utilize these and other types of formulations has been significantly limited due, in many cases, to solubility challenges.

[007] The oral route of administration may be considered sub-optimal due to several disadvantages. For example, the amount of time required for an orally administered benzodiazepine drug to reach therapeutically relevant concentrations in blood plasma may be rather long, such as an hour or more. Moreover, as benzodiazepine drugs pass through the liver a significant amount may be metabolized. Thus, it may require large doses to achieve therapeutic plasma levels. Furthermore, due to the nature of seizures and muscle spasms, it can be extremely difficult for either a patient or a care-giver to administer the benzodiazepine drug orally.

[008] Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings.

Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.

[009] Suppository compositions of benzodiazepine drugs can have a rapid onset of action. However, the inconvenience of suppositories is an obvious impediment to their being administered by anyone outside a very small group of the patient's intimate acquaintances and the patient's professional medical caretakers.

SUMMARY OF THE INVENTION

[010] In some embodiments, the pharmaceutical composition for nasal administration comprises: a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w) in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of the patient. In some embodiments the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w), preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form comprising benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[011] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the benzodiazepine drug is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[012] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

[013] In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the glycols exclude glycol polymers having an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.

[014] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in a carrier system in a concentration from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine is present in a carrier system in a concentration from about 20 mg/mL to about 50 mg/mL.

[015] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

[016] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount of about 30% (w/w).

[017] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[018] In some embodiments, the composition comprises one or more additional excipients, such as one or more parabens, one or more povidones, and/or one or more alkyl glycosides.

[019] The invention also discloses a method of treating a patient with a disorder that may be treatable with a benzodiazepine drug. In some embodiments, the patient is a human. In some embodiments, the method comprises: administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration comprising a benzodiazepine drug; one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70%, preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine is dissolved in the one or more natural or

synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70%, preferably about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, the benzodiazepine drug includes benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[020] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug is fully dissolved in a single phase comprising one or more one or more natural or synthetic tocopherols or tocotrienols and one or more alcohols or glycols. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some such embodiments, the composition further comprises water. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[021] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ-tocotrienol, δ- tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

[022] In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the alcohol or glycol is free of water (dehydrated, USP). In some embodiments, the alcohol is ethanol (dehydrated, USP).

[023] In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration from about 1 mg/mL to about 600 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 10 mg/mL to about 250 mg/mL. In some embodiments, the benzodiazepine drug is present in the carrier system in a concentration of from about 20 mg/mL to about 50 mg/mL.

[024] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some

embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w).

[025] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 30% (w/w).

[026] In some embodiments, the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

[027] In some embodiments, the composition is in a pharmaceutically-acceptable spray formulation, and further comprising administering the composition to one or more nasal mucosal membranes of the patient. In some embodiments, the therapeutically effective amount is from about 1 mg to about 20 mg of the benzodiazepine. In some embodiments, the pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to 200 μL.

[028] In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first 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.

[029] 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.

[030] 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

[031] 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.

DETAILED DESCRIPTION OF THE INVENTION

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

[033] 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.

[034] 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.

[035] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[036] 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.

[037] 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.

[038] 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.

[039] 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.

[040] 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.

[041] 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).

[042] 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.

[043] 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.

[044] 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.)

[045] 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.)

[046] 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.

[047] 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.

[048] 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.

[049] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug 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.

[050] 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.

[051] 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.

[052] 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.

[053] 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.

[054] 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).

[055] 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.

[056] 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).

[057] 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.

[058] 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.

[059] 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.

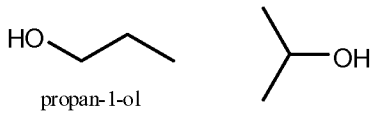
Definitions

[060] 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.

[061] 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.

[062] 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.

[063] 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

[064] 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.)

[065] 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.

[066] 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."

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

[068] 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.

[069] 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.

[070] 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

[071] 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.

[072] 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.

[073] 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

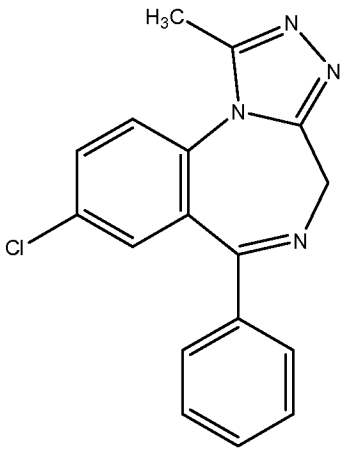
bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

[074] 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.

[075] 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.

[076] 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.

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



[078] 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.

[079] 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.

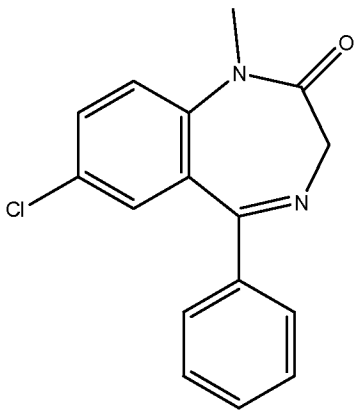
[080] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the

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.

[081] 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.

[082] 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.

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



[084] 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.

[085] 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.

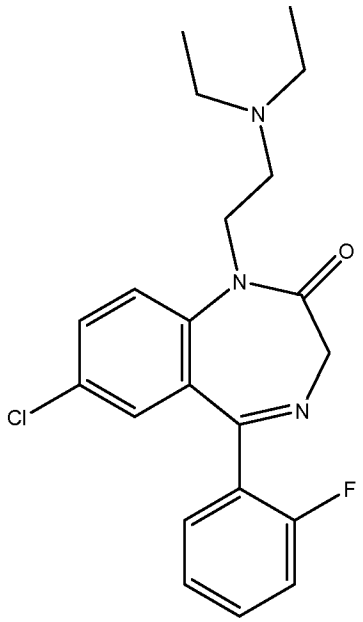
[086] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam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

[087] 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.

[088] 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.

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



[090] 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.

[091] 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.

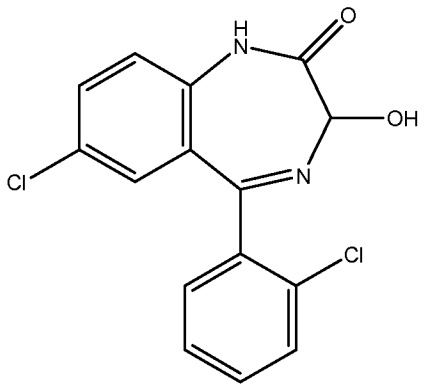
[092] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam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

[093] 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.

[094] 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.

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



[096] 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.

[097] 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.

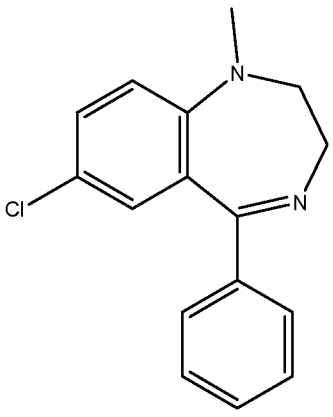
[098] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam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

[099] 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.

[0100] 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.

[0101] **Medazepam** ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



[0102] 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.

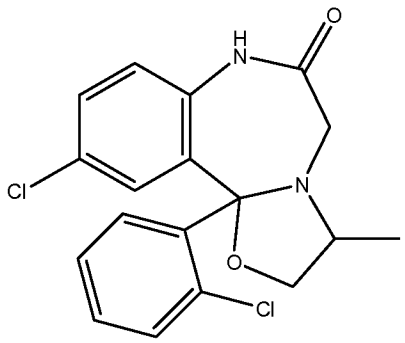
[0103] In some embodiments, medazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] **Mexazolam** (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methyloxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



[0108] 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.

[0109] 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.

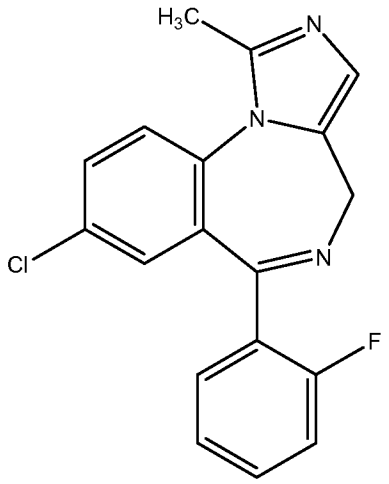
[0110] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam 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.

[0111] 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.

[0112] 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.

[0113] **Midazolam** (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



[0114] 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.

[0115] 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.

[0116] 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.

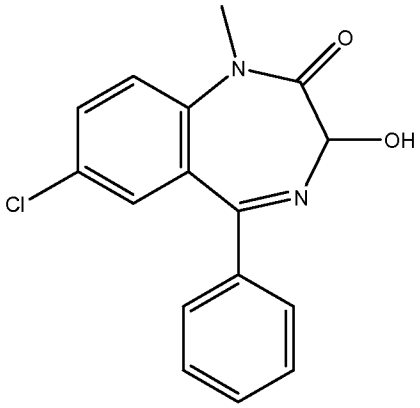
[0117] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam 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.

[0118] 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.

[0119] 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.

[0120] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0121] 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.

[0122] 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.

[0123] 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.

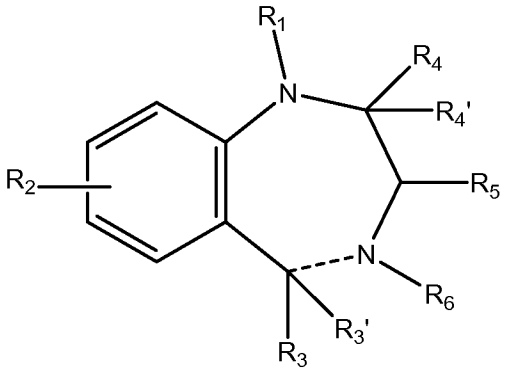
[0124] Temazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability 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.

[0125] 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

[0126] 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.

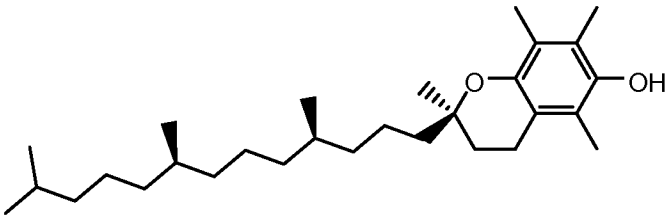
[0127] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4, H_2SO_3, H_3PO_4, H_3PO_3, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic 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.

[0128] 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.

[0129] 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

[0130] 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

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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

[0136] 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).

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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

[0142] 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.

[0143] 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

[0144] 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.

[0145] 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

[0146] 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.

[0147] 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

[0148] 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.

[0149] 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

[0150] 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.

[0151] 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

[0152] 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.

[0153] 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

[0154] 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.

[0155] 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

[0156] 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.

[0157] 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

[0158] 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.

[0159] 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

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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.

Formulation Process

[0164] 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.

[0165] The aforementioned formulations are preferably sterile with a bacteria count of 10 below the allowable level on a per mL basis. Additionally, pathogens are preferably absent.

[0166] 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.

[0167] 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

[0168] 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.

[0169] 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.

[0170] 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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

[0176] 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

[0177] 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.

[0178] 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

[0179] 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.

[0180] 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

[0181] 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.

[0182] 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

[0183] 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.

[0184] 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

[0185] 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.

[0186] 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

[0187] 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.

[0188] 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

[0189] 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.

[0190] 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

[0191] 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.

[0192] 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.

[0193] 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

[0194] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

[0195] 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

[0196] 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

[0197] 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.

[0198] 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

[0199] 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

[0200] 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.

[0201] 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

[0202] 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

[0203] 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

[0204] 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>.

[0205] 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.

[0206] 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.

[0207] 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%

[0208] 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

Solution02, 70mg/mI, 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%	100.5	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	**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 solution	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%	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	Meets USP	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not	not

Limits	{61}									tested	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

[0209] 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

[0210] 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.

[0211] 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

[0212] 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

[0213] 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

[0214] 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.

[0215] 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 composition for nasal administration comprising:

(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); and

(c) 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.

2. The pharmaceutical composition 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 composition 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, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

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

5. The pharmaceutical composition of claim 1, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

6. The pharmaceutical composition of claim 5, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

7. The pharmaceutical composition 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 composition 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 composition of claim 1, wherein the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof.

10. The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 1 mg/mL to about 600 mg/mL.

11. The pharmaceutical composition of claim 1, wherein the benzodiazepine drug is present in the pharmaceutical composition in a concentration from about 10 mg/mL to about 250 mg/mL.

12. The pharmaceutical composition of claim 11, wherein the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 50 mg/mL.

13. The pharmaceutical composition 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 composition of claim 13, wherein the 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).

15. The pharmaceutical composition 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 composition 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 composition of one of claims 1 - 16, further comprising 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.

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

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

20. A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising:

(a) 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 10% to about 70% (w/w).

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

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

23. The method of claim 20, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, or any pharmaceutically-acceptable salts thereof, and any combinations thereof.

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

25. The method of claim 20, wherein the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof.

26. The method of claim 25, wherein the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm.

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

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

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

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

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

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

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

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

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

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

37. The method of claim 20, wherein 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.

38. The method of claim 20, wherein the composition is in a pharmaceutically-acceptable spray formulation.

39. The method of claim 38, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.

40. The method of claim 39, wherein said pharmaceutical composition is in a pharmaceutically-acceptable spray formulation having volume from about 10 μL to about 200 μL.

41. The method of claim 40, wherein 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.

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

43. The method of claim 42, wherein the 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.

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

45. The method of claim 43, wherein 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.

46. The composition of claim 20, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.

47. The composition of claim 21, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside.

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

ABSTRACT

[0216] The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	32103-716.201
	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.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Steve		Cartt	

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

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Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

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

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	David		Medeiros	

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

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Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Gary	Thomas	Gwozdz	

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

City	Nazareth	State/Province	PA	Country of Residence	US

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	32103-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	329 South Main Street				
Address 2					
City	Nazareth	**State/Province**	PA		
Postal Code	18064	**Country**i	US		

Applicant 4 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118			
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**	
	Andrew		Loxley		
Residence Information (Select One) ◉ US Residency	○ Non US Residency	○ Active US Military Service			
City	Philadelphia	**State/Province**	OA	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	GB				
Mailing Address of Applicant:					
Address 1	126 Market Street, #5				
Address 2					
City	Philadelphia	**State/Province**	PA		
Postal Code	19106	**Country**i	US		

Applicant 5 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118			
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
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	80 Three Mile Harbor Drive				
Address 2					
City	East Hampton	**State/Province**	NY		
Postal Code	11937	**Country**i	US		

Applicant 6 Remove

Applicant Authority ◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118			
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**	
	David		Hale		
Residence Information (Select One) ◉ US Residency	○ Non US Residency	○ Active US Military Service			
City	San Diego	**State/Province**	CA	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				

PTO/SB/14 (07-07)
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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	32103-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Mailing Address of Applicant:			
Address 1	9232 Bernardo Lakes Drive		
Address 2			
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Postal Code	92127	Country[i]	US

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	mgrumbling@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		
Attorney Docket Number	32103-716.201	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Publication Information:

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

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

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either 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		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	32103-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
61040558	non provisional of		2008-03-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

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

Assignee Information:

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

Assignee 1 Remove

If the Assignee is an Organization check here. [X]

Organization Name	Hale Biopharma Ventures, LLC		
Mailing Address Information:			
Address 1	1042-B N. El Camino Real, Suite 430		
Address 2			
City	Encinitas	**State/Province**	CA
Country [i]	US	Postal Code	92024
Phone Number		Fax Number	
Email Address			

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

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Peter R. Munson/	Date (YYYY-MM-DD)	2009-03-27

PTO/SB/14 (07-07)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	32103-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

First Name	Peter	Last Name	Munson	Registration Number	43821

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.**

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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:

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

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

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

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

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

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Peter R. Munson./Linda Anders/PM/MG
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	82	82
Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Claims:				
Claims in excess of 20	2202	43	26	1118
Multiple dependent claims	2203	1	195	195
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1775**

Electronic Acknowledgement Receipt

EFS ID:	5053670
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Peter R. Munson./Linda Anders/PM/MG
Filer Authorized By:	Peter R. Munson.
Attorney Docket Number:	35401-716.201
Receipt Date:	27-MAR-2009
Filing Date:	
Time Stamp:	19:59:04
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	Transmittal of New Application	35401-716-201-transmittal.pdf	72738 71592a369edab69bf47b158662ea6fdd2c59b79b	no	2

Warnings:

Information:

2		35401-716-201-nonprovisional.pdf	399017 050dd2cf8484ad92d1299d46e673e26a336ebb03	yes	65

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	59
Claims	60	64
Abstract	65	65

Warnings:

Information:

3	Application Data Sheet	35401-716-201-ADS.pdf	1554995 ea6535df25bf9ed2c19cc5c585d418379e160d1c	no	6

Warnings:

Information:

4	Fee Worksheet (PTO-06)	fee-info.pdf	38008 9698f28724faba1b0707321a9a5f4727ed1c2c87	no	2

Warnings:

Information:

Total Files Size (in bytes):	2064758

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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.

PTO/SB/06 (12-04)

Filing Date: 03/27/09

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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 12/413,439

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	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	62 minus 20 =	42	x$26	1092	OR	x$52	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195	195		390	
			TOTAL	1749		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

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))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B

	(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))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/413,439	03/27/2009	1614	0.00	35401-716.201	47	2

CONFIRMATION NO. 9049

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

FILING RECEIPT

Date Mailed: 04/29/2009

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**

Applicant(s)

Steve Cartt, Union City, CA;
David Medeiros, South San Francisco, CA;
Gary Thomas Gwozdz, Nazareth, PA;
Andrew Loxley, Philadelphia, OA;
Mark Mitchnick, East Hampton, NY;
David Hale, San Diego, CA;

Assignment For Published Patent Application

HALE BIOPHARMA VENTURES, LLC, Encinitas, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/040,558 03/28/2008

Foreign Applications

If Required, Foreign Filing License Granted: 04/20/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/413,439**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

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

Title

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Preliminary Class

514

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 (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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

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

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/413,439	03/27/2009	Steve Cartt	35401-716.201

CONFIRMATION NO. 9049

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

FORMALITIES LETTER

OC000000035574846

Date Mailed: 04/29/2009

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 and pay any fees required 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).

- The statutory basic filing fee is missing.
  *Applicant must submit $**82** to complete the basic filing fee for a small entity.*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $**1287** 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.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**1814** for a small entity
- $**82** Statutory basic filing fee.
- $**65** Surcharge.
- The application search fee has not been paid. Applicant must submit $**270** to complete the search fee.

- The application examination fee has not been paid. Applicant must submit $**110** to complete the examination fee for a small entity in compliance with 37 CFR 1.27.
- Total additional claim fee(s) for this application is $**1287**
  - $**1092** for **42** total claims over 20.
  - $**195** for multiple dependent claim surcharge.

Replies should be mailed to:

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

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

/rfthomas/

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

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/413,439	03/27/2009	Steve Cartt	35401-716.201

CONFIRMATION NO. 9049

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

FORMALITIES LETTER

OC000000035574846

Date Mailed: 04/29/2009

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FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

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  Applicant must submit $82 to complete the basic filing fee for a small entity.
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

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- Additional claim fees of **$1287** 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.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of **$65** for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

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Total additional fee(s) required for this application is **$1814** for a small entity
- **$82** Statutory basic filing fee.
- **$65** Surcharge.
- The application search fee has not been paid. Applicant must submit **$270** to complete the search fee.

- The application examination fee has not been paid. Applicant must submit $**110** to complete the examination fee for a small entity in compliance with 37 CFR 1.27.
- Total additional claim fee(s) for this application is $**1287**
  - $**1092** for **42** total claims over 20.
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Doc Code: OATH
Document Description: Oath or declaration filed

PTO/SB/01 (10-08)
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing *OR* ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(f) required)

Attorney Docket Number	35401-716.201
First Named Inventor	Steve Cartt
COMPLETE IF KNOWN	
Application Number	12/413,439
Filing Date	03/27/2009
Art Unit	1614
Examiner Name	Not yet assigned

I hereby declare that:

(1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and

(2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 03/27/2009 as United States Application Number or PCT International

Application Number 12/413,439 and was amended on (MM/DD/YYYY) ☐ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Authorization to Permit Access To Application by Participating Offices

☒ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified application is filed access to the above-identified 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, or other intellectual property office in which a foreign application claiming priority to the above-identified application is filed to have access to the application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the application-as-filed with respect to: 1) the above-identified application, 2) any foreign application to which the above-identified application claims priority under 35 USC 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 above-identified US application, and 3) any U.S. application from which benefit is sought in the above-identified application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

DECLARATION — Utility or Design Patent Application

Claim of Foreign Priority Benefits

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? Yes	No
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

PTO/SB/01 (10-08)
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DECLARATION — Utility or Design Patent Application

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Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type or personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2083) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any]) **Steve**		Family Name or Surname **Cartt**	
Inventor's Signature			Date 6-4-09
Residence: City **Union City**	State **CA**	Country **US**	Citizenship **US**
Mailing Address **3260 Whipple Road**			
City **Union City**	State **CA**	ZIP **94587**	Country **US**

☒ Additional inventors or a legal representative are being named on the 1 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

PTO/SB/02A (02-08)
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U.S.Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet Page 1 of 1

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any)	Family Name or Surname		
David	**Medeiros**		
Inventor's Signature			Date 06/09/09
Residence: City **South San Francisco**	State **CA**	Country **US**	Citizenship **US**
Mailing Address **212 Crown Circle**			
Mailing Address			
City **South San Francisco**	State **CA**	ZIP **94080**	Country **US**
Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Gary Thomas	**Gwozdz**		
Inventor's Signature			Date
Residence: City **Nazareth**	State **PA**	Country **US**	Citizenship **US**
Mailing Address **329 South Main Street**			
Mailing Address			
City **Nazareth**	State **PA**	ZIP **18064**	Country **US**
Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Andrew	**Loxley**		
Inventor's Signature			Date
Residence: City **Philadelphia**	State **PA**	Country **US**	Citizenship **GB**
Mailing Address **126 Market Street, #5**			
City **Philadelphia**	State **PA**	ZIP **19106**	Country **US**

PTO/SB/02A (02-08)
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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any)	Family Name or Surname		
David	**Medeiros**		
Inventor's Signature			Date
Residence: City **South San Francisco**	State **CA**	Country **US**	Citizenship **US**
Mailing Address **212 Crown Circle**			
Mailing Address			
City **South San Francisco**	State **CA**	ZIP **94080**	Country **US**

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Gary Thomas	**Gwozdz**		
Inventor's Signature			Date 27-June-2009
Residence: City **Nazareth**	State **PA**	Country **US**	Citizenship **US**
Mailing Address **329 South Main Street**			
Mailing Address			
City **Nazareth**	State **PA**	ZIP **18064**	Country **US**

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Andrew	**Loxley**		
Inventor's Signature			Date June 23rd 2009
Residence: City **Philadelphia**	State **PA**	Country **US**	Citizenship **GB**
Mailing Address **126 Market Street, #5**			
City **Philadelphia**	State **PA**	ZIP **19106**	Country **US**

PTO/SB/02A (07-07)
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U.S.Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any)	Family Name or Surname		
Mark	Mitchnick		
Inventor's Signature Mark Mitchnick			Date 22 June 2009
Residence: City East Hampton	State NY	Country US	Citizenship US
Mailing Address 80 Three Mile Harbor Drive			
City East Hampton	State NY	Zip 11937	Country US

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
David F.	Hale		
Inventor's Signature			Date
Residence: City San Diego	State CA	Country US	Citizenship US
Mailing Address 1042-B N. El Camino Real, Suite 430			
City Encinitas	State CA	Zip 92024	Country US

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Inventor's Signature			Date
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	Zip	Country

PTO/SB/02A (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S.Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION	ADDITIONAL INVENTOR(S) Supplemental Sheet Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any)	Family Name or Surname		
Mark	**Mitchnick**		
Inventor's Signature			Date
Residence: City **East Hampton**	State **NY**	Country **US**	Citizenship **US**
Mailing Address **80 Three Mile Harbor Drive**			
City **East Hampton**	State **NY**	Zip **11937**	Country **US**
Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
David F	**Hale**		
Inventor's Signature			Date 6/19/09
Residence: City **San Diego**	State **CA**	Country **US**	Citizenship **US**
Mailing Address **1042-B N. El Camino Real, Suite 430**			
City **Encinitas**	State **CA**	Zip **92024**	Country **US**
Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Inventor's Signature			Date
Residence: City	State	Country	Citizenship
Mailing Address			
City	State	Zip	Country

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Peter R. Munson./Linda Anders/PM/MG
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	82	82
Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Claims:				
Claims in excess of 20	2202	42	26	1092
Multiple dependent claims	2203	1	195	195
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1814**

Electronic Acknowledgement Receipt

EFS ID:	5608447
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Peter R. Munson./Linda Anders/PM/MG
Filer Authorized By:	Peter R. Munson.
Attorney Docket Number:	35401-716.201
Receipt Date:	29-JUN-2009
Filing Date:	27-MAR-2009
Time Stamp:	17:34:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1814
RAM confirmation Number	4174
Deposit Account	232415
Authorized User	

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-201-responseMP.pdf	294130 f2881374bf04b540fdc22940f3cf3e4b63d8f89e	yes	9

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Applicant Response to Pre-Exam Formalities Notice	1	2
Oath or Declaration filed	3	9

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	40105 d47e3052037c20e7125f4b2bded18360b9ff0d36	no	2

Warnings:

Information:

Total Files Size (in bytes):	334235

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

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Electronic Acknowledgement Receipt

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-201-responseMP.pdf	294130 f2881374bf04b540fdc22940f3cf3e4b63d8f89e	yes	9

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Applicant Response to Pre-Exam Formalities Notice	1	2
Oath or Declaration filed	3	9

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	40105 d47e3052037c20e7125f4b2bded18360b9ff0d36	no	2

Warnings:

Information:

Total Files Size (in bytes):	334235

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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
12/413,439	03/27/2009	1614	1814	35401-716.201	47	2

CONFIRMATION NO. 9049

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

UPDATED FILING RECEIPT

Date Mailed: 07/09/2009

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**

Applicant(s)

Steve Cartt, Union City, CA;
David Medeiros, South San Francisco, CA;
Gary Thomas Gwozdz, Nazareth, PA;
Andrew Loxley, Philadelphia, PA;
Mark Mitchnick, East Hampton, NY;
David F. Hale, San Diego, CA;

Assignment For Published Patent Application

HALE BIOPHARMA VENTURES, LLC, Encinitas, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/040,558 03/28/2008

Foreign Applications

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: 04/20/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/413,439**

Projected Publication Date: 10/15/2009

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Preliminary Class

514

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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.

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PTO/SB/08 (01-08)
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	12/413,439
				Filing Date	March 27, 2009
				First Named Inventor	Steve Cartt
				Art Unit	1614
				Examiner Name	Not Yet Assigned
Sheet	1	Of	3	Attorney Docket Number	35401-716.201

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-7,037,528	05-02-2006	Kipp	
	2.	US-6,869,617	03-22-2005	Kipp	
	3.	US-6,884,436	04-26-2005	Kipp	
	4.	US-6,607,784	08-19-2003	Kipp et al.	
	5.	US-6,458,387	10-01-2002	Scott et al.	
	6.	US-6,375,986	04-23-2002	Ryde et al.	
	7.	US-6,268,053	07-31-2001	Woiszwillo et al.	
	8.	US-6,235,224	05-22-2001	Mathiowitz et al.	
	9.	US-6,193,985	02-27-2001	Sonne	
	10.	US-6,143,211	11-07-2000	Mathiowitz et al.	
	11.	US-6,090,925	07-18-2000	Woiszwillo et al.	
	12.	US-5,981,719	11-09-1999	Woiszwillo et al.	
	13.	US-5,849,884 (withdrawn)		Woiszwillo et al.	
	14.	US-5,831,089	11-03-1998	Huber	
	15.	US-5,780,062	07-14-1998	Frank et al.	
	16.	US-5,716,642	02-10-1998	Bagchi et al.	
	17.	US-5,665,331	09-09-1997	Bagchi et al.	
	18.	US-5,662,883	09-02-1997	Bagchi et al.	
	19.	US-5,661,130	08-26-1997	Meezan et al.	
	20.	US-5,560,932	10-01-1996	Bagchi et al.	
	21.	US-5,188,837	02-23-1993	Domb	
	22.	US-5,145,684	09-08-1992	Liversidge et al.	
	23.	US-5,118,528	06-02-1992	Fessi et al.	
	24.	US-5,100,591	03-31-1992	Leclef et al.	
	25.	US-5,091,188	02-25-1992	Haynes	

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Sheet	2	Of	3	Attorney Docket Number	35401-716.201

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	26.	US-4,997,454	03-05-1991	Violanto et al.	
	27.	US-4,826,689	05-02-1989	Violanto et al.	
	28.	US-4,608,278	08-26-1986	Frank et al.	
	29.	US-4,280,957	07-28-1981	Walser et al.	
	30.	US-3,987,052	10-19-1976	Hester Jr.	
	31.	US-3,722,371	03-27-1973	Boyle	
	32.	US-3,567,710	03-02-1971	Fryer et al.	
	33.	US-3,374,225	03-19-1968	Reeder et al.	
	34.	US-3,371,085	02-27-1968	Reeder et al.	
	35.	US-3,340,253	09-05-1967	Reeder et al.	
	36.	US-3,299,053	01-17-1967	Archer et al.	
	37.	US-3,296,249	01-03-1967	Bell	
	38.	US-3,243,427	03-29-1966	Reeder et al.	
	39.	US-3,136,815	06-09-1964	Reeder et al.	
	40.	US-3,109,843	11-05-1963	Reeder et al.	
	41.	US-3,102,116	08-27-1963	Chase et al.	
	42.	US-2009-0047347	02-19-2009	Maggio	
	43.	US-2006-0198896	09-07-2006	Liversidge et al.	
	44.	US-2003-0181411	09-25-2003	Bosch et al.	
	45.	US-2001-0042932	11-22-2001	Mathiowitz et al.	

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Sheet	3	Of	3	Attorney Docket Number	35401-716.201

FOREIGN PATENT DOCUMENTS

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	46.	WO-1997-14407 A1	04-24-1997	Research Triangle Pharmaceuticals Board of Regents, U. Tx. System		

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[6]
	47.	PCT/US08/62961 Search Report dated 7/25/08	

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/14

A1

(11) International Publication Number: **WO 97/14407**

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(21) International Application Number: PCT/US96/16841

(22) International Filing Date: 17 October 1996 (17.10.96)

(30) Priority Data:
60/005,340 17 October 1995 (17.10.95) US

(71) Applicants *(for all designated States except US)*: RESEARCH TRIANGLE PHARMACEUTICALS [US/US]; Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HENRIKSEN, Inge, B. [NO/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). MISHRA, Awadesh, K. [IN/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). PACE, Gary, W. [US/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). JOHNSTON, Keith, P. [US/US]; University of Texas, Dept. Chemical Engineering, 26th and Speedway, Austin, TX 78712-1062 (US). MAWSON, Simon [US/US]; University of Texas, Dept. Chemical Engineering, 26th and Speedway, Austin, TX 78712-1062 (US).

(74) Agent: CRAWFORD, Arthur, R.; Nixon & Vanderhye P.C., 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).

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

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(54) Title: INSOLUBLE DRUG DELIVERY

(57) Abstract

Particles of water insoluble biologically active compounds, particularly water-insoluble drugs, with an average size of 100 nm to about 300 nm, are prepared by dissolving the compound in a solution then spraying the solution into compressed gaz, liquid or supercritical fluid in the presence of appropriate surface modifiers.

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INSOLUBLE DRUG DELIVERY

This invention provides a novel process for producing sub-micron sized particles of water insoluble compounds with biological uses, particularly water insoluble drugs.

BACKGROUND AND SUMMARY OF THE INVENTION

Approximately one-third of the drugs in the United States Pharmacopoeia are water-insoluble or poorly water-soluble. Many currently available injectable formulations of such drugs carry important adverse warnings on their labels that originate from detergents and other agents used for their solubilization. Oral formulations of water-insoluble drugs or compounds with biological uses frequently show poor and erratic bioavailability. In addition, water-solubility problems delay or completely block the development of many new drugs and other biologically useful compounds.

Two alternative approaches for insoluble drug delivery are microparticles which involves forming a phospholipid stabilized aqueous suspension of submicron sized particles of the drug (see U.S. 5,091,187; 5,091,188 and 5,246,707) and microdroplets which involves forming a phospholipid stabilized oil in water emulsion by dissolving the drug in a suitable bio-compatible hydrophobic carrier (see U.S. 4,622,219 and 4,725,442).

The pharmacokinetic properties of both oral and injectable microparticle formulations are dependent on both the particle size and phospholid surface modifier. However, with certain water insoluble compounds the current employed methods of particle size reduction are problematic. Thus, the overall objective of this invention is to develop a novel process based on the use of compressed fluids, including supercritical fluid technology, that yields surface modifier stabilized suspensions of water insoluble drugs with an average particle size of 100 nm to about 300 nm and a narrow size

distribution. The inventive process is robust, scalable and applicable to a wide range of water-insoluble compounds with biological uses.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further explained with reference to the attached drawings in which

Figure 1 is a schematic representation of an apparatus for carrying out the present invention by precipitating the bioactive substance by rapid expansion from a supercritical solution;

Figure 2A is a more detailed representation of the preheater assembly of Figure 1;

Figure 2B is an enlarged perspective view of the expansion nozzle of Figure 1;

Figure 3 is a schematic representation of an apparatus for preparing sub-micronsized particles according to the invention by precipitating a bioactive substance, suitably solubilized, into a compressed gas, liquid or supercritical fluid;

Figure 4 is a graph showing the particle size distribution on a volume weighted basis of the cyclosporine particles produced in Example 1 expanded into a phospholipid containing 1 wt% stabilizer;

Figure 5 is a graph showing the particle size distribution on a volume weighted basis of the cyclosporine particles produced in Example 1 expanded into a phospholipid containing 2 wt% stabilizer;

Figure 6 is a graph showing the particle size distribution on a volume weighted basis of the indomethacin particles produced in Example 3 sprayed directly into carbon dioxide;

Figure 7 is a graph showing the particle size Gaussian distribution on a volume weighted basis of the indomethacin particles produced in Example 3 sprayed into a phospholipid containing 2 wt% stabilizer;

Figure 8 is a graph showing the particle size distribution on a volume weighted basis of the tetracaine hydrochloride particles produced in Example 4 sprayed into carbon dioxide and water;

Figure 9 is a graph showing the particle size distribution on a volume weighted basis of the tetracaine hydrochloride particles produced in Example 4 sprayed into carbon dioxide and water also containing 1 wt% of stabilizer; and

Figure 10 is a graph showing the particle size Gaussian distribution on a volume weighted basis of tetracaine hydrochloride particles produced in Example 4 sprayed into carbon dioxide, water and 2 wt% stabilizer.

DESCRIPTION OF THE INVENTION

This invention is a process using compressed fluids to produce submicron sized particles of industrially useful poorly soluble or insoluble compounds with biological uses by: (1) precipitating a compound by rapid expansion from a supercritical solution (Rapid expansion from supercritical solution) in which the compound is dissolved, or (2) precipitating a compound by spraying a solution, in which the compound is soluble, into compressed gas, liquid or supercritical fluid which is miscible with the solution but is antisolvent for the compound. In this manner precipitation with a compressed fluid antisolvent (Compressed fluid antisolvent) is achieved. Optionally, the process combines or integrates a phospholipid in water or other suitable surface modifiers such as surfactants, as may be required, into the processes. The surfactant is chosen to be active at the compound-water interface, but is not chosen to be active at the carbon dioxide-organic solvent or carbon dioxide- compound interface when carbon dioxide is used as the supercritical solution. A unique feature of this invention is the combination of either rapid expansion from supercritical solution or compressed fluid antisolvent with recovery of surface modified stable submicron particles in an aqueous phas-

By industrially useful insoluble or poorly soluble compounds we include biologically useful compounds, imaging agents, pharmaceutically useful compounds and in particular drugs for human and veterinary medicine. Water insoluble compounds are those having a poor solubility in water, that is less than 5 mg/ml at a physiological pH of 6.5 to 7.4, although the water solubility may be less than 1 mg/ml and even less than 0.1 mg/ml.

Examples of some preferred water-insoluble drugs include immunosuppressive and immunoactive agents, antiviral and antifungal agents, antineoplastic agents, analgesic and anti-inflammatory agents, antibiotics, anti-epileptics, anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, anticonvulsant agents, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergic and antarrhythmics, antihypertensive agents, antineoplastic agents, hormones, and nutrients. A detailed description of these and other suitable drugs may be found in *Remington's Pharmaceutical Sciences*, 18th edition, 1990, Mack Publishing Co. Philadelphia, PA.

Cyclosporine, a water insoluble immunosuppressive drug, is used as a model to illustrate the invention. This drug was chosen since it has not been possible by using conventional size reduction techniques to achieve the particle size and distribution believed necessary to reach the desired pharmacokinetic performance.

Cyclosporine is a water insoluble, lipophilic 11 amino acid polypeptide with unique immunosuppressive properties. Its major use is as an immunosuppressant in solid organ transplantation. The clinical utility of the currently available pharmaceutical dosage forms are severely limited by the drug's insolubility. That is, the bioavailability of the oral form is low and the intra and inter patient absorption is variable.

The phospholipid may be any natural or synthetic phospholipid, for example phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg or soybean phospholipid or a combination thereof. The phospholipid may be salted or desalted, hydrogenated or partially hydrogenated or natural semisynthetic or synthetic.

Examples of some suitable second surface modifiers include: (a) natural surfactants such as casein, gelatin, tragacanth, waxes, enteric resins, paraffin, acacia, gelatin, cholesterol esters and triglycerides, (b) nonionic surfactants such as polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, polyvinylpyrrolidone, and synthetic phospholipids, (c) anionic surfactants such as potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively charged phospholipids (phosphatidyl glycerol, phosphatidyl inosite, phosphatidylserine, phosphatidic acid and their salts), and negatively charged glyceryl esters, sodium carboxymethylcellulose, and calcium carboxymethylcellulose, (d) cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride, (e) colloidal clays such as bentonite and veegum. A detailed description of these surfactants may be found in *Remington's Pharmaceutical Sciences*, and Theory and Practice of Industrial Pharmacy, Lachman et al, 1986.

More specifically, examples of suitable second surface modifiers include one or combination of the following: polaxomers, such as Pluronic™ F68, F108

and F127, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylene-diamine available from BASF, Triton™ X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas. Tween 20, 40, 60 and 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Speciality Chemicals, Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, hydroxy propylmethylcellulose, dimyristoyl phosphatidylglycerol sodium salt, sodium dodecylsulfate, sodium deoxycholate, and cetyltrimethylammonium bromide.

Particles produced by the process of this invention are generally at most 500 nm in size usually below 300 nm, desirably less than 200 nm, preferably less than about 100 nm and often in a range of 0.1 to 100 nm in size. These particles are narrowly distributed in that 99% of the particles are below 500 nm and preferably below 400 nm with peaks at half width at half height at about 200 nm and preferably below 100 nm. The particles may be recovered from suspension by any convenient means such as spray drying, lyophilization, diafiltration, dialysis or evaporation.

The solvent properties of supercritical fluids are strongly affected by their fluid density in the vicinity of the fluid's critical point. In rapid expansion from supercritical solutions, a non volatile solute is dissolved in a supercritical fluid. Nucleation and crystallization are triggered by reducing the solution density through rapid expansion of the supercritical fluid to atmospheric conditions. To achieve this the supercritical fluid is typically sprayed through 10-50 microns (internal diameter) nozzles with aspect ratios (L/D) of 5-100. The fluid approaches sonic terminal velocity at the nozzle tip and high levels of supersaturation result in rapid nucleation rates and limited crystal growth. The combination of a rapidly propagating mechanical perturbation and high

supersaturation is a distinguishing feature of rapid expansion from a supercritical solution. These conditions lead to the formation of very small particles with a narrow particle distribution.

The first comprehensive study of rapid expansion from a supercritical solution was reported by Krukonis (1984) [V.J.Krukonis: *AIChE Annual Meeting San Francisco* (1984), as cited in J.W.Tom *et al.*: *Supercritical Fluid Engineering Science*, Chapter 19, p238, (1993)] who formed micro-particles of an array of organic, inorganic, and biological materials. Most particle sizes reported for organic materials, such as lovastatin, polyhydroxyacids, and mevinolin, were in the 5-100 micron range. Nanoparticles of beta-carotene (300 nm) were formed by expansion of ethane into a viscous gelatin solution in order to inhibit post expansion particle aggregation.

Most rapid expansion from supercritical solution studies on organic materials utilize supercritical carbon dioxide. However, ethane was preferred to carbon dioxide for beta-carotene because of certain chemical interactions. Carbon dioxide is generally preferred, alone or in combination with a cosolvent. Minute additions of a cosolvent can increase the solubility of some solutes by orders of magnitude. When cosolvents are used in rapid expansion from a supercritical solution, care is required to prevent desolution of the particles due to solvent condensing in the nozzle. Normally, this is achieved by heating the supercritical fluid, prior to expansion, to a point where no condensate (mist) is visible at the nozzle tip.

A similar problem occurs when carbon dioxide is used alone. During adiabatic expansion (cooling), carbon dioxide will be in two phases unless sufficient heat is provided at the nozzle to maintain a gaseous state. Most investigators recognize this phenomenon and increase the pre-expansion temperature to prevent condensation and freezing in the nozzle. A significant heat input is required (40-50 kcal/kg) to maintain carbon dioxide in the gaseous

state. If this energy is supplied by increasing the pre-expansion temperature the density drops and consequently reduces the supercritical fluid's solvating power. This can lead to premature precipitation and clogging of the nozzle.

There are a number of advantages in utilizing compressed carbon dioxide in the liquid and supercritical fluid states, as a solvent or anti-solvent for the formation of materials with submicron particle features. Diffusion coefficients of organic solvents in supercritical fluid carbon dioxide are typically 1-2 orders of magnitude higher than in conventional liquid solvents. Furthermore, carbon dioxide is a small linear molecule that diffuses more rapidly in liquids than do other antisolvents. In the antisolvent precipitation process, the accelerated mass transfer in both directions can facilitate very rapid phase separation and hence the production of materials with sub-micron features. It is easy to recycle the supercritical fluid solvent at the end of the process by simply reducing pressure. Since supercritical fluids do not have a surface tension, they can be removed without collapse of structure due to capillary forces. Drying of the product is unusually rapid. No carbon dioxide residue is left in the product, and carbon dioxide has a number of other desirable characteristics, for example it is non-toxic, nonflammable, and inexpensive. Furthermore, solvent waste is greatly reduced since a typical ratio of antisolvent to solvent is 30:1.

As an antisolvent, carbon dioxide has broad applicability in that it lowers the cohesive energy of nearly all organic solvents. In 1992, D.J. Dixon, PhD. Dissertation, University of Texas at Austin, described a process in which liquid solutions of polymer in solvent are sprayed into compressed carbon dioxide to form microspheres and fibers. In this process, so called precipitation with a compressed fluid antisolvent, the polymer is insoluble in carbon dioxide, and the organic solvent is fully miscible with CO_2. This concept has been used to form biologically active insulin particles (4 microns) [Yeo, S. D., Lim, G.B. and Debenedetti, P.G. Formation of Microparticulate Protein Powders using a

Supercritical Fluid Anti-Solvent Biotechnol. and Bioeng. 1993, 341], several micron biodegradable L-poly(lactic acid) particles [Randolph, T. W. B., R.A.; Johnston, K.P. Micron Sized Biodegradeable Particles of Poly(L-lactic Acid) via the Gas Antisolvent Spray Precipitation Process. Biotechnology Progress. 1993, 9, 429] and methylprednisolone acetate particles (<5 microns) [W.J. Schmitt, M. C. S., G.G. Shook, S. M. Speaker. Finely-Divided Powders by Carrier Solution Injection into a Near or Supercritical Fluid. Am. Inst. Chem. Eng. J. 1995, 41, 2476-2486]. Somewhat surprisingly, the particle sizes have been as small as those made by rapid expansion from a supercritical solution, despite the potentially faster times for depressurization in rapid expansion from a supercritical solution versus two-way mass transfer in the Compressed fluid antisolvent process. Not only can the compressed fluid antisolvent process produce PS particles, but also solid and hollow fibers highly oriented microfibrils biocontinuous networks and 100 nm microballoons with porous shells.

To date, it has not been possible to make submicron particles by the compressed fluid antisolvent process without particle aggregation or flocculation. Our objective is to overcome this limitation with the use of surface modifiers, also termed surfactant stabilizers, such as phospholipids, salts of cholic and deoxycholic acids, Tweens (polyoxyethylene sorbitan esters), Pluronic F-68, Tetronic-908, hydroxypropylmethyl cellulose (HPMC), Triton X-100, cetyltrimethylammonium bromide, PEG-400 or combinations of these compounds as described in more detail above.

Considerable variations as to the identities and types of phospholipid and especially the surface active agent or agents should be expected depending upon the water-insoluble or poorly water-soluble biologically active substance selected as the surface properties of these small particles are different. The most advantageous surface active agent for the insoluble compound will be apparent following empirical tests to identify the surfactant or surfactant

system/combination resulting in the requisite particle size and particle size stability on storage over time.

Appropriate choice of stabilizers will prevent flocculation in the aqueous phase. The surfactant is chosen to be active at the compound water interface, but it is not chosen to be active at the carbon dioxide-organic solvent or carbon dioxide-drug interface. It is not necessary for the stabilizer to be soluble in CO_2; it can be soluble in the liquid to be sprayed, as it only needs to be active at the CO_2/solute interface.

This invention provides a supercritical fluid/compressed fluid based process to produce suspensions of water insoluble drugs with an average particle size of less than 100 nm and a narrow size distribution. An essential element is the use of phospholipids and other surfactants to modify the surface of the drug particles to prevent particle aggregation and thereby improve both their storage stability and pharmacokinetic properties.

DETAILED DESCRIPTION OF THE INVENTION

Materials and methods: Particle sizing was based on the principle of photon correlation spectroscopy using Submicron Particle Sizer-Autodilute Model 370 (NICOMP Particle Sizing Systems, Santa Barbara, CA). This instrument provides number weighted, intensity weighted, and volume weighted particle size distributions as well as multimodality of the particle size distribution, if present.

Separation and quantitation of cyclosporine was carried out with a Waters HPLC system utilizing reverse phase chromatography. The drug was extracted from the sample with methanol and injected for analysis on a C-18 analytical column at 60-80°C with a mobile phase consisting of acetonitrile, methanol, and water. Anylate was detected though its absorbance at 214nm. Operation of the chromatography system and data processing was conducted by Waters Millennium v2.1 software.

Carbon dioxide was used to prepare rapid expansion supercritical solutions since there is no literature reference to any chemical interaction with cyclosporine. Carbon dioxide has been used as a solvent for cyclosporine in fermentation recovery and in HPLC. The relative solubilities of cylclosporine dissolved in a solvent that is expanded with compressed carbon dioxide will be established.

A gas will approach sonic terminal velocity when expanded in a nozzle. Therefore it is important to determine the maximum nozzle diameter and aspect ratio (L/D) that will maintain these conditions in scaleup. Nozzle diameters of 10-50 microns are reported to be used in conjunction with aspect ratios ranging from 5 to 200.

The apparatus for rapid expansion from supercritical solution shown in Figure 1 included a high pressure vessel 1 for formulating the drug/CO_2 solution. Because the drug solution was isolated from the pressurizing fluid by the piston 2 and the valve 2a, the concentration of the drug was constant during the spray. The solution was mixed with a stir bar 14a and a magnetic stirrer 14. The temperature was controlled with heating tape 4. The pressure on the piston and hence the drug solution was controlled via line 3 by an automated syringe pump 5 (ISCO model 100DX) containing pure carbon dioxide.

The preheater as shown in Figure 2A consisted of a hole (0.030" i.d. and 4" long) 8a bored axially along the center of a 2" o.d. x 0.030" i.d. x 4" long copper rod to preheat the solution to a desired temperature before expansion. The preheater assembly 8 and the expansion valve 7 are connected to the high pressure vessel 1 via outlet tube 6. The assembly 8 and the expansion valve 7 were heated with high temperature heating tape 12 and were highly insulated. To monitor the temperature, a thermocouple 13 was placed directly into the preheater assembly close to the orifice.

The expansion nozzle as shown in more detail in Fig. 2B included a 0.254 mm thick, 30 micron diameter laser-drilled orifice 11 (length to diameter ratio ~8.5), which was placed between two copper gaskets 15 (10 mm o.d., 6 mm i.d. and 1 mm thick) and sealed in a 1/4" tubing assembly. The downstream end of the orifice was counterbored into a V-shape as shown in Fig. 2B to prevent the expanding jet from hitting the walls and distorting the morphology of the precipitating solute. To prevent plugging of the orifice, a 1/4" inch diameter, 0.5 micron metal filter 9 was inserted upstream of the nozzle preheater assembly (Figure 1). In addition, a bypass line 10 was used to pre-pressurize the preheater assembly with pure solvent (CO_2) before each spray, otherwise the initial pressure drop across the filter would precipitate the drug and plug the orifice 11. After displacing pure solvent from the preheater, the orifice was submerged into 25 mL aqueous solution in order to trap and stabilize the precipitating drug microparticles. The high kinetic energy of the jet forced the spray 2 cm below the surface of the aqueous phase.

The apparatus used to carry out the Compressed fluid antisolvent sprays is shown in Figure 3. A 300 mL high pressure vessel 16 equipped with a magnetically coupled agitator (Parr) depicted in outline above vessel 16 was used to precipitate the drug. Prior to spraying the drug solution, 50 mL of aqueous solution was added to this precipitator. The aqueous solutions were either pure water, 1.0 wt % Tween 80 in water 10 wt % phospholipid dispersion in water or 10 wt % phospholipid dispersion with 2.0 wt % Tween 80 in water Phospholipid and phospholipid plus Tween-80 dispersions were made by high shear homogenization of their aqueous suspension by passing through a microfluidizer (model M110EH, Microfluidics). Tween-80 was purchased from ICI and egg phospholipid was from Pfansthiel. Aqueous sodium hydroxide solution (1N) was used to adjust the pH of these dispersions to 7.5. Carbon dioxide was compressed with a Haskel air driven gas booster 17 (model AC-152), regulated with a Tescom

pressure regulator (model 26-1021) 18 and monitored by pressure gauge 19. The CO_2 pressure was monitored to within ±0.2 bar. A water bath with a recirculator 30 was used to control the precipitator temperature. The solution was sprayed through 50 micron i.d. fused silica capillary tubing 27 (Polymicro Technology) with a length/diameter ratio of 2800. To maintain a constant flow rate, the solution was pumped through the solution valve 28 to the capillary atomizer using an automated syringe pump 20 (ISCO model 100DX).

A 0.5 μm filter 21 was threaded into the CO_2 effluent line 22 to prevent loss of the water insoluble compound from the precipitation vessel. The filter assembly included an in-line sintered filter element (Swagelok "F" series) which was welded onto a 1/4" i.d. NPT fitting. The effluent vent valve 23 (Whitey, SS-21RS4) connected to rotameter 24 was heated in a water bath 29 to at least 50°C to prevent the expanding CO_2 from freezing. During precipitation, a known amount of aqueous solution 25 was agitated using a 45° pitched blade impeller 26. After precipitation, agitation was discontinued and the vessel was isolated to depressurize for 30-45 min. The aqueous solution was then recovered for particle size analysis.

Unless otherwise specified, all parts and percentages reported herein are weight per unit volume (w/v), in which the volume in the denominator represents the total volume of the system. Diameters of dimensions are given in millimeters (mm = 10^{-3} meters), micrometers (μm = 10^{-6} meters), nanometers (nm = 10^{-9} meters) or Angstrom units (= 0.1 nm). Volumes are given in liters (L), milliliters (mL = 10^{-3} L) and microliters (μL = 10^{-6}L). Dilutions are by volume. All temperatures are reported in degrees Celsius. The compositions of the invention can comprise, consist essentially of or consist of the materials set forth and the process or method can comprise, consist essentially of or consist of the steps set forth with such materials.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

The following examples further explain and illustrate the invention:

Example 1

Cyclosporine Microparticle Formation by the Rapid Expansion from Supercritical Solution Process

A homogeneous solution of cyclosporine in supercritical CO_2 was expanded by rapid expansion from supercritical solution into various aqueous solutions to study microparticle stabilization. The aqueous solutions were pure water 1.0 wt % Tween 80, phospholipid dispersion or 2.0 wt % Tween 80 with phospholipid dispersion. An amount of 0.0480 g of cyclosporine was charged to a variable volume view cell and 20 mL of CO_2 were added to formulate a 0.25 wt % solution. After the solution came to thermal equilibrium (T=35°C) the cyclosporine/CO_2 solution at 3000 psia was sprayed through a 0.30 μm orifice (L/D of 8) into an aqueous solution for 25 seconds. The pre-expansion temperature was 40°C. The volume weighted particle size of the cyclosporine microparticles expanded into pure phospholipid was 153.7 nm (peak 2) as shown in Figure 4. Most of the mass that constitutes the peak 1 of 20-50 nm diameter may originate largely from the phospholipid; however, this population may also possess some particles that contain cyclosporine. The volume weighted mean particle size of the cyclosporine microparticles expanded into phospholipid dispersion with 2.0 wt % Tween 80 was 80.9 nm (peak 2) as shown in Figure 5. In this case again the smaller peak (26.8 nm) may originate largely from the phospholipid and Tween 80 dispersion and a small fraction of cyclosporine containing particulates. A control experiment was performed in which pure

carbon dioxide at 3000 psia was sprayed into the phospholipid dispersion. The mean diameter of the particulates in the dispersion was 9 nm. Therefore, the particles greater than 100 nm in Figures 4 and 5 were not originating from purely the phospholipids, but were drug microparticles. Similarly, for the phospholipid dispersion with 2 wt % Tween 80, the mean diameter of the was 28 nm.

Example 2

Water Insoluble Compound Phase Behavior in Compressed CO_2.

In order to assess whether a particular water insoluble compound should be processed by rapid expansion from supercritical solution or compressed fluid antisolvent, the solubility of the candidate drugs in carbon dioxide was measured. Cyclosporine, nifedipine, piroxicam, carbamazepine, indomethacin and tetracaine HI were studied. To prepare solutions with a constant molar composition, measured amounts of drug and CO_2 were charged to the variable volume view cell from Example 1. To increase the solubility, a cosolvent, i.e., acetone or ethanol, was added to the view cell. The temperature and pressure were varied from 25-45°C and 1200 to 4500 psia, respectively. The phase behavior was determined visually by noting when phase separation occurred as the pressure was slowly reduced at 1-2 psia/sec. Table 1 shows a summary of the solubility behavior in CO_2. Cyclosporine was soluble in CO_2 up to 0.5 wt %. Solutions containing 0.01 wt % carbamazepine, tetracaine HI, nifedipine and piroxicam were insoluble in CO_2. With the addition of 2.40 wt % acetone, 0.026 wt % piroxicam was soluble in CO_2 at 25°C for all pressures down to the vapor pressure of CO_2, which is 930 psia. A solution containing 0.028 wt % nifedipine and 2.26 wt % acetone cosolvent was insoluble in CO_2 at 25°C. At 45°C, the nifedipine was solvated with no visible phase separation down to 2000 psia.

SOLUTE	CONC. (wt%)	TEMP. (°C)	CLOUD POINT (psia)
Cyclosporine	0.25	25	soluble down to 1200
Cyclosporine	0.25	30	1850
Cyclosporine	0.25	35	2060
Piroxicam	0.069	25	insoluble up to 4500
Nifedipine	0.088	25	insoluble up to 4000
Nifedipine	0.029 (a)	25	insoluble up to 3500
Carbamazepine	0.0085	25, 40	insoluble up to 4500
Tetracaine HI	0.0097	25, 45	insoluble up to 4500
Indomethacin	0.0098	25	insoluble up to 4000

(a) with 2.0% ethanol as a co-solvent.

Example 3

Indomethacin Microparticle Formation by the Compressed fluid antisolvent Process

A 9.9 wt % solution of indomethacin in acetone was sprayed into carbon dioxide with the aqueous solution using the Compressed fluid antisolvent process. The duration of the spray was 30 s at 1 mL/min. The volume weighted mean particle size of the phospholipid dispersion was 26 nm (peak 1) as shown in Figure 6. A bimodal size distribution was observed for the indomethacin particles with mean diameters of 143.0 nm (peak 2) and 1088.9 nm (peak 3), respectively. Particles with such a size difference are easily separated by filtration. For the microparticles precipitated into phospholipid dispersion in the presence of 2.0 wt

% Tween 80, the volume weighted mean particle diameter was 126 nm as shown in Figure 7.

Example 4

Tetracaine HI Microparticle Formation by the Compressed fluid antisolvent Process

A 0.97 wt % solution of Tetracaine HI in acetone was sprayed into the precipitator containing carbon dioxide and pure water. The volume weighted mean particle sizes of the Tetracaine HI microparticles were 31.8, 193.4 and 2510.1 nm, respectively (Figure 8). This illustrates that the Compressed fluid antisolvent process can produce extremely small particles even without surfactant stabilizer. With 1.0 wt % Tween 80 added to the water, three peaks were observed with mean diameters of 9.5 nm, 38.3 nm and 169.1 nm (Figure 9). The particle size distribution for 1.0 wt % Tetracaine HI stabilized with phospholipid dispersion and 2.0 wt % Tween 80 is shown in Figure 10. A monomodal distribution is observed between 8-200 nm with a mean diameter of 27.3 nm. This peak includes both the surfactant aggregates and drug particles. No drug particles above 200 nm were observed.

WHAT IS CLAIMED IS:

1. A process of preparing microparticles up to 300 nm in size of water-insoluble or substantially water-insoluble biologically active compounds comprising the steps of :
(1) dissolving a water-insoluble or substantially water-insoluble biologically active compound in a solvent therefor to form a solution; and
(2) spraying the solution prepared in step (1) into a compressed gas, liquid or supercritical fluid in the presence of a surface modifier dispersed or dissolved in an aqueous phase.

2. A process of preparing microparticles up to 300 nm in size of a water-insoluble or substantially water-insoluble biologically active compound comprising the steps of:
(1) dissolving a water-insoluble or substantially water-insoluble biologically active compound in a compressed fluid;
(2) preparing an aqueous phase containing a surface modifier active at the compound-water interface; and
(3) spraying the compressed fluid of step (1) into the aqueous phase of step (2) to form microparticles of the compound.

3. The process according to claim 1 or 2, including the additional step of recovering the microparticles so produced.

4. The process according to claim 1 or 2, wherein the surface modifier is a phospholipid.

5. The process according to claim 1 or 2, wherein the surface modifier is a surfactant.

6. The process according to claim 1 or 2, wherein the surface modifier is a mixture of two or more surfactants.

7. The process according to claim 1 or 2, wherein the surface modifier is at least one surfactant devoid or substantially completely devoid of phospholipids.

8. The process of claim 1 or claim 2 wherein the surface modifier is a polyoxyethylene sorbitan fatty acid ester, a block copolymer of ethylene oxide and propylene oxide, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, an alkyl aryl polyether sulfonate, polyethylene glycol, hydroxy propylmethylcellulose, sodium dodecylsulfate, sodium deoxycholate, cetyltrimethylammonium bromide or combinations thereof.

9. The process of claim 1 or 2 wherein the surface modifier is of egg or plant phospholipid or semisynthetic or synthetic in partly or fully hydrogenated or in a desalted or salt phospholipid such as phosphatidylcholine, phospholipon 90H or dimyristoyl phosphatidylglyerol sodium salt, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, lysophospholipids or combinations thereof.

10. The process of claim 1 or 2 wherein the compound is a cyclosporine, indomethacin, or tetracaine.

11. The process of claim 1 or 2 wherein the particles are less than 100 nm in size.

12. The process of claim 1 or 2 wherein the particles range from 5 up to about 50 nm in size.

13. The process of claim 1 or 2 wherein 99% of the particles produced are below 500 nm.

14. The process of claim 1 or 2 wherein 99% of the particles produced are below 400 nm with peaks at half width at half height at about 200 nm.

15. The process of claim 14 when the peaks are below 100 nm.

16. The process of claim 1 or 2 wherein the compressed gas or fluid is gas, liquid or supercritical carbon dioxide.

17. The process according to claim 2, wherein the compressed fluid sprayed in step (3) is sprayed through a capillary orifice.

Fig. 1

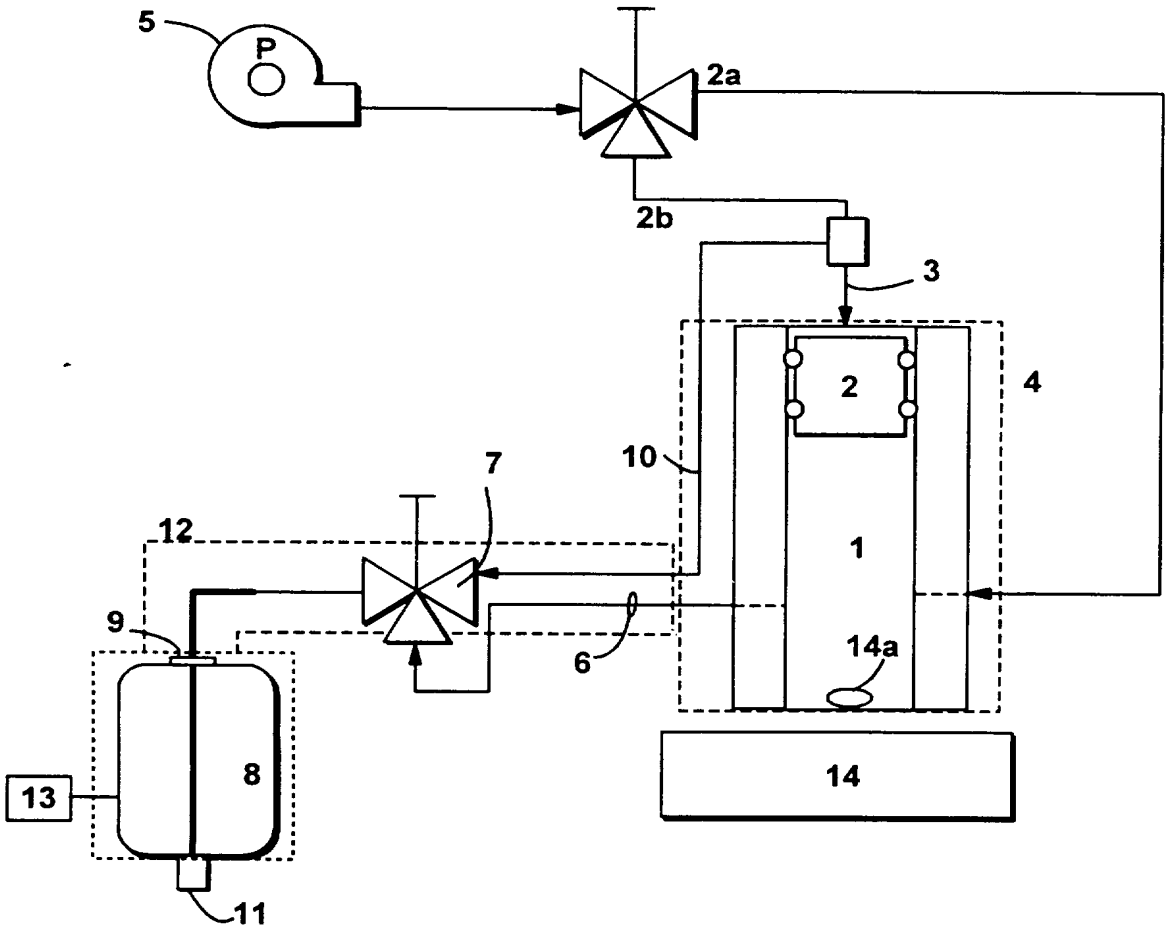


Fig. 2A

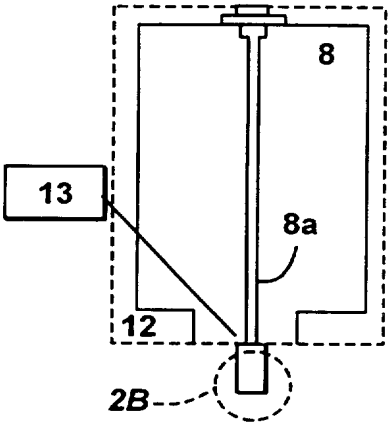


Fig. 2B

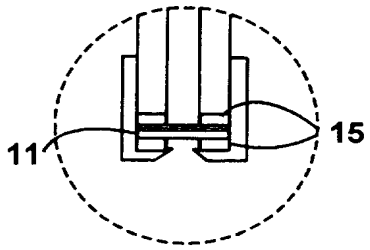
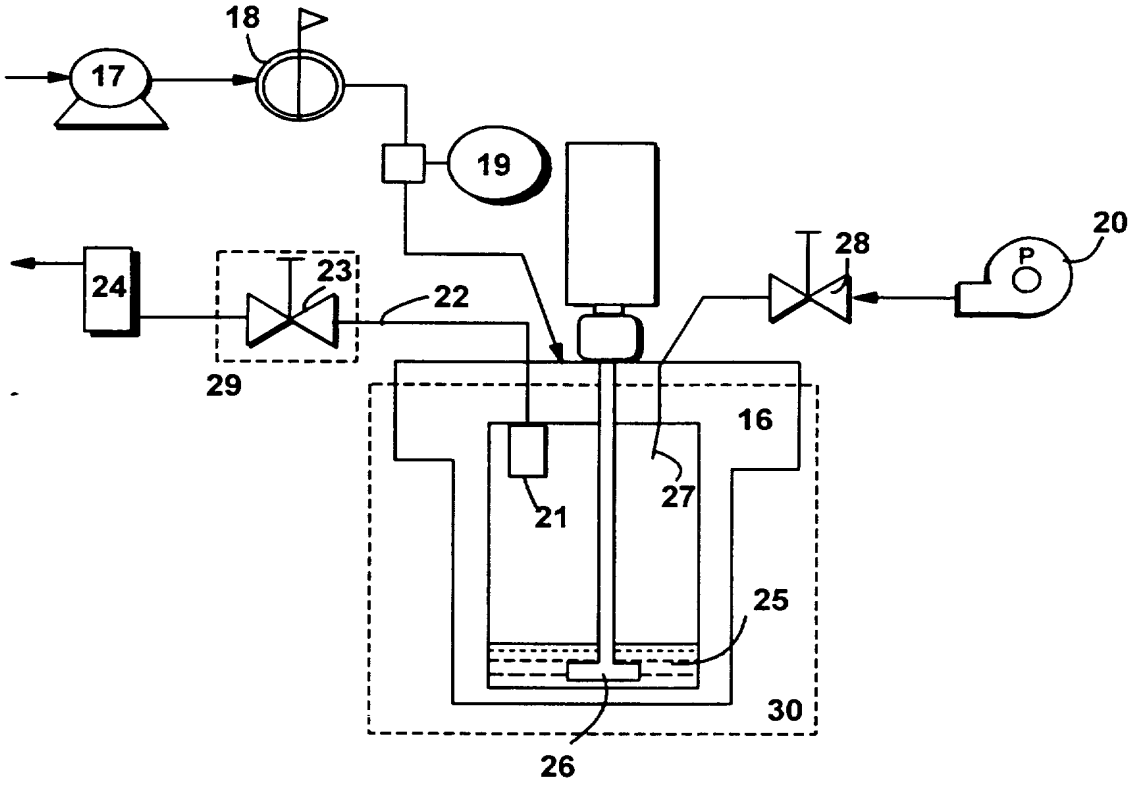
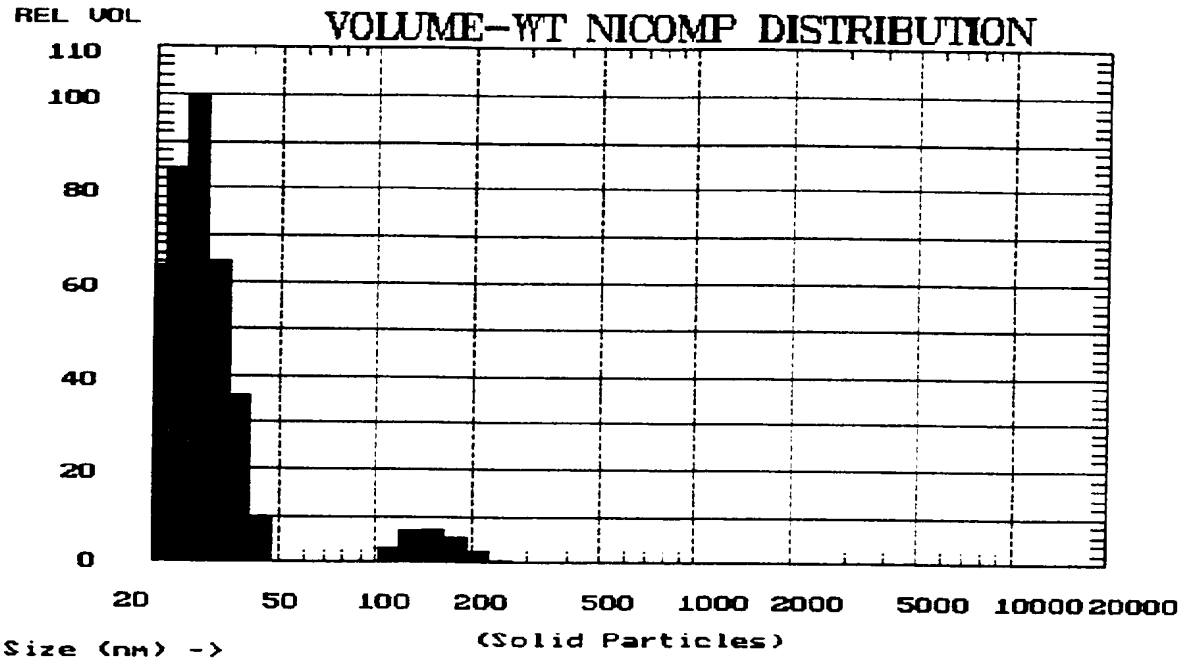


Fig. 3

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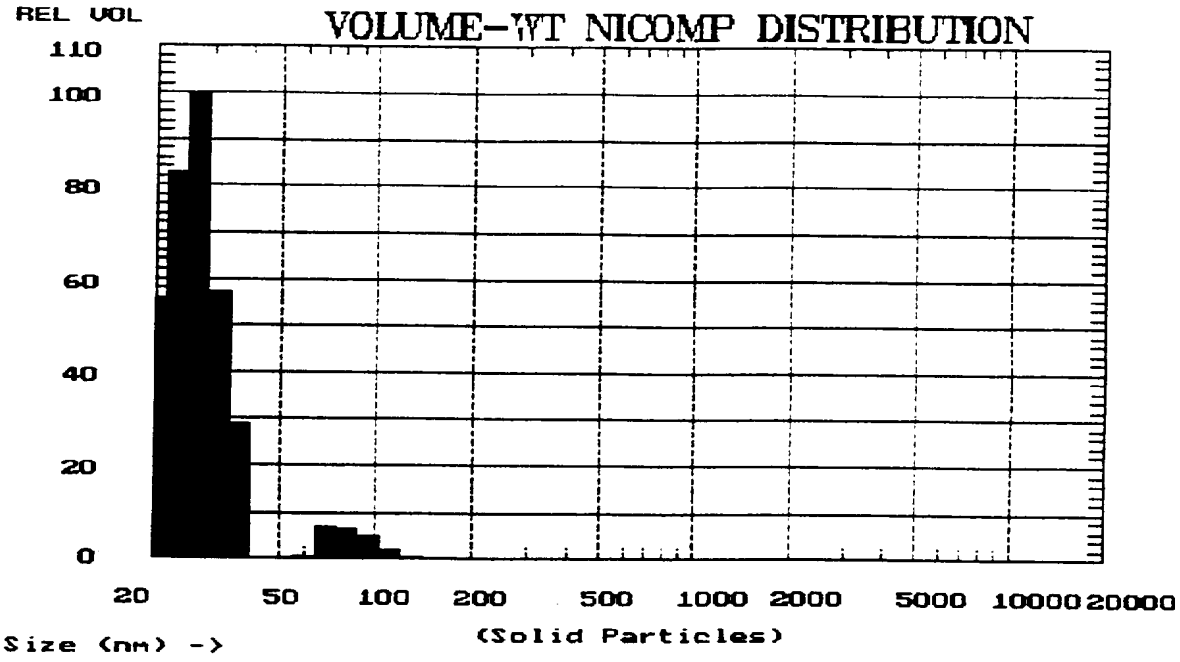
Size (nm) ->
(Solid Particles)

Fig. 4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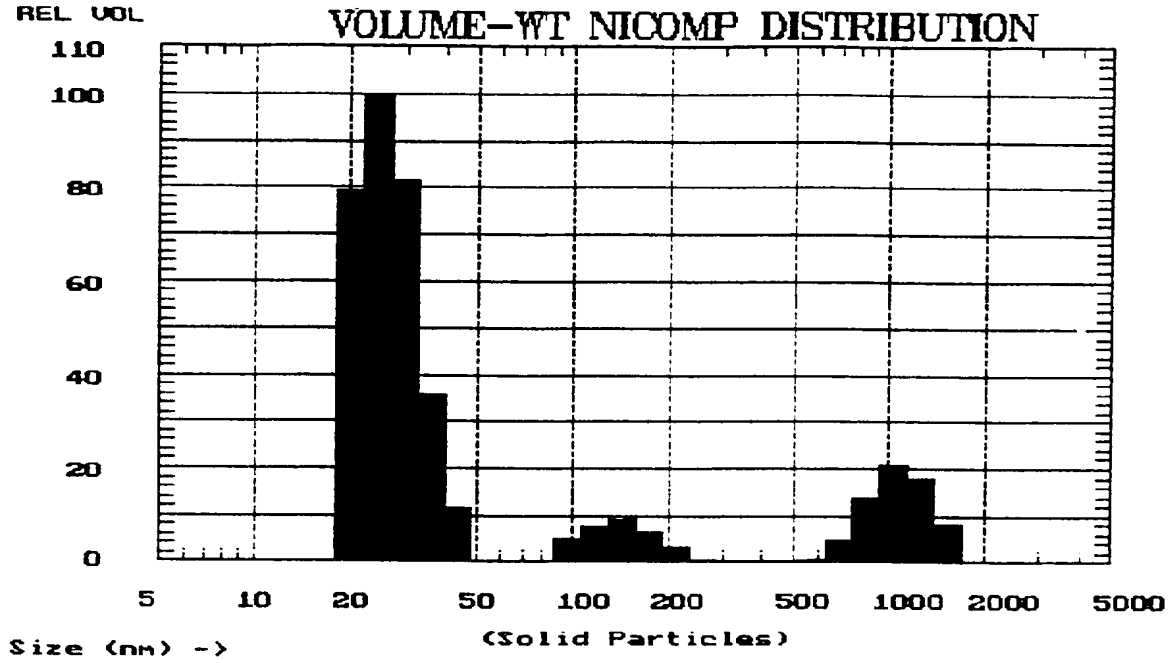
Size (nm) ->
(Solid Particles)

Fig. 5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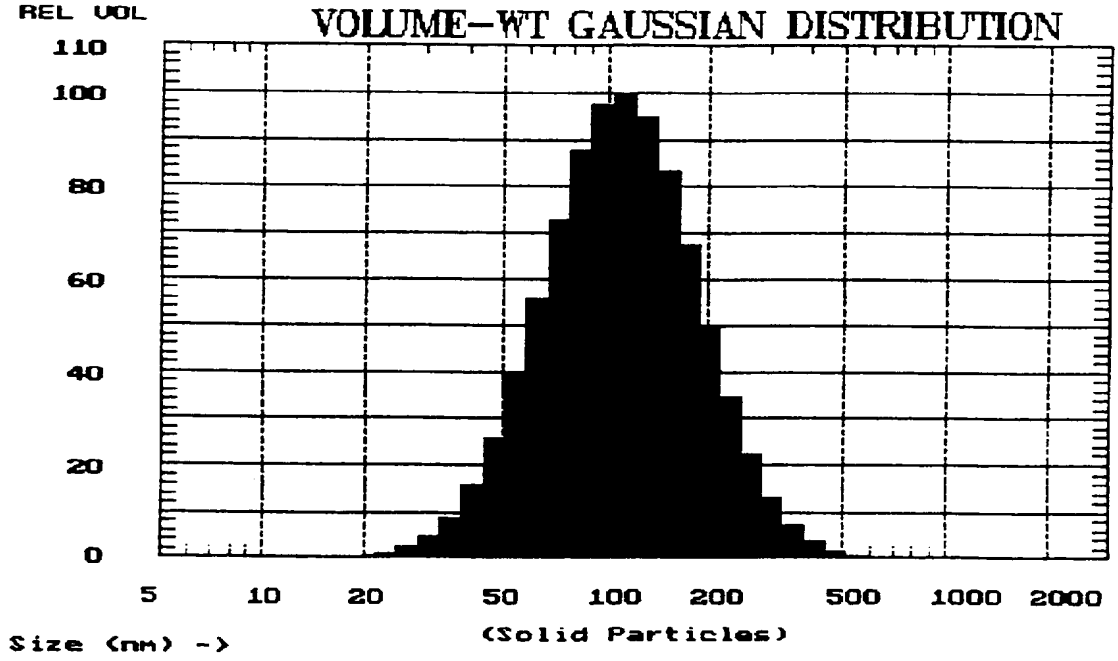
Size (nm) ->
(Solid Particles)

Fig. 6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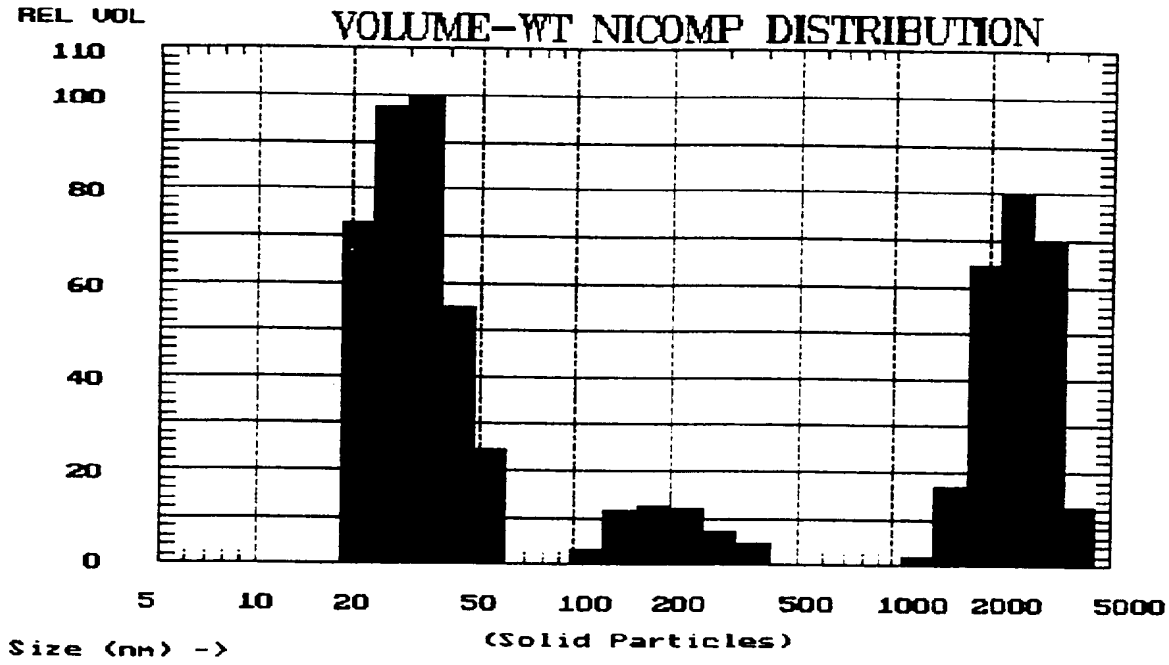
Size (nm) ->
(Solid Particles)

Fig. 7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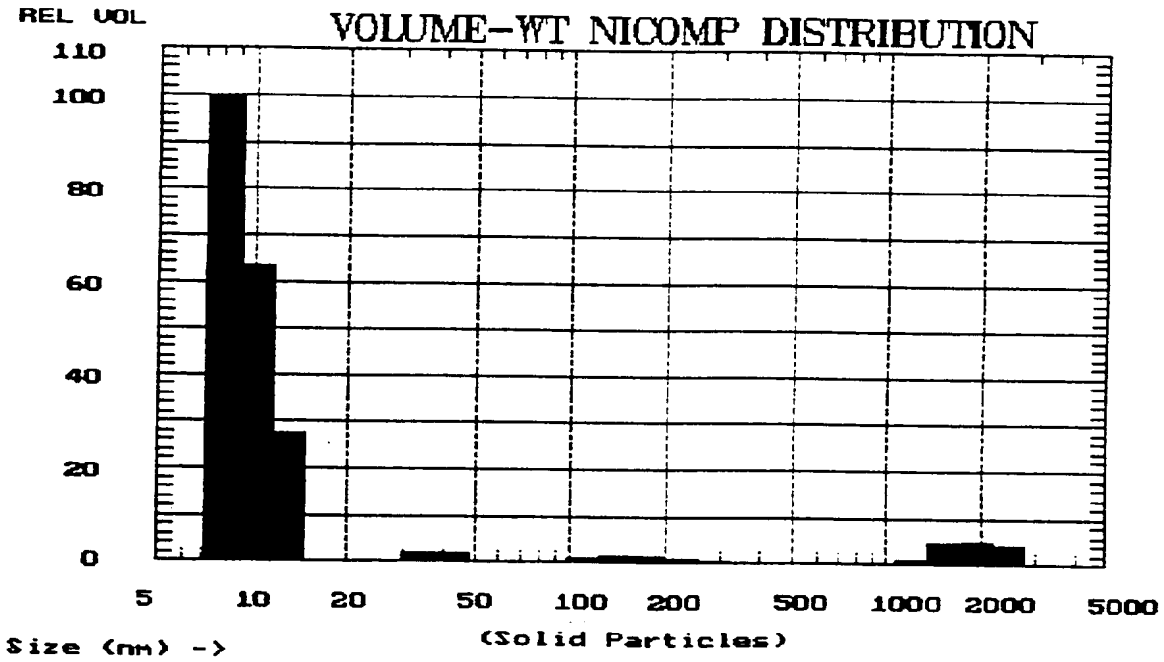
Size (nm) ->
(Solid Particles)

Fig. 8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VOLUME-WT NICOMP DISTRIBUTION
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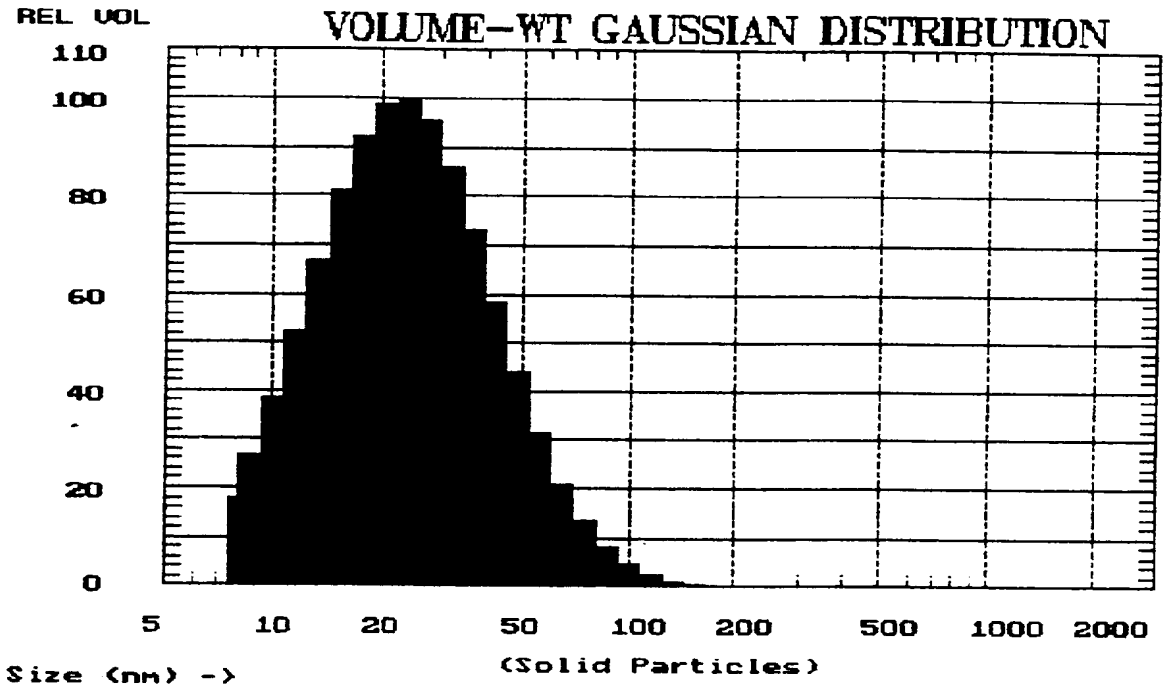
Size (nm) ->
(Solid Particles)

Fig. 9

Fig. 10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1000
2000
Size (nm) ->
(Solid Particles)

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/US 96/16841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 542 314 A (UNIV PRINCETON) 19 May 1993 see column 1 - column 2; claims 1-12 ---	1-17
Y	EP 0 322 687 A (SANOL ARZNEI SCHWARZ GMBH) 5 July 1989 see claims 1-11 ---	1-17
Y	INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 94, 1993, pages 1-10, XP002027507 PHILLIPS E.M. ET AL: "Rapid expansion from supercritical solutions: applications to pharmaceutical processes" see page 7 - page 8 --- -/--	1-17

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 1997	04.04.97

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

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

INTERNATIONAL SEARCH REPORT

Int...ational Application No
PCT/US 96/16841

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 601 618 A (STERLING WINTHROP INC) 15 June 1994 see page 2, line 6 - line 25; claims 1-18 ---	1-17
P,Y	EP 0 706 821 A (MICROENCAPSULATION CENTRE) 17 April 1996 see column 1, line 5 - line 18 see column 4, line 40 - line 42 -----	1-17

1

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 96/16841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0542314 A	19-05-93	AU 668367 B	02-05-96
		AU 2831092 A	20-05-93
		CA 2083027 A	15-05-93
		JP 5293361 A	09-11-93
EP 0322687 A	05-07-89	DE 3744329 A	06-07-89
		DE 3880808 A	09-06-93
		ES 2056890 T	16-10-94
		JP 2004439 A	09-01-90
		US 5043280 A	27-08-91
EP 0601618 A	15-06-94	US 5336507 A	09-08-94
		AU 662453 B	31-08-95
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		CA 2102267 A	12-06-94
		CZ 9302602 A	15-06-94
		FI 935305 A	12-06-94
		HU 65758 A	28-07-94
		JP 6211646 A	02-08-94
		NO 934204 A	13-06-94
		NZ 250062 A	27-04-95
		SK 139093 A	07-12-94
		US 5470583 A	28-11-95
EP 0706821 A	17-04-96	WO 9611055 A	18-04-96

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/62961

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/55 (2008.04)
USPC - 514/220; 514/221
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/220; 514/221

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/58; 514/219; 514/220; 536/103; 536/46; 540/569

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google: nasal; nose; nostril; NEAR3 administ$; composition; particle size; benzodiazepine; (coat$; active agent); particle size distribution; multimodal; distribution; greater than NEAR3 nm; plasma concentration maximum; Csubmax; particulate; heterogen$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2003/0181411 A1 (Bosch, et. al.) 25 Sep 2003 (25.09.2003); claims 1, 6, 12, 17; para [0033], [0037], [0043], [0070]-[0074], [0116], [0117], [0140], [0147], [0187]	1, 4, 5, 7-9, 14-16 --- 2, 3, 6, 10-13, 17-26, 46-60
X -- Y	US 2006/0198896 A1 (Liversidge, et. al.) 7 Sep 2006 (07.09.2006); claims 1-4, 5, 8, 13, 16, 17, 20; para [0001], [0032], [0033], [0036], [0067], [0068], [0074], [0091], [0154], [0209]	27-45 and 61-65 --- 2, 3, 6, 10-13, 17-26, 46-60

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2008 (25.07.2008)	04 AUG 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

Electronic Acknowledgement Receipt

EFS ID:	6081148
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Peter R. Munson./Ann Lygas/Matthew V. Grumbling
Filer Authorized By:	Peter R. Munson.
Attorney Docket Number:	35401-716.201
Receipt Date:	16-SEP-2009
Filing Date:	27-MAR-2009
Time Stamp:	11:01:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	35401-716-201IDSTransmittal.pdf	307329 98688cac700b9cc2a871b0a7ac9b1e6bc866ccb0	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Filed (SB/08)	35401-716-201IDSFiled.pdf	330916 e268951eca99564780d0b1c57d3522d80c7cb3c8	no	3
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO97014407A1.pdf	1013800 683536ca4877198ee7c064b3462a8b543a4f880e	no	32
Warnings:					
Information:					
4	NPL Documents	PCTUS0862961SrchRpt.pdf	58571 31b4ab2b3a5fb309e8264f8f4f9ca099833446ba	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	1710616		

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: 1614
Serial Number: 12/413,439	Examiner: Not Yet Assigned
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: Administration of Benzodiazepine Compositions	

Certificate of Electronic Filing

I hereby certify that the attached Information Disclosure Statement and all marked attachments are being deposited by Electronic Filing on September 16 2009 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Ann Lygas
Ann Lygas

Date: September 16, 2009

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Sir:

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 for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

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

I. ☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: 9/14/09

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

650 Page Mill Road
Palo Alto, 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
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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
12/413,439	03/27/2009	Steve Cartt	35401-716.201

CONFIRMATION NO. 9049

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

PUBLICATION NOTICE

Title:ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Publication No.US-2009-0258865-A1
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NOTICE OF PUBLICATION OF APPLICATION

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FOREIGN PATENT DOCUMENTS

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	1.	WO-2007-043057 A2	04-19-2007	Touitou, Elka et al.		
	2.	WO-2007-144081 A1	12-21-2007	LTS Lohmann Therapie-System		
	3.	WO-2006-75123 A1	07-20-2006	Comurus AB, Swed		
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(54) Title: LIQUID DEPOT FORMULATIONS

(57) Abstract: The present invention relates to pre-formulations comprising low viscosity, non-liquid crystalline, mixtures of: a) at least one neutral diacyl lipid and/or at least one tocopherol; b) at least one phospholipid; c) at least one biocompatible, oxygen containing, low viscosity organic solvent; wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture and wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid. The preformulations are suitable for generating parenteral, non-parenteral and topical depot compositions for sustained release of active agents. The invention additionally relates to a method of delivery of an active agent comprising administration of a preformulation of the invention, a method of treatment comprising administration of a preformulation of the invention and the use of a preformulation of the invention in a method for the manufacture of a medicament.

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Lipid Depot Formulations

The present invention relates to formulation precursors (pre-formulations) for the *in situ* generation of controlled release lipid compositions. In particular, the invention relates to pre-formulations in the form of low viscosity mixtures (such as molecular solutions) of amphiphilic components and at least one bioactive agent which undergo at least one phase transition upon exposure to aqueous fluids, such as body fluids, thereby forming a controlled release matrix which optionally is bioadhesive.

Many bioactive agents including pharmaceuticals, nutrients, vitamins and so forth have a "functional window". That is to say that there is a range of concentrations over which these agents can be observed to provide some biological effect. Where the concentration in the appropriate part of the body (e.g. locally or as demonstrated by serum concentration) falls below a certain level, no beneficial effect can be attributed to the agent. Similarly, there is generally an upper concentration level above which no further benefit is derived by increasing the concentration. In some cases increasing the concentration above a particular level results in undesirable or even dangerous effects.

Some bioactive agents have a long biological half-life and/or a wide functional window and thus may be administered occasionally, maintaining a functional biological concentration over a substantial period of time (e.g. 6 hours to several days). In other cases the rate of clearance is high and/or the functional window is narrow and thus to maintain a biological concentration within this window regular (or even continuous) doses of a small amount are required. This can be particularly difficult where non-oral routes of administration (e.g. parenteral administration) are desirable. Furthermore, in some circumstances, such as in the fitting of implants (e.g. joint replacements or oral implants) the area of desired action may not remain accessible for repeated administration. In such cases a single administration must provide active agent at a therapeutic level over the whole period during which activity is needed.

Various method have been used and proposed for the sustained release of biologically active agents. Such methods include slow-release, orally administered compositions, such as coated tablets, formulations designed for gradual absorption,

such as transdermal patches, and slow-release implants such as "sticks" implanted under the skin.

One method by which the gradual release of a bioactive agent has been proposed is a so-called "depot" injection. In this method, a bioactive agent is formulated with carriers providing a gradual release of active agent over a period of a number of hours or days. These are often based upon a degrading matrix which gradually disperses in the body to release the active agent.

The most common of the established methods of depot injection relies upon a polymeric depot system. This is typically a biodegradable polymer such poly (lactic acid) (PLA) and/or poly (lactic-co-glycolic acid) (PLGA) and may be in the form of a solution in an organic solvent, a pre-polymer mixed with an initiator, encapsulated polymer particles or polymer microspheres. The polymer or polymer particles entrap the active agent and are gradually degraded releasing the agent by slow diffusion and/or as the matrix is absorbed. Examples of such systems include those described in US 4938763, US 5480656 and US 6113943 and can result in delivery of active agents over a period of up to several months. These systems do, however, have a number of limitations including the complexity of manufacturing and difficulty in sterilising (especially the microspheres). The local irritation caused by the lactic and/or glycolic acid which is released at the injection site is also a noticeable drawback. There is also often quite a complex procedure to prepare the injection dose from the powder precursor

From a drug delivery point of view, polymer depot compositions also have the disadvantage of accepting only relatively low drug loads and having a "burst/lag" release profile. The nature of the polymeric matrix, especially when applied as a solution or pre-polymer, causes an initial burst of drug release when the composition is first administered. This is followed by a period of low release, while the degradation of the matrix begins, followed finally by an increase in the release rate to the desired sustained profile. This burst/lag release profile can cause the *in vivo* concentration of active agent to burst above the functional window immediately following administration, then drop back through the bottom of the functional window during the lag period before reaching a sustained functional concentration. Evidently, from a functional and toxicological point of view this burst/lag release profile is undesirable and could be dangerous. It may also limit the equilibrium

concentration which can be provided due to the danger of adverse effects at the "peak" point.

Previous depot systems have been sought to address the problem of burst release. In particular, the use of hydrolysed polylactic acid and the inclusion of poly lactic acid-polyethylene glycol block copolymers have been proposed to provide the "low burst" polymeric system described in US 6113943 and US 6630115. These systems provide improved profiles but the burst/lag effect remains and they do not address other issues such as the irritation caused by the use of polymers producing acidic degradation products.

One alternative to the more established, polymer based, depot systems was proposed in US 5807573. This proposes a lipid based system of a diacylglycerol, a phospolipid and optionally water, glycerol, ethylene glycol or propylene glycol to provide an administration system in the reversed micellar "L2" phase or a cubic liquid crystalline phase. Since this depot system is formed from physiologically well tolerated diacyl glycerols and phospholipids, and does not produce the lactic acid or glycolic acid degradation products of the polymeric systems, there is less tendency for this system to produce inflammation at the injection site. The liquid crystalline phases are, however, of high viscosity and the L2 phase may also be too viscous for ease of application. The authors of US 5807573 also do not provide any *in vivo* assessment of the release profile of the formulation and thus it is uncertain whether or not a "burst" profile is provided.

The use of non-lamellar phase structures (such as liquid crystalline phases) in the delivery of bioactive agents is now relatively well established. Such structures form when an amphiphilic compound is exposed to a solvent because the amphiphile has both polar and apolar groups which cluster to form polar and apolar regions. These regions can effectively solubilise both polar and apolar compounds. In addition, many of the structures formed by amphiphiles in polar and/or apolar solvents have a very considerable area of polar/apolar boundary at which other amphiphilic compounds can be adsorbed and stabilised. Amphiphiles can also be formulated to protect active agents, to at least some extent, from aggressive biological environments, including enzymes, and thereby provide advantageous control over active agent stability and release..

The formation of non-lamellar regions in the amphiphile/water, amphiphile/oil and amphiphile/oil/water phase diagrams is a well known phenomenon. Such phases include liquid crystalline phases such as the cubic P, cubic D, cubic G and hexagonal phases, which are fluid at the molecular level but show significant long-range order, and the L3 phase which comprises a multiply interconnected bi-continuous network of bilayer sheets which are non-lamellar but lack the long-range order of the liquid crystalline phases. Depending upon their curvature of the amphiphile sheets, these phases may be described as normal (mean curvature towards the apolar region) or reversed (mean curvature towards the polar region).

The non-lamellar liquid crystalline and L3 phases are thermodynamically stable systems. That is to say, they are not simply a meta-stable state that will separate and/or reform into layers, lamellar phases or the like, but are the stable thermodynamic form of the lipid/solvent mixture.

While the effectiveness of known lipid depot formulations is high, there are certain aspects in which the performance of these is less than ideal. In particular, cubic liquid crystalline phases proposed are relatively viscous in nature. This makes application with a standard syringe difficult, and possibly painful to the patient, and makes sterilisation by filtration impossible because the composition cannot be passed through the necessary fine-pored membrane. As a result, the compositions must be prepared under highly sterile conditions, which adds to the complexity of manufacturing. Where L2 phases are used, these are generally of lower viscosity but these may still cause difficulty in application and allow access to only a small region of the phase diagram. Specifically, the solvents used in known lipid formulations have only a limited effect in reducing the viscosity of the mixture. Water, for example, will induce the formation of a highly viscous liquid crystalline phase and solvents such as glycerol and glycols have a high viscosity and do not provide any greatly advantageous decrease in the viscosity of the composition. Glycols are also typically toxic or poorly tolerated *in vivo* and can cause irritation when applied topically.

Furthermore, the known lipid compositions in the low-solvent L2 phase may support only a relatively low level of many bioactive agents because of their limited solubility in the components of the mixture in the absence of water. In the presence of water, however, the formulations adopt a highly viscous cubic liquid crystalline

phase. It would be a clear advantage to provide a depot system that could be injected at low viscosity and allowed release of the required concentration of bioactive with a smaller depot composition volume.

The known lipid depot compositions also have practical access to only certain phase structures and compositions because other mixtures are either too highly viscous for administration (such as those with high phospholipid concentrations) or run the risk of separation into two or more separate phases (such as an L2 phase in equilibrium with a phase rich in phospholipid). In particular, phospholipid concentrations above 50% are not reachable by known methods and from the phase diagram shown in US 5807573 it appears that the desired cubic phase is stable at no higher than 40% phospholipid. As a result, it has not been possible in practice to provide depot compositions of high phospholipid concentration or having a hexagonal liquid crystalline phase structure.

The present inventors have now established that by providing a pre-formulation comprising certain amphiphilic components, at least one bioactive agent and a biologically tolerable solvent, especially in a low viscosity phase such as molecular solution, the pre-formulation may be generated addressing many of the shortfalls of previous depot formulations. In particular, the pre-formulation is easy to manufacture, may be sterile-filtered, it has low viscosity (allowing easy and less painful administration), allows a high level of bioactive agent to be incorporated (thus allowing a smaller amount of composition to be used) and/or forms a desired non-lamellar depot composition *in vivo* having a controllable "burst" or "non-burst" release profile. The compositions are also formed from materials that are non-toxic, biotolerable and biodegradable. Furthermore, the pre-formulation is suitable for the formation of depot compositions following parenteral administration and also following non-parenteral (e.g. topical) administration to body cavities and/or surfaces of the body or elsewhere.

In a first aspect, the present invention thus provides a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, (preferably oxygen containing) organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture and wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid.

Generally, the aqueous fluid will be a body fluid such as fluid from a mucosal surface, tears, sweat, saliva, gastro-intestinal fluid, extra-vascular fluid, extracellular fluid, interstitial fluid or plasma, and the pre-formulation will form a liquid crystalline phase structure when contacted with a body surface, area or cavity (e.g. *in vivo*) upon contact with the aqueous body fluid. The pre-formulation of the invention will generally not contain any significant quantity of water prior to administration.

In a second aspect of the invention, there is also provided a method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising administering (preferably parenterally) a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, (preferably oxygen containing) organic solvent;

and at least one bioactive agent is dissolved or dispersed in the low viscosity mixture, whereby to form at least one liquid crystalline phase structure upon contact with an aqueous fluid *in vivo* following administration. Preferably, the pre-formulation administered in such a method is a pre-formulation of the invention as described herein.

The method of administration suitable for the above method of the invention will be a method appropriate for the condition to be treated and the bioactive agent used. A parenteral depot will thus be formed by parenteral (e.g. subcutaneous or intramuscular) administration while a bioadhesive non-parenteral (e.g. topical) depot composition may be formed by administration to the surface of skin, mucous membranes and/or nails, to opthalmological, nasal, oral or internal surfaces or to cavities such as nasal, rectal, vaginal or buccal cavities, the periodontal pocket or cavities formed following extraction of a natural or implanted structure or prior to insertion of an implant (e.g a joint, stent, cosmetic implant, tooth, tooth filling or other implant).

In a further aspect, the present invention also provides a method for the preparation of a liquid crystalline composition (especially a depot composition) comprising exposing a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

and at least one bioactive agent dissolved or dispersed in the low viscosity mixture, to an aqueous fluid (particularly *in vivo and/or particularly a body fluid as indicated herein*). Preferably the pre-formulation administered is a pre-formulation of the present invention as described herein. The exposure to a fluid "in vivo" may evidently be internally within the body or a body cavity, or may be at a body surface such as a skin surface, depending upon the nature of the composition.

The liquid crystalline composition formed in this method is preferably bioadhesive as described herein.

In a still further aspect the present invention provides a process for the formation of a pre-formulation suitable for the administration of a bioactive agent to a (preferably mammalian) subject, said process comprising forming a low viscosity mixture of

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

and dissolving or dispersing at least one bioactive agent in the low viscosity mixture, or in at least one of components a, b or c prior to forming the low viscosity mixture. Preferably the pre-formulation so-formed is a formulation of the invention as described herein.

In a yet still further aspect the present invention provides the use of a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained administration of said active agent, wherein said pre-formulation is capable of

forming at least one liquid crystalline phase structure upon contact with an aqueous fluid.

As used herein, the term "low viscosity mixture" is used to indicate a mixture which may be readily administered to a subject and in particular readily administered by means of a standard syringe and needle arrangement. This may be indicated, for example by the ability to be dispensed from a 1 ml disposable syringe through a 22 awg (or a 23 gauge) needle by manual pressure. In a particularly preferred embodiment, the low viscosity mixture should be a mixture capable of passing through a standard sterile filtration membrane such as a 0.22 μm syringe filter. In other preferred embodiments, a similar functional definition of a suitable viscosity can be defined as the viscosity of a pre-formulation that can be sprayed using a compression pump or pressurized spray device using conventional spray equipment. A typical range of suitable viscosities would be, for example, 0.1 to 5000 mPas, preferably 1 to 1000 mPas at 20°C.

It has been observed that by the addition of small amounts of low viscosity solvent, as indicated herein, a very significant change in viscosity can be provided. As indicated in Figure 2, for example, the addition of only 5% solvent can reduce viscosity 100-fold and addition of 10% may reduce the viscosity up to 10,000 fold. In order to achieve this non-linear, synergistic effect, in lowering viscosity it is important that a solvent of appropriately low viscosity and suitable polarity be employed. Such solvents include those described herein infra.

Particularly preferred examples of low viscosity mixtures are molecular solutions and/or isotropic phases such as L2 and/or L3 phases. As describe above, the L3 is a non-lamellar phase of interconnected sheets which has some phase structure but lacks the long-range order of a liquid crystalline phase. Unlike liquid crystalline phases, which are generally highly viscous, L3 phases are of lower viscosity. Obviously, mixtures of L3 phase and molecular solution and/or particles of L3 phase suspended in a bulk molecular solution of one or more components are also suitable. The L2 phase is the so-called "reversed micellar" phase or microemulsion. Most preferred low viscosity mixtures are molecular solutions, L3 phases and mixtures thereof. L2 phases are less preferred, except in the case of swollen L_2 phases as described below.

The present invention provides a pre-formulation comprising components a, b, c and at least one bioactive agent as indicated herein. One of the considerable advantages of the pre-formulations of the invention is that components a and b may be formulated in a wide range of proportions. In particular, it is possible to prepare and use pre-formulations of the present invention having a much greater proportion of phospholipid to neutral, diacyl lipid and/or tocopherol than was previously achievable without risking phase separation and/or unacceptably high viscosities in the pre-formulation. The weight ratios of components a:b may thus be anything from 5:95 right up to 95:5. Preferred ratios would generally be from 90:10 to 20:80 and more preferably from 85:15 to 30:70. In one preferred embodiment of the invention, there is a greater proportion of component b than component a. That is, the weight ratio a:b is below 50:50, e.g. 48:52 to 2:98, preferably, 40:60 to 10:90 and more preferably 35:65 to 20:80.

The amount of component c in the pre-formulations of the invention will be at least sufficient to provide a low viscosity mixture (e.g. a molecular solution, see above) of components a, b and c and will be easily determined for any particular combination of components by standard methods. The phase behaviour itself may be analysed by techniques such as visual observation in combination with polarized light microscopy, nuclear magnetic resonance, and cryo-transmission electron microscopy (cryo-TEM) to look for solutions, L2 or L3phases, or liquid crystalline phases. Viscosity may be measured directly by standard means. As described above, an appropriate practical viscosity is that which can effectively be syringed and particularly sterile filtered. This will be assessed easily as indicated herein. The maximum amount of component c to be included will depend upon the exact application of the pre-formulation but generally the desired properties will be provided by any amount forming a low viscosity mixture (e.g. a molecular solution, see above) and/or a solution with sufficiently low viscosity. Since the administration of unnecessarily large amounts of solvent to a subject is generally undesirable the amount of component c will typically be limited to no more than ten times (e.g. three times) the minimum amount required to form a low viscosity mixture, preferably no more than five times and most preferably no more than twice this amount. The composition of the present invention may, however, contain a greater quantity of solvent than would be acceptable in an immediate dosage composition. This is because the process by which the active agents are slowly released (e.g. formation of shells of liquid crystalline phase se described herein) also

serve to retard the passage of solvent from the composition. As a result, the solvent is released over some time (e.g. minutes or hours) rather than instantaneously and so can be better tolerated by the body.

Higher proportions of solvent may also be used for non-parenteral (e.g. topical) applications, especially to body surfaces, where the solvent will be lost by evaporation rather than absorbed into the body. For such applications up to 100 times the minimum amount of solvent may be used (e.g. up to 95% by weight of the composition, preferably up to 80% by weight and more preferably up to 50% by weight), especially where a very thin layer of the resulting non-parenteral depot is desired.

Where the compositions of the invention are formulated as (non-parenteral) aerosol spray compositions (e.g. for topical or systemic delivery of an active), the composition may also comprise a propellant. Such compositions may also include a high proportion of solvent component c), as considered above, since much of the solvent will evaporate when the composition is dispensed.

Suitable propellants are volatile compounds which will mix with the composition of the invention under the pressure of the spray dispenser, without generating high viscosity mixtures. They should evidently have acceptable biocompatibility. Suitable propellants will readily be identified by simple testing and examples include hydrocarbons (especially C_1 to C_4 hydrocarbons) , carbon dioxide and nitrogen. Volatile hydrofluorocarbons such as HFCs 134, 134a, 227ea and/or 152a may also be suitable.

As a general guide, the weight of component c will typically be around 0.5 to 50% of the total weight of the a-b-c solution. This proportion is preferably (especially for injectable depots) 2 to 30% and more preferably 5 to 20% by weight.

Component "a" as indicated herein is a neutral lipid component comprising a polar "head" group and also non-polar "tail" groups. Generally the head and tail portions of the lipid will be joined by an ester moiety but this attachment may be by means of an ether, an amide, a carbon-carbon bond or other attachment. Preferred polar head groups are non-ionic and include polyols such as glycerol, diglycerol and sugar moieties (such as inositol and glucosyl based moieties); and esters of polyols, such

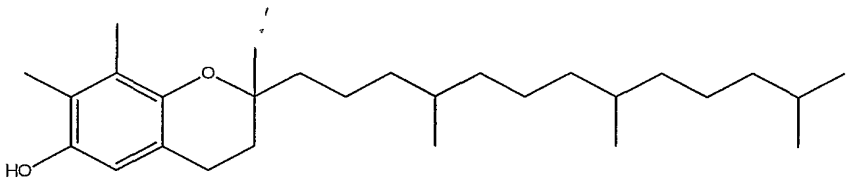
as acetate or succinate esters. Preferred polar groups are glycerol and diglycerol, especially glycerol.

In one preferred aspect, component a is a diacyl lipid in that it has two non-polar "tail" groups. This is generally preferable to the use of mono-acyl ("lyso") lipids because these are typically less well tolerated *in vivo*. The two non-polar groups may have the same or a differing number of carbon atoms and may each independently be saturated or unsaturated. Examples of non-polar groups include C_6-C_{32} alkyl and alkenyl groups, which are typically present as the esters of long chain carboxylic acids. These are often described by reference to the number of carbon atoms and the number of unsaturations in the carbon chain. Thus, CX:Z indicates a hydrocarbon chain having X carbon atoms and Z unsaturations. Examples particularly include caproyl (C6:0), capryloyl (C8:0), capryl (C10:0), lauroyl (C12:0), myristoyl (C14:0), palmitoyl (C16:0), phytanoly (C16:0), palmitoleoyl (C16:1), stearoyl (C18:0), oleoyl (C18:1), elaidoyl (C18:1), linoleoyl (C18:2), linolenoyl (C18:3), arachidonoyl (C20:4), behenoyl (C22:0) and lignoceroyl (C24:9) groups. Thus, typical non-polar chains are based on the fatty acids of natural ester lipids, including caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, or the corresponding alcohols. Preferable non-polar chains are palmitic, stearic, oleic and linoleic acids, particularly oleic acid.

The diacyl lipid, when used as all or part of component "a", may be synthetic or may be derived from a purified and/or chemically modified natural sources such as vegetable oils. Mixtures of any number of diacyl lipids may be used as component a. Most preferably this component will include at least a portion of diacyl glycerol (DAG), especially glycerol dioleate (GDO). In one favoured embodiment, component a consists of DAGs. These may be a single DAG or a mixture of DAGs. A highly preferred example is DAG comprising at least 50%, preferably at least 80% and even comprising substantially 100% GDO.

An alternative or additional highly preferred class of compounds for use as all or part of component a are tocopherols. As used herein, the term "a tocopherol" is used to indicate the non-ionic lipid tocopherol, often known as vitamin E, and/or any suitable salts and/or analogues thereof. Suitable analogues will be those providing the phase-behaviour, lack of toxicity, and phase change upon exposure to aqueous

fluids, which characterise the compositions of the present invention. Such analogues will generally not form liquid crystalline phase structures as a pure compound in water. The most preferred of the tocopherols is tocopherol itself, having the structure below. Evidently, particularly where this is purified from a natural source, there may be a small proportion of non-tocopherol "contaminant" but this will not be sufficient to alter the advantageous phase-behaviour or lack of toxicity. Typically, a tocopherol will contain no more than 10% of non-tocopherol - analogue compounds, preferably no more than 5% and most preferably no more than 2% by weight.



Tocopherol

In a further advantageous embodiment of the invention, component a) consists essentially of tocopherols, in particular tocopherol as shown above.

A preferred combination of constituents for component a) is a mixture of at least one DAG (e.g. GDO) with at least one tocopherol. Such mixtures include 2:98 to 98:2 by weight tocopherol:GDO, e.g.10:90 to 90:10 tocopherol:GDO and especially 20:80 to 80:20 of these compounds. Similar mixtures of tocopherol with other DAGs are also suitable.

Component "b" in the present invention is at least one phospholipid. As with component a, this component comprises a polar head group and at least one non-polar tail group. The difference between components a and b lies principally in the polar group. The non-polar portions may thus suitably be derived from the fatty acids or corresponding alcohols considered above for component a. It will typically be the case that the phospholipid will contain two non-polar groups, although one or more constituents of this component may have one non-polar moiety. Where more than one non-polar group is present these may be the same or different.

Preferred phospholipid polar "head" groups include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol. Most preferred is phosphatidylcholine (PC). In a preferred embodiment, component b)

thus consists of at least 50% PC, preferably at least 70% PC and most preferably at least 80% PC. Component b) may consist essentially of PC.

The phospholipid portion, even more suitably than any diacyl lipid portion, may be derived from a natural source. Suitable sources of phospholipids include egg, heart (e.g. bovine), brain, liver (e.g. bovine) and plant sources including soybean. Such sources may provide one or more constituents of component b, which may comprise any mixture of phospholipids.

Since the pre-formulations of the invention are to be administered to a subject for the controlled release of an active agent, it is preferable that the components a and b are biocompatible. In this regard, it is preferable to use, for example, diacyl lipids and phospholipids rather than mono-acyl (lyso) compounds. A notable exception to this is tocopherol, as described above. Although having only one alkyl chain, this is not a "lyso" lipid in the convention sense. The nature of tocopherol as a well tolerated essential vitamin evidently makes it highly suitable in biocompatibility.

It is furthermore most preferable that the lipids and phospholipids of components a and b are naturally occurring (whether they are derived from a natural source or are of synthetic origin). Naturally occurring lipids tend to cause lesser amounts of inflammation and reaction from the body of the subject. Not only is this more comfortable for the subject but it may increase the residence time of the resulting depot composition, especially for parenteral depots, since less immune system activity is recruited to the administration site. In certain cases it may, however, be desirable to include a portion of a non-naturally-occurring lipid in components a and/or b. This might be, for example an "ether lipid" in which the head and tail groups are joined by an ether bond rather than an ester. Such non-naturally-occurring lipids may be used, for example, to alter the rate of degradation of the resulting depot-composition by having a greater or lesser solubility or vulnerability to breakdown mechanisms present at the site of active agent release. Although all proportions fall within the scope of the present invention, generally, at least 50% of each of components a and b will be naturally occurring lipids. This will preferably be at least 75% and may be up to substantially 100%.

Two particularly preferred combinations of components a and b are GDO with PC and tocopherol with PC, especially in the region 30-90wt% GDO/tocopherol, 10-60 wt% PC and 1-30% solvent (especially ethanol, NMP and/or ispropanol).

In addition to amphiphilic components a and b, the pre-formulations of the invention may also contain additional amphiphilic components at relatively low levels. In one embodiment of the invention, the pre-formulation contains up to 10% (by weight of components a and b) of a charged amphiphile, particularly an anionic amphiphile such as a fatty acid. Preferred fatty acids for this purpose include caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, or the corresponding alcohols. Preferable fatty acids are palmitic, stearic, oleic and linoleic acids, particularly oleic acid. It is particularly advantageous that this component be used in combination with a cationic peptide active agent (see below). The combination of an anionic lipid and a cationic peptide is believed to provide a sustained release composition of particular value. This may in part be due to increased protection of the peptide from the degradative enzymes present *in vivo*.

Component "c" of the pre-formulations of the invention is an oxygen containing organic solvent. Since the pre-formulation is to generate a depot composition following administration (e.g. *in vivo),* upon contact with an aqueous fluid, it is desirable that this solvent be tolerable to the subject and be capable of mixing with the aqueous fluid, and/or diffusing or dissolving out of the pre-formulation into the aqueous fluid. Solvents having at least moderate water solubility are thus preferred.

In a preferred version, the solvent is such that a relatively small addition to the composition comprising a and b, i.e. below 20%, or more preferably below 10%, give a large viscosity reductions of one order of magnitude or more. As described herein, the addition of 10% solvent can give a reduction of two, three or even four orders of magnitude in viscosity over the solvent-free composition, even if that composition is a solution or L_2 phase containing no solvent, or an unsuitable solvent such as water (subject to the special case considered below), or glycerol.

Typical solvents suitable for use as component c include at least one solvent selected from alcohols, ketones, esters (including lactones), ethers, amides and sulphoxides. Examples of suitable alcohols include ethanol, isopropanol and glycerol formal.

Monools are preferred to diols and polyols. Where diols or polyols are used, this is preferably in combination with an at least equal amount of monool or other preferred solvent. Examples of ketones include acetone, n-methyl pyrrolidone (NMP), 2-pyrrolidone, and propylene carbonate. Suitable ethers include diethylether, glycofurol, diethylene glycol monoethyl ether, dimethylisobarbide, and polyethylene glycols. Suitable esters include ethyl acetate and isopropyl acetate and dimethyl sulphide is as suitable sulphide solvent. Suitable amides and sulphoxides include dimethylacetamide (DMA) and dimethylsulphoxide (DMSO), respectively. Less preferred solvents include dimethyl isosorbide, tetrahydrofurfuryl alcohol, diglyme and ethyl lactate.

Since the pre-formulations are to be administered to a living subject, it is necessary that the solvent component c is sufficiently biocompatible. The degree of this biocompatibility will depend upon the application method and since component c may be any mixture of solvents, a certain amount of a solvent that would not be acceptable in large quantities may evidently be present. Overall, however, the solvent or mixture forming component c must not provoke unacceptable reactions from the subject upon administration. Generally such solvents will be hydrocarbons or preferably oxygen containing hydrocarbons, both optionally with other substituents such as nitrogen containing groups. It is preferable that little or none of component c contains halogen substituted hydrocarbons since these tend to have lower biocompatibility. Where a portion of halogenated solvent such as dichloromethane or chloroform is necessary, this proportion will generally be minimised. Where the depot composition is to be formed non-parenterally a greater range of solvents may evidently be used than where the depot is to be parenteral.

Component c as used herein may be a single solvent or a mixture of suitable solvents but will generally be of low viscosity. This is important because one of the key aspects of the present invention is that it provides preformulations that are of low viscosity and a primary role of a suitable solvent is to reduce this viscosity. This reduction will be a combination of the effect of the lower viscosity of the solvent and the effect of the molecular interactions between solvent and lipid composition. One observation of the present inventors is that the oxygen-containing solvents of low viscosity described herein have highly advantageous and unexpected molecular interactions with the lipid parts of the composition, thereby providing a non-linear reduction in viscosity with the addition of a small volume of solvent.

The viscosity of the "low viscosity" solvent component c (single solvent or mixture) should typically be no more than 18 mPas at 20°C. This is preferably no more than 15 mPas, more preferably no more than 10 mPas and most preferably no more than 7 mPas at 20°C.

The solvent component c will generally be at least partially lost upon *in vivo* formation of the depot composition, or diluted by absorption of water from the surrounding air and/or tissue. It is preferable, therefore, that component c be at least to some extent water miscible and/or dispersible and at least should not repel water to the extent that water absorption is prevented. In this respect also, oxygen containing solvents with relatively small numbers of carbon atoms (for example up to 10 carbons, preferably up to 8 carbons) are preferred. Obviously, where more oxygens are present a solvent will tend to remain soluble in water with a larger number of carbon atoms. The carbon to heteroatom (e.g. N, O, preferably oxygen) ratio will thus often be around 1:1 to 6:1, preferably 2:1 to 4:1. Where a solvent with a ratio outside one of these preferred ranges is used then this will preferably be no more than 75%, preferably no more than 50%, in combination with a preferred solvent (such as ethanol). This may be used, for example to decrease the rate of evaporation of the solvent from the pre-formulation in order to control the rate of liquid crystalline depot formation.

A further advantage of the present pre-formulations is that a higher level of bioactive agent may be incorporated into the system. In particular, by appropriate choice of components a-c (especially c), high levels of active agent may be dissolved or suspended in the pre-formulations. Generally, the lipid components in the absence of water are relatively poorly solubilising but in the presence of water form phases too viscous to administer easily. Higher proportions of bioactive agent may be included by use of appropriate solvents as component c and this level will either dissolve in the depot composition as it forms *in situ* or may form microdrops or microcrystals which will gradually dissolve and release active agent. A suitable choice of solvent will be possible by routine experimentation within the guidelines presented herein.

The pre-formulations of the present invention typically do not contain significant amounts of water. Since it is essentially impossible to remove every trace of water

from a lipid composition, this is to be taken as indicating that only such minimal trace of water exists as cannot readily be removed. Such an amount will generally be less than 1% by weight, preferably less that 0.5% by the weight of the pre-formulation. In one preferred aspect, the pre-formulations of the invention do not contain glycerol, ethylene glycol or propylene glycol and contain no more than a trace of water, as just described.

There is, however, a certain embodiment of the present invention in which higher proportions of water may be tolerated. This is where water is present as a part of the solvent component in combination with an additional water-miscible component c (single solvent or mixture). In this embodiment, up to 10 wt% water may be present providing that at least 3 wt%, preferably at least 5% and more preferably at least 7 wt% component c is also present, that component c is water miscible, and that the resulting preformulation remains non-viscous and thus does not form a liquid crystalline phase. Generally there will be a greater amount of component c) by weight than the weight of water included in the preformulation. Most suitable solvents of use with water in this aspect of the invention include ethanol, isopropyl alcohol, NMP, acetone and ethyl acetate.

The pre-formulations of the present invention contain one or more bioactive agents (described equivalently as "active agents" herein). Active agents may be any compound having a desired biological or physiological effect, such as a protein, drug, antigen, nutrient, cosmetic, fragrance, flavouring, diagnostic, pharmaceutical, vitamin, or dietary agent and will be formulated at a level sufficient to provide an *in vivo* concentration at a functional level (including local concentrations for topical compositions). Under some circumstances one or more of components a, b and/or c may also be an active agent, although it is preferred that the active agent should not be one of these components. Most preferred active agents are pharmaceutical agents including drugs, vaccines, and diagnostic agents.

Drug agents that may be delivered by the present invention include drugs which act on cells and receptors, peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulation system, endocrine and hormone system, blood circulatory system, synoptic sites, neuroeffector junctional sites, the immunological system, the

reproductive system, the skeletal system, autacoid system, the alimentary and excretory systems, the histamine system, and the central nervous system.

Examples of drugs which may be delivered by the composition of the present invention include, but are not limited to, antibacterial agents such as β-lactams or macrocyclic peptide antibiotics, anti fungal agents such as polyene macrolides (e.g. amphotericin B) or azole antifungals, anticancer and/or anti viral drugs such as nucleoside analogues, paclitaxel and derivatives thereof, anti inflammatorys, such as non-steroidal anti inflammatory drugs and corticosteroids, cardiovascular drugs including cholesterol lowering and blood-pressure lowing agents, analgesics, antipsychotics and antidepressants including seritonin uptake inhibitors, prostaglandins and derivatives, vaccines, and bone modulators. Diagnostic agents include radionuclide labelled compounds and contrast agents including X-ray, ultrasound and MRI contrast enhancing agents. Nutrients include vitamins, coenzymes, dietary supplements etc.

Particularly suitable active agents include those which would normally have a short residence time in the body due to rapid breakdown or excretion and those with poor oral bioavailability. These include peptide, protein and nucleic acid based active agents, hormones and other naturally occurring agents in their native or modified forms. By administering such agents in the form of a depot composition formed from the pre-formulation of the present invention, the agents are provided at a sustained level for a length of time which may stretch to days, weeks or even several months in spite of having rapid clearance rates. This offers obvious advantages in terms of stability and patient compliance over dosing multiple times each day for the same period. In one preferred embodiment, the active agent thus has a biological half life (upon entry into the blood stream) of less than 1 day, preferably less than 12 hours and more preferably less than 6 hours. In some cases this may be as low as 1-3 hours or less. Suitable agents are also those with poor oral bioavailability relative to that achieved by injection, for where the active agent also or alternatively has a bioavailability of below 0.1%, especially below 0.05% in oral formulations.

Peptide and protein based active agents include human and veterinary drugs selected from the group consisting of adrenocorticotropic hormone (ACTH) and its fragments, angiotensin and its related peptides, antibodies and their fragments, antigens and their fragments, atrial natriuretic peptides, bioadhesive peptides,

Bradykinins and their related peptides, calcitonins and their related peptides, cell surface receptor protein fragments, chemotactic peptides, cyclosporins, cytokines, Dynorphins and their related peptides, endorphins and P-lidotropin fragments, enkephalin and their related proteins, enzyme inhibitors, immunostimulating peptides and polyaminoacids, fibronectin fragments and their related peptides, gastrointestinal peptides, gonadotrophin-releasing hormone (GnRH) agonists and antagonist, glucagons like peptides, growth hormone releasing peptides, immunostimulating peptides, insulins and insulin-like growth factors, interleukins, luthenizing hormone releasing hormones (LHRH) and their related peptides, melanocyte stimulating hormones and their related peptides, nuclear localization signal related peptides, neurotensins and their related peptides, neurotransmitter peptides, opioid peptides, oxytocins, vasopressins and their related peptides, parathyroid hormone and its fragments, protein kinases and their related peptides, somatostatins and their related peptides, substance P and its related peptides, transforming growth factors (TGF) and their related peptides, tumor necrosis factor fragments, toxins and toxoids and functional peptides such as anticancer peptides including angiostatins, antihypertension peptides, anti-blood clotting peptides, and antimicrobial peptides; selected from the group consisting of proteins such as immunoglobulins, angiogenins, bone morphogenic proteins, chemokines, colony stimulating factors (CSF), cytokines, growth factors, interferons (Type I and II), interleukins, leptins, leukaemia inhibitory factors, stem cell factors, transforming growth factors and tumor necrosis factors.

A further considerable advantage of the depot compositions of the present invention is that active agents are released gradually over long periods without the need for repeated dosing. The composition are thus highly suitable for situations where patient compliance is difficult, unreliable or where a level dosage is highly important, such as mood-altering actives, those actives with a narrow therapeutic window, and those administered to children or to people who's lifestyle is incompatible with a reliable dosing regime. Also for "lifestyle" actives where the inconvenience of repeated dosing might outweigh the benefit of the active. Particular classes of actives for which this aspect offers a particular advantage include contraceptives, hormones including contraceptive hormones, and particularly hormones used in children such as growth hormone, anti-addictive agents, supplements such as vitamin or mineral supplements, anti-depressants and anticonvulsants

Cationic peptides are particularly suitable for use where a portion of the pre-formulation comprises an anionic amphiphile such as a fatty acid. In this embodiment, preferred peptides include octreotide, lanreotide, calcitonin, oxytocin, interferon-beta and -gamma, interleukins 4, 5, 7 and 8 and other peptides having an isoelectric point above pH 7, especially above pH 8.

In one preferred aspect of the present invention, the composition of the invention is such that an I_2 phase, or a mixed phase including I_2 phase is formed upon exposure to aqueous fluids and a polar active agent is included in the composition. Particularly suitable polar active agents include peptide and protein actives, oligo nucleotides, and small water soluble actives, including those listed above. Of particular interest in this aspect are the peptide octreotide and other somatostatin related peptides, interferons alpha and beta, glucagon-like peptides 1 and 2, luprorelin and other GnRH agonist, abarelix and other GnRH antagonists, interferon alpha and beta, zolendronate and ibandronate and other bisphosponates, and polar active chlorhexidine (e.g. chlorhexidine digluconate or chlorhexidine dihydrochloride).

A particular advantage of the present invention when used in combination with protein / peptide active agents is that aggregation of the active agent is suppressed. In one preferred embodiment, the present invention thus provides a depot precursor and particularly a depot composition as described herein comprising at least one peptide (e.g. antibody) or protein active agent wherein no more than 5% of the active agent is in aggregated form. Preferably no more than 3% is aggregated and most preferably no more than 2% (especially less than 2%) is in aggregated form. This stabilisation of non-aggregated protein is highly advantageous from the point of view of high effectiveness, low side effects and predictable absorption profile. Furthermore, it is increasingly expected that protein / peptide therapeutics will have low levels of protein aggregation in order to secure regulatory approval.

The amount of bioactive agent to be formulated with the pre-formulations of the present invention will depend upon the functional dose and the period during which the depot composition formed upon administration is to provide sustained release. Typically, the dose formulated for a particular agent will be around the equivalent of the normal daily dose multiplied by the number of days the formulation is to provide release. Evidently this amount will need to be tailored to take into account any adverse effects of a large dose at the beginning of treatment and so this will

generally be the maximum dose used. The precise amount suitable in any case will readily be determined by suitable experimentation.

In one embodiment, the pre-formulations of the present invention will generally be administered parenterally. This administration will generally not be an intravascular method but will preferably be subcutaneous intracavitary or intramuscular. Typically the administration will be by injection, which term is used herein to indicate any method in which the formulation is passed through the skin, such as by needle, catheter or needle-less injector.

In parenteral (especially sub cutaneous) depot precursors, preferred active agents are those suitable for systemic administration including antibacterials (including amicacin, monocycline anddoxycycline), local and systemic anagesics (including bupivacain, tramadol, fentanyl, morphine, hydromorphone, methadone, oxycodone, codeine, asperine, acetaminophen), NSAIDS (such as ibuprofene, naproxene, keteprofene, indomethansine, sulindac, tolmethin, salysylic acids such as salisylamide, diflunisal), Cox1 or Cox2 inhibitors (such as celecoxib, rofecoxib, valdecoxib) anticancer agents (including octreotide, lanreotide, buserelin, luprorelin, goserelin, triptorelin, avorelin, deslorein, abarelix, degarelix, fulvestrant, interferon alpha, interferon beta, darbepoetin alpha, epoetin alpha, beta, delta, and paclitaxel), antipsychotics (like bromperidol, risperidone, olanzapine, iloperidone, paliperadone, pipotiazine and zuclopenthixol), antivirals, anticonvulsants (for instance tiagabine topiramate or gabapentin) or nicotine, hormones (such as testosterone, and testosterone undecanoate, medroxyprogesterone, estradiol) growth hormones (like human growth hormone), and growth factors (like granulocyte macrophage colony-stimulating factor)

In an alternative embodiment, the formulations of the present invention may form non-parenteral depots where the active agent is slowly released at a body surface. It is especially important in this embodiment that the pre-formulations of the invention and/or the liquid crystalline depot compositions formed therefrom should preferably be bioadhesive. That is to say that the compositions should coat the surface to which they are applied and/or upon which they form as appropriate and should remain even when this surface is subject to a flow of air or liquid and/or rubbing. It is particularly preferable that the liquid crystalline depot compositions formed should be stable to rinsing with water. For example, a small volume of depot

precursor may be applied to a body surface and be exposed to a flow of five hundred times its own volume of water per minute for 5 minutes. After this treatment, the composition can be considered bioadhesive if less than 50% of the bioactive agent has been lost. Preferably this level of loss will be matched when water equalling 1000 times and more preferably 10 000 times the volume of the composition is flowed past per minute for five, or preferably 10, minutes.

Although the non-parenteral depot compositions of the present invention may absorb some or all of the water needed to form a liquid crystalline phase structure from the biological surfaces with which they are contacted, some additional water may also be absorbed from the surrounding air. In particular, where a thin layer of high surface area is formed then the affinity of the composition for water may be sufficient for it to form a liquid crystalline phase structure by contact with the water in the air. The "aqueous fluid" are referred to herein is thus, at least partially, air containing some moisture in this embodiment.

Non-parenteral depot compositions will typically be generated by applying the pre-formulation topically to a body surface or to a natural or artificially generated body cavity and/or to the surface of an implant. This application may be by direct application of liquid such as by spraying, dipping, rinsing, application from a pad or ball roller, intra-cavity injection (e.g to an open cavity with or without the use of a needle), painting, dropping (especially into the eyes) and similar methods. A highly effective method is aerosol or pump spraying and evidently this requires that the viscosity of the pre-formulation be as low as possible and is thus highly suited to the compositions of the invention. Non-parenteral depots may, however, be used to administer systemic agents e.g. transmucosally or transdermally.

Non-parenteral depots may also be used for application to surfaces, particularly of implants and materials which will be in contact with the body or a body part or fluid. Devices such as implants, catheters etc. may thus be treated e.g. by dipping or spraying with the preformulations of the invention, which will form a robust layer to reduce the introduction of infection. Anti-infective actives are particularly suited to this aspect.

Conditions particularly suitable for causative or symptomatic treatment by topical bioadhesive depot compositions of the present invention include skin conditions

(such as soreness resulting from any cause including chapping, scratching and skin conditions including eczema and herpes) eye conditions, genital soreness (including that due to genital infection such as genital herpes), infections and conditions for the finger and/or toe nails (such as bacterial or fungal infections of the nails such as onychomycosis or poronychia). Topical-type bioadhesive formulations may also be used to administer systemic active agents (e.g. medication), particularly by skin adsorption, oral, transdermal or rectal routes. Travel sickness medication is a preferred example, as is nicotine (e.g. in anti-smoking aids). Where context permits, "topical application" as referred to herein includes systemic agents applied non-parenterally to a specific region of the body.

Periodontal infections are particularly suitable for treatment by the compositions of the present invention. In particular, known compositions for treating periodontal infection are difficult to apply or are generally ineffective. The most widely used periodontal depot composition comprises insertion of a collagen "chip" into the periodontal space, from which an anti-infective agent is released. This chip is difficult to insert and does not form to match the shape and volume of the periodontal space, so that pockets of infection may remain untreated. In contrast to this, the compositions of the present invention, applied as a low viscosity preformulation, can be easily and quickly injected into the periodontal space and will flow to conform exactly to that space and fill the available volume. The compositions then quickly absorb water to form a robust gel which is resistant to aqueous conditions of the mouth. The only known previous attempt at such an injectible periodontal treatment relied on dispersions of relatively high viscosity which were difficult to apply and were subject to undesirable phase separation. All of these drawbacks are now addressed in the compositions of the present invention as described herein. Highly suitable actives for periodontal administration are antiinfectives, especially benzydamine, tramadol and chlorhexidine.

Non-parenteral depot compositions are also of significant benefit in combination with non-pharmaceutical active agents, such as cosmetic actives, fragrances, essential oils etc. Such non-pharmaceutical depots will maintain the important aspects of bioadhesion and sustained release to provide prolonged cosmetic effects, but may easily be applied by spraying or wiping. This additionally applies to agents which have both cosmetic and medical (especially prophylactic) benefits such as sun-protective agents. Since the topical depot compositions provide robust, water

resistant barriers which can solubilise high levels of actives, they are especially suitable for sunscreens and sunblocks in combination with ultra violet light (UV, e.g. UVa, UVb and/or UVc) absorbing and/or scattering agents, particularly where high levels of protection is desirable. The compositions are furthermore highly biocompatible and may act to moisten and soothe the skin during sun exposure. Compositions of the invention containing soothing agents such as aloe vera are also highly suitable for soothing and moistening application after exposure to sunlight, or to skin which is dry, inflamed or damaged due to, for example irritation, burning or abrasion.

Active agents particularly suited to non-parenteral (e.g. topical) depot administration, which comprises intra oral, buccal, nasal, ophthalmic, dermal, vaginal delivery routes, include antibacterials such as chlorhexidine, chloramphenicol, triclosan, tetracycline, terbinafine, tobramycin, fusidate sodium, butenafine, metronidazole (the latter particularly for the (e.g. symtomatic) treatment of acne rosacea - adult acne or some vaginal infections), antiviral, including acyclovir, anti infectives such as bibrocathol, ciprofloxacin, levofloxacin, local analgesics such as benzydamine, lidocaine, prilocaine, xylocaine, bupivacaine, analgesics such as tramadol, fentanyl, morphine, hydromorphone, methadone, oxycodone, codeine, asperine, acetaminophen, NSAIDS such as ibuprofen, flurbiprofen, naproxene, ketoprofen, fenoprofen, diclofenac, etodalac, diflunisal, oxaproxin, piroxicam, piroxicam, indomethansine, sulindac, tolmethin, salysylic acids such as salisylamide and diflunisal, Cox1 or Cox2 inhibitors such as celecoxib, rofecoxib or valdecoxib, corticosteroids, anticancer and immuno stimulating agents (for instance ,metylaminolevulinat hydrocloride, interferon alpha and beta), anticonvulsants (for instance tiagabine topiramate or gabapentin), hormones (such as testosterone, and testosterone undecanoate, medroxyprogesterone, estradiol) growth hormones (like human growth hormone), and growth factors (like granulocyte macrophage colony-stimulating factor), immuno suppressants (cyclosporine, sirolimus, tacrolimus), nicotine and antivirals (e.g. acyclovir).

Some specific actives found by the inventors to form highly effective depots of the present invention include the following:

For long acting injectable depot products of hydrophilic active agents;

i. octreotide (or other somatostatin analogues such as lanreotide for treatment of carcoid and VIP producing tumours and acromegali). Subcutaneous depots formable, especially with GDO and PC having a sustained release duration of more than one month and showing less than 20% octreotide degraded in one month in water-swollen depot at 37°C. Surprisingly good stability was observed and found to be better than octreotide formulated in microspheres. Depot showed less than 5% degradation in product preformulation over eight weeks at 4°C.

ii. human growth hormone. For treatment of growth disorders and growth hormone deficiencies. Subcutaneous depot formable, especially with GDO and PC having a sustained release duration of more than two weeks

iii. interferon alpha, for treatment of cancer and viral infections. Subcutaneous depots formable, especially with GDO and PC, having a sustained release duration of more than one month

iv. leuprolide. Depots formable having continuous delivery (preferably continuous delivery inside therapeutic window) for minimum of one month.

For long acting injectable depots of lipophilic/amphiphilic actives;

i. risperidone

ii. olanzapine

iii. testosterone undecanoate

Depots i to iii formable having continuous delivery (preferably continuous delivery inside therapeutic window) for minimum of two weeks.

For topical bioadhesive, controlled release products for intraoral (including buccal & periodontal) administration;

i. benzydamine (local analgesic, anti inflammatory,) or other local analgesic, analgesic, anti inflammatory, anti bacterial, anti fungal or combination thereof. Composition provides sustained effect at intraoral mucosa, in particular damaged, sensitised, infected mucosa e.g. in patients suffering from oral mucositis (induced by e.g. chemo- and radiotherapy). In particular for treatment of oral mucositis.

ii. tramadol (analgesic). Provides a composition with sustained systemic analgesic effect.

iii. chlorhexidine gluconate (antibacterial) for treatment of periodontal and topical infections. Particularly for long acting effect in periodontal pocket. Compositions result in depots releasing chlorhexidine over more than 1h, preferably more than 6h, most preferably more than 24 h when applied as a liquid, forming a bioadhesive gel *in situ*. Surface gel formation time observed to be between 1 second. and 5 min.

Depots i to iii formable having high level of active agent incorporation and high degree of resistance to washing away. Preformulations in the form of a liquid administered as spray or liquid wash/rinse for i and ii and gel-forming liquid for iii, *wherein liquid is applied to periodontal pocket, e.g. by injection.*

For non-parenteral (e.g. topical or systemic) bioadhesive, controlled release products for nasal administration;

i. fentanyl (analgesic) provides rapid onset and sustained duration analgesia when administered as spray

ii. diazepam (anti anxiety) provides non-parenteral, nasal depot with systemic effect giving rapid onset and sustained duration. Administered as a spray

For topical bioadhesive, controlled release products for ophthalmic administration;

i. diclofenac (NSAID) with sustained duration. Administered as in situ phase forming liquid

ii. pilocarpine (parasymptomimetic, cholinergic agonist) for treatment of glaucoma.

iii levocabastine hydrochloride, ketotifen fumarate providing liquid for eye-*dropping to give long lasting relief from allergic conjunctivitis with long* period between reapplication.

iv Pilocarpine hydrochloride for the treatment of Sjögrens syndrome.

v dexamethasone, (corticosteroid)

vi chloramphenicol (primarily bacteriostatic antiinfective)

vii indomethacin (NSAID)

Depots i to vii formulated as liquid spray or more preferably drops for direct application to eye surface and provide *in situ* depot formation with high resistance to washing out by tears and wear from blinking/eye rubbing.

Other actives suitable for ophthalmic compositions include Antihistamines, Mast cell stabilizers, Nonsteroidal anti-inflammatory drugs (NSAIDs), Corticosteroids (e.g. to treat allergic conjunctivitis), Anti-Glaucoma actives including inflow suppressing/inhibiting agents (beta blocking agents: timolol, betaxolol, carteolol, levobunolol, etc., topical carbonic anhydrase inhibitors: dorzolamide, brinzolamide, sympathomimetics: epinephrine, dipivefrin, clonidine, apraclonidine, brimonidine), outflow facilitating agents (parasympathomimetics (cholinergic agonists): pilocarpine prostaglandin analogues and related compounds: atanoprost, travoprost, bimatoprost, unoprostone)

For non-parenteral (e.g. topical or systemic) bioadhesive, controlled release products for dermatological administration;

i. acyclovir (antiviral). Composition generates a bioadhesive, film forming product with sustained duration. Applied as spray or liquid

ii. testosterone undecanoate (hormone deficiency). bioadhesive, film forming composition with sustained duration. May be applied as aerosol- or pump-spray, or as liquid.

Particularly suitable applications of dermatological formulations are anti-infective dermatological bioadhesive depots for protection in environments where contact with infective agents likely (e.g. human or veterinary surgery, abattoir work, certain types of cleaning etc.). Bioadhesive depots generated from composition of the invention provide robust and sustained protection for the wearer. The compositions with antiinfective agents may also be used in situations where skin sterility of the wearer is important for the health of others, such as for nurses or doctors visiting multiple patients in hospital, where cross-infection must be avoided. A prior coating with a composition of the present invention may serve to provide resistance against picking up of infectives from one area and thus prevent transmission to another.

The pre-formulations of the present invention provide non-lamellar liquid crystalline depot compositions upon exposure to aqueous fluids, especially *in* vivo and in contact with body surfaces. As used herein, the term "non-lamellar" is used to indicate a normal or reversed liquid crystalline phase (such as a cubic or hexagonal phase) or the L3 phase or any combination thereof. The term liquid crystalline indicates all hexagonal, all cubic liquid crystalline phases and/or all mixtures

thereof. Hexagonal as used herein indicates "normal" or "reversed" hexagonal (preferably reversed) and "cubic" indicates any cubic liquid crystalline phase unless specified otherwise. By use of the pre-formulations of the present invention it is possible to generate any phase structure present in the phase-diagram of components a and b with water. This is because the pre-formulations can be generated with a wider range of relative component concentrations than previous lipid depot systems without risking phase separation or resulting in highly viscous solutions for injection. In particular, the present invention provides for the use of phospholipid concentrations above 50% relative to the total amphiphile content. This allows access to phases only seen at high phospholipid concentrations, particularly the hexagonal liquid crystalline phases.

For many combinations of lipids, only certain non-lamellar phases exist, or exist in any stable state. It is a surprising feature of the present invention that compositions as described herein frequently exhibit non-lamellar phases which are not present with many other combinations of components. In one particularly advantageous embodiment, therefore, the present invention relates to compositions having a combination of components for which an I_2 and/or L_2 phase region exists when diluted with aqueous solvent. The presence or absence of such regions can be tested easily for any particular combination by simple dilution of the composition with aqueous solvent and study of the resulting phase structures by the methods described herein.

In a highly advantageous embodiment, the compositions of the invention may form an I_2 phase, or a mixed phase including I_2 phase upon contact with water. The I_2 phase is a reversed cubic liquid crystalline phase having discontinuous aqueous regions. This phase is of particular advantage in the controlled release of active agents and especially in combination with polar active agents, such as water soluble actives because the discontinuous polar domains prevent rapid diffusion of the actives. Depot precursors in the L_2 are highly effective in combination with an I_2 phase depot formation. This is because the L_2 phase is a so-called "reversed micellar" phase having a continuous hydrophobic region surrounding discrete polar cores. L_2 thus has similar advantages with hydrophilic actives.
In transient stages after contact with body fluid the composition can comprise multiple phases since the formation of an initial surface phase will retard the passage of solvent into the core of the depot, especially with substantial sized

administrations of internal depots. Without being bound by theory, it is believed that this transient formation of a surface phase, especially a liquid crystalline surface phase, serves to dramatically reduce the "burst/lag" profile of the present compositions by immediately restricting the rate of exchange between the composition and the surroundings. Transient phases may include (generally in order from the outside towards the centre of the depot): H_{II} or L_α, I_2, L_2, and liquid (solution). It is highly preferred that the composition of the invention is capable forming at least two and more preferably at least three of these phases simultaneously at transient stages after contact with water at physiological temperatures. In particular, it is highly preferred that one of the phases formed, at least transiently, is the I_2 phase.

It is important to appreciate that the preformulations of the present invention are of low viscosity. As a result, these preformulations must not be in any bulk liquid crystalline phase since all liquid crystalline phases have a viscosity significantly higher than could be administered by syringe or spray dispenser. The preformulations of the present invention will thus be in a non-liquid crystalline state, such as a solution, L_2 or L_3 phase, particularly solution or L_2. The L_2 phase as used herein throughout is preferably a "swollen" L_2 phase containing greater than 10 wt% of solvent (component c) having a viscosity reducing effect. This is in contrast to a "concentrated" or "unswollen" L_2 phase containing no solvent, or a lesser amount of solvent, or containing a solvent (or mixture) which does not provide the decrease in viscosity associated with the oxygen-containing, low viscosity solvents specified herein.

Upon administration, the pre-formulations of the present invention undergo a phase structure transition from a low viscosity mixture to a high viscosity (generally tissue adherent) depot composition. Generally this will be a transition from a molecular mixture, swollen L_2 and/or L3 phase to one or more (high viscosity) liquid crystalline phases such as normal or reversed hexagonal or cubic liquid crystalline phases or mixtures thereof. As indicated above, further phase transitions may also take place following administration. Obviously, complete phase transition is not necessary for the functioning of the invention but at least a surface layer of the administered mixture will form a liquid crystalline structure. Generally this transition will be rapid for at least the surface region of the administered formulation (that part in direct contact with air, body surfaces and/or body fluids). This will

most preferably be over a few seconds or minutes (e.g. up to 30 minutes, preferably up to 10 minutes, more preferably 5 minutes of less). The remainder of the composition may change phase to a liquid crystalline phase more slowly by diffusion and/or as the surface region disperses.

In one preferred embodiment, the present invention thus provides a pre-formulation as described herein of which at least a portion forms a hexagonal liquid crystalline phase upon contact with an aqueous fluid. The thus-formed hexagonal phase may gradually disperse, releasing the active agent, or may subsequently convert to a cubic liquid crystalline phase, which in turn then gradually disperses. It is believed that the hexagonal phase will provide a more rapid release of active agent, in particular of hydrophilic active agent, than the cubic phase structure, especially the I_2 and L_2 phase. Thus, where the hexagonal phase forms prior to the cubic phase, this will result in an initial release of active agent to bring the concentration up to an effective level rapidly, followed by the gradual release of a "maintenance dose" as the cubic phase degrades. In this way, the release profile may be controlled.

Without being bound by theory, it is believed that upon exposure (e.g. to body fluids), the pre-formulations of the invention lose some or all of the organic solvent included therein (e.g. by diffusion and/or evaporation) and take in aqueous fluid from the bodily environment (e.g. moist air close to the body or the *in vivo* environment) such that at least a part of the formulation generates a non-lamellar, particularly liquid crystalline phase structure. In most cases these non-lamellar structures are highly viscous and are not easily dissolved or dispersed into the *in vivo* environment and are bioadhesive and thus not easily rinsed or washed away. Furthermore, because the non-lamellar structure has large polar, apolar and boundary regions, it is highly effective in solubilising and stabilising many types of active agents and protecting these from degradation mechanisms. As the depot composition formed from the pre-formulation gradually degrades over a period of days, weeks or months, the active agent is gradually released and/or diffuses out from the composition. Since the environment within the depot composition is relatively protected, the pre-formulations of the invention are highly suitable for active agents with a relatively low biological half-life (see above).

It is an unexpected finding of the present inventors that the pre-formulations result in a depot composition that have very little "burst" effect in the active agent release

profile. This is unexpected because it might be expected that the low viscosity mixture (especially if this is a solution) of the pre-composition would rapidly lose active agent upon exposure to water. In fact, pre-formulations of the invention have shown considerably less of an initial "burst" than previously known polymer-base depot compositions. This is illustrated in the Examples below and Figures attached hereto. In one embodiment, the invention thus provides injectable preformulations and resulting depot compositions wherein the highest plasma concentration of active after administration is no more than 5 times the average concentration between 24 hours and 5 days of administration. This ratio is preferably no more than 4 times and most preferably no more than 3 times the average concentration.

In an additional aspect of the invention, the topical compositions may be used to provide a physical barrier on body surfaces, in the absence of any active agent. In particular, because of the very high bioadherance of the compositions, "barrier" coatings formed by spraying or application of liquid may be formed from the present compositions so as to reduce contact with potential infective or irritant agents or to reduce soiling of the body surfaces. The robust nature of the compositions and resistance to washing provide advantageous characteristics for such barriers, which could conveniently be applied as a liquid or by spraying.

The Invention will now be further illustrated by reference to the following non-limiting Examples and the attached Figures, in which;

Figure 1 shows the cumulative release of methylene blue (MB) from a depot formulation comprising PC/GDO/EtOH (45/45/10 wt%) when injected into excess water;

Figure 2 demonstrates the non-linear decrease of pre-formulation viscosity upon addition of N-methyl pyrolidinone (NMP) and EtOH;

Figure 3 shows the plasma concentration (in rats) of salmon calcitonin (sCT) after subcutaneous injection of various PC/GDO/EtOH depot precursors containing 500 μg sCT / g of formulation;

Figure 4 shows the initial *in vivo* release (up to 48 hours) to plasma (in rats) of sCT from two different depot formulations following subcutaneous injection;

Figure 5 shows the plasma concentration (in rats) of octreotide (OCT) following subcutaneous injection of a depot formulation comprising PC/GDO/EtOH (36/54/10 wt%) containing 5 mg OCT / g formulation, corresponding to 0.5% drug load.

Figure 6 shows the plasma concentration (in rats) of octreotide (OCT) following subcutaneous injection of a depot formulation comprising PC/GDO/EtOH (47.5/47.5/5.0 wt%) containing 30 mg OCT / g formulation, corresponding to 3% drug load.

Figure 7 displays the *in vitro* release in excess aqueous phase of chlorhexidine from a depot formulation comprising PC/GDO/EtOH (36/54/10 wt%) containing 50 mg chlorhexidine / g of formulation, corresponding to 5% drug load.

Examples:

Example 1

Availability of various liquid crystalline phases in the depot by choice of composition

Injectable formulations containing different proportions of phosphatidyl choline ("PC" - Epikuron 200) and glycerol dioleate (GDO) and with EtOH as solvent were prepared to illustrate that various liquid crystalline phases can be accessed after equilibrating the depot precursor formulation with excess water.

Appropriate amounts of PC and EtOH were weighed in glass vials and the mixture was placed on a shaker until the PC completely dissolved to form a clear liquid solution. GDO was then added to form an injectable homogenous solution.

Each formulation was injected in a vial and equilibrated with excess water. The phase behaviour was evaluated visually and between crossed polarizes at 25°C. Results are presented in Table 1.

TABLE 1

Formulation	PC (wt%)	GDO (wt%)	EtOH (wt%)	Phase in H_2O
A	22.5	67.5	10.0	L_2
B	28.8	61.2	10.0	I_2
C	45.0	45.0	10.0	H_{II}
D	63.0	27.0	10.0	H_{II}/L_α

L_2 = reversed micellar phase

I_2 = reversed cubic liquid crystalline phase

H_{II} = reversed hexagonal liquid crystalline phase

L_α = lamellar phase

Example 2

In vitro release of a water-soluble substance

A water-soluble colorant, methylene blue (MB) was dispersed in formulation C (see Example 1) to a concentration of 11 mg/g formulation. When 0.5 g of the formulation was injected in 100 ml water a stiff reversed hexagonal H_{II} phase was formed. The absorbency of MB released to the aqueous phase was followed at 664 nm over a period of 10 days. The release study was performed in an Erlenmeyer flask at 37°C and with low magnetic stirring.

The release profile of MB (see Figure 1) from the hexagonal phase indicates that this (and similar) formulations are promising depot systems. Furthermore, the formulation seems to give a low initial burst, and the release profile indicates that the substance can be released for several weeks; only about 50% of MB is released after 10 days.

Example 3

Viscosity in PC/GDO (6:4) or PC/GDO (3:7) on addition of solvent (EtOH, PG and NMP)

A mixture of PC/GDO/EtOH was manufactured according to the method in Example 1. All, or nearly all, of the EtOH was removed from the mixture with a

rotary evaporator (vacuum, 40°C, 1h) and the resulting solid mixture were weighed in glass vial after which 2, 5, 10 or 20% of a solvent (EtOH, propylene glycol (PG) or n-methyl pyrrolidone (NMP)) was added. The samples were allowed to equilibrate several days before the viscosity was measured at a shear rate of $0.1s^{-1}$ with a Physica UDS 200 rheometer at 25°C.

This example clearly illustrates the need for solvent with certain depot precursors in order to obtain an injectable formulation (see Figure 2). The viscosity of solvent-free PC/GDO mixtures increases with increasing ratio of PC. Systems with low PC/GDO ratio (more GDO) are injectable with a lower concentration of solvent.

Example 4

Composition and in vitro phase study

The formulations were manufactured according to the method described in Example 1 with compositions according to Table 2. An active substance (peptide), salmon calcitonin (sCT), was added to each formulation to a concentration of 500 µg sCT/g formulation. The formulations were designed as homogenous suspensions for parenteral administration (mixing required shortly prior to use since the drug is not completely dissolved in the PC/GDO/EtOH system).

The phase study in this example is performed in excess of rat serum at 37°C in order to simulate an *in vivo* situation. Table 2 shows that the same phases as those in water are formed (compare Table 1).

TABLE 2

Formulation	PC (wt%)	GDO (wt%)	OA (wt%)	EtOH (wt%)	Phase in rat serum
E	18	72	-	10	L_2
F	36	54	-	10	I_2
G	34	51	5	10	I_2
H	54	36	-	10	H_{II}
I	72	18	-	10	H_{II}/L_α

OA = Oleic Acid

Example 5

Sterile filtration of formulations with reduced viscosity

To lower the viscosity with various solvents is sometimes necessary in order to obtain an injectable formulation and to be able to administrate the system with a regular syringe (see Example 3). Another important effect from the viscosity-lowering solvent is that the formulations can be sterile filtrated.

Formulations E to I in Example 4 were studied in a sterile filtration test by using a 0.22µm filter (before addition of the active substance). Formulations E to H were successfully filtrated, but formulation I failed since the viscosity was too high. An aseptic manufacturing procedure was therefore needed for this formulation.

Example 6

***In vivo* release study from depot formulations subcutaneously administered**

Formulations E to I in Example 4 were used in an *in vivo* drug release study in rat. The formulations were administrated subcutaneously between the scapulae by using a syringe (21G, 0.6mm x 30mm) and the dose of sCT was 500 µg/ kg body weight. The release profile was monitored for a period of 13 days. The sCT concentration in the rat plasma samples was analysed with sandwich-type immunoassay using a commercial kit from DSLabs.

Figure 3 shows the results (n=4). A pure triglyceride vehicle based on sesame oil was selected as a lipid reference system.

Example 7

***In vivo* release study in the initial phase**

Formulations F and G as in Example 6 were used in an *in vivo* study in rat designed to investigate the initial "burst effect". From Figure 4 (n=8) it appears that none of the investigated formulations has a severe burst effect.

Example 8: Preparation of depot precursor compositions with various solvents.

Depending on composition of the formulation and the nature and concentration of active substance certain solvents may be preferable.

Depot precursor formulations (PC/GDO/solvent (36/54/10)) were prepared by with various solvents; NMP, PG, PEG400, glycerol/EtOH (90/10) by the method of Example 1. All depot precursor compositions were homogeneous one phase solutions with a viscosity that enabled injection through a syringe (23G - i.e. 23 gauge needle; 0.6mm x 30mm). After injecting formulation precursors into excess water a liquid crystalline phase in the form of a high viscous monolith rapidly formed with NMP and PG containing precursors. The liquid crystalline phase had a reversed cubic micellar (I_2) structure. With PEG400, glycerol/EtOH (90/10) the viscosification/solidification process was much slower and initially the liquid precursor transformed to a soft somewhat sticky piece. The difference in appearance probably reflects the slower dissolution of PEG400 and glycerol towards the excess aqueous phase as compared to that of EtOH, NMP and PG.

Example 9: Preparation of depot composition containing human growth hormone (HGH).

Human growth hormone (hGH) plays a critical role in stimulating body growth and development, and is involved in the production of muscle protein and in the breakdown of fats. A deficiency of the hormone adversely affects numerous body processes such as lipid profile, insulin status, physical performance, bone-mineral density and quality of life. A targeted dose every 2 weeks is estimated at 0.10 to 0.24 mg/kg of body weight.
1ml of a 2 weeks depot formulation precursor was formed by sequentially mixing 10mg hGH and 360mg PC in 0.1ml NMP. 540mg GDO was added to the mixture to obtain a low viscosity depot formulation precursor. Injecting the formulation precursor into excess water (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase (I_2 structure).

Example 10: Preparation of depot composition containing a sparingly soluble active substance.

Risperidone is an antipsychotic medication agent belonging to the chemical class of benzisoxazole derivatives. It is a very strong dopamine blocker (antagonist); ie, it inhibits functioning of dopamine receptors, it is practically insoluble in water, and it has log(P)= 3.49.

1g of a depot formulation containing 50mg of risperidone was prepared by dissolving the active substance in 0.7g of a mixture 95%wt in EtOH (99.5%) and 5%wt in acetic acid. 0.34g PC and 0.51g GDO were subsequently dissolved in this solution followed by solvent reduction to remaining 0.15g solvent (0.55g was evaporated under vacuum). The composition of the final homogenous and clear depot formulation with 50mg risperidone was PC/GDO/solvent/risperidone (32/49/14/5). Injecting the formulation precursor into excess water (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase (I_2 structure). I.e. the amount of active substance (5%) did not change monolith formation and phase behavior after exposure to an aqueous environment.

Example 11: Alternate preparation of depot composition containing risperidone.

A risperidone depot precursor formulation could also be prepared by using a solvent mixture composed of 90%wt EtOH (99.5%) and 10%wt in acetic acid.

50mg of risperidone was dissolved in 0.7g of the solvent mixture, after which 0.36g PC and 0.54g GDO were subsequently dissolved in this solution. 0.60g of the solvent mixture was evaporated under vacuum to a homogenous and clear depot formulation precursor with 50mg risperidone (PC/GDO/solvent/risperidone (34/51/10/5)). Injecting the formulation precursor into excess water (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase (I_2 structure). I.e. the amount of active substance (5%) did not change monolith formation and phase behavior after exposure to an aqueous environment.

Example 12: Temperature stability of depot composition containing a sparingly soluble active substance.

The risperdone depot precursor formulations in examples 10 and 11 were tested for stability against crystallization during storage. Each formulation was stable at 25°C for at least two weeks and at +8°C for at least one week.

Example 13: Preparation of depot composition containing benzydamine.

Benzydamine is a non-steroidal antiinflammatory drug and is extensively used as a topical drug in inflammatory conditions.

1g of a depot formulation containing 1.5mg benzydamine was prepared by dissolving the active substance in a mixture of PC/GDO/EtOH (36/54/10) prepared as described in Example 1. The depot composition was stable against crystallization during storage at 25°C for at least two weeks. Equilibration of the formulation precursor with excess water resulted in a high viscous monolithic liquid crystalline phase (I_2 structure).

Example 14: Robustness of the behaviour of the formulation against variations in the excipient quality.

Depot precursor formulations were prepared with several different GDO qualities (supplied by Danisco, Dk), Table 3, using the method of Example 1. The final depot precursors contained 36%wt PC, 54%wt GDO, and 10%wt EtOH. The appearance of the depot precursors was insensitive to variation in the quality used, and after contact with excess water a monolith was formed with a reversed micellar cubic phase behaviour (I_2 structure).

Table 3. Tested qualities of GDO.

GDO quality	Monoglyceride (%wt)	Diglyceride (%wt)	Triglyceride (%wt)
A	10.9	87.5	1.6
B	4.8	93.6	1.6
C	1.0	97.3	1.7
D	10.1	80.8	10.1
E	2.9	88.9	8.2
F	0.9	89.0	10.1

Example 15: Preparation of depot composition containing saturated PC (Epikuron 200SH).

Depot precursor formulations were prepared with various amounts PC comprising saturated hydrocarbon chains by addition of Epikuron 200SH directly to a mixture of PC/GDO/EtOH, prepared as for Example 1. The formulations are shown in Table 4. All precursor formulations were homogenous one phase samples in RT, while they became more viscous with increasing amount Epikuron 200SH. Injecting the depot precursor into excess water gave a monolith comprising a reversed miceller cubic (I_2) structure. Monoliths formed from samples containing higher amounts of Epikuron 200SH became turbid, possibly indicating segregation between Epikuron 200SH and the other components upon exposure to water and formation of the I2 phase.

Table 4. Depot composition containing saturated PC

Formulation	Saturated PC, Epikuron 200SH (%wt)	PC (%wt)	GDO (%wt)	EtOH (%wt)
G1	3.9	34.6	51.9	9.6
G2	7.0	33.5	50.2	9.3
G3	14.3	30.8	46.3	8.6

Example 16: Preparation of depot precursor being a dispersion or solution of the peptide salmon calcitonin.

By adding 500µg sCT/g formulation to a solution of PC/GDO/EtOH (36/54/10), obtained as in Example 1, a dispersion of sCT was formed.

In an alternative method, 500µg sCT was dissolved in excess of EtOH followed by addition of PC and GDO. The solvent concentration was then reduced (EtOH evaporation) to form a homogenous (active drug in solution) formulation. This latter technique can be used to obtain higher drug loads. Precursor compositions corresponding to at least 1500µg dissolved sCT per gram of the final depot precursor composition could be obtained by this method.

Example 17: In vivo release study from depot formulation subcutaneously administered.

The two sCT compositions described in Example 16 were administered in an *in vivo* rat model by subcutaneous injection (between the scapulae). The first depot precursor having dispersed sCT was found to give somewhat unstable initial plasma concentrations, while the second depot precursor, having sCT dissolved therein, gave much more stable initial plasma levels (see Table 5).

Table 5

Formulations	Coefficient of variation (%CV)
Dispersed: 500μg sCT/g PC/GDO/EtOH (36/54/10)	32-127
Dissolved: 500μg sCT/g PC/GDO/EtOH (36/54/10)	20-37

Example 18: Preparation of depot composition containing the peptide octreotide.

Octreotide is an acetate salt of a synthetic octa-peptide and is similar to the hormone somatostatin. Octreotide decreases production of substances such as growth hormone, insulin and glucagons. It is used in treatment of acromegaly, and to reduce flushing and watery diarrhoea caused by metastatic cancerous tumors (carcinoid syndrome) or tumors called vasoactive intestinal peptide tumors (VIPomas).

24mg or 60mg octreotide was dissolved in 0.1g EtOH. 0.36g PC and 0.54g GDO were subsequently dissolved in this solution and a depot formulation precursor was obtained. Injecting the formulation precursor into excess aqueous phase (syringe 23G; 0.6mm x 30mm) resulted in a monolithic liquid crystalline phase (I_2 structure). I.e. octreotide (2.4% or 6.0%) did not change monolith formation and phase behaviour after exposure to an aqueous environment.

The octreotide depot precursor formulations in this Example were tested for stability against crystallization during storage. Each formulation was stable at 4-8°C for at least two weeks.

Example 19: In vivo release study from depot formulation containing octreotide subcutaneously administered.

In an in vivo rat model the drug release of octreotide was followed during 28 days. The formulations were administered subcutaneously between the scapulae by using a syringe (23G, 0.6mm x 25mm). The octreotide concentration in the rat plasma was followed for a period of 28 days (see Figure 5). The dose was 5 mg/kg and volume 1 ml/kg corresponding to a drug load of 0.5% octreotide in the depot formulation precursor (PC/GDO/EtOH (36/54/10)).
From Figure 5 (n=3) it appears that the investigated formulation gives a release profile essentially without a burst effect.

Figure 5 shows Octreotide plasma levels in the rat model following administration of octreotide formulation precursor (0.5% in octreotide).

Example 20: Degradation of depot formulation in the rat.

Various volumes (1, 2, 6 ml/kg) of the depot precursor (36%wt PC, 54%wt GDO, and 10%wt EtOH) were injected in the rat and were removed again after a period of 14 days. It was found that substantial amounts of the formulations were still present subcutaneously in the rat after this time, see Table 6.

Table 6. Mean diameter of depot monolith.

Dose (ml/kg)	Mean diameter day 3 (mm)	Mean diameter day 14 (mm)
1 (n=3)	15.8	12.5
2 (n=3)	18.5	15.3
6 (n=3)	23.3	19.3

Example 21: In vitro study of formation of depot monolith after injection of depot formulation precursor between the bone and periostium.

A precursor (36%wt PC, 54%wt GDO, and 10%wt EtOH prepared as described in Example 1) was injected by syringe between the bone and periostium. The composition was observed to spread to fill voids and after uptake of aqueous fluids formed a monolith that was bioadhesive to both the bone and periostium.

Example 22: Bioadhesive spray of depot precursor formulation.

A pump spray bottle was found to be a convenient way to apply the formulation topically, e.g. to the skin or the oral mucosa.

A depot precursor formulation prepared as in Example 1 (36%wt PC, 54%wt GDO, and 10%wt EtOH) was sprayed with a pump spray bottle onto the skin and oral mucosa. A film with solid mechanical properties formed shortly after application.

Example 23: Robustness of a topical film.

After applying the depot precursor formulation, as described in Example 22, (36%wt PC, 54%wt GDO, and 10%wt EtOH) to the skin, the applied formulation was exposed to flushing water (10L/min) for 10 minutes. The formulation showed excellent bioadhesive properties and resistance against rinsing and no loss of the formulation could be discerned.

Example 24: Formation of cubic phase with solid properties after exposure of depot precursor formulation to air.

After exposing a depot precursor formulation prepared as described in Example 1 (36%wt PC, 54%wt GDO, and 10%wt EtOH) to air (RT, relative humidity 40%) for at least 3 hours, a solid cubic phase was formed. This formation of a cubic phase structure demonstrates that a topical film will acquire bulk non-lamellar depot properties after application without the need for direct exposure to excess aqueous fluid.

Example 25: Formulation to treat periodontitis or perimplantitis.

In order to treat periodontitis or perimplantitis an antibacterial formulation is injected in the periodontal pocket, and a prolonged effect of the formulation is normally desired.

100μL of a formulation as prepared in Example 1, with the addition of the antibiotic chlorohexidine (PC/GDO/EtOH/chlorhexidine (35/53/10/2)), is injected via a syringe into a rat peridontal pocket. The injected composition is observed to

transform from the low viscous formulation, and which initially spreads out to fill voids, to form a solid mass by uptake of gingival fluids. An antibacterial depot system is thus provided.

Chlorhexidine remains at clinically effective levels (MIC 125µg/ml) in the GCF of the periodontal pockets for over 1 week. The depot system is completely degraded by enzymes within 7 to 10 days and does not need to be removed.

Example 26: Alternate antibacterial formulation to treat periodontitis or perimplantitis.

An alternate antibacterial formulation was provided by a formulation prepared as described in Example 1 and containing the antibacterial detergent Gardol (Glycine, N-methyl-N-(1-oxododecyl)-, sodium salt) (PC/GDO/EtOH/Gardol (34/51/10/5)). This formulation is injected into the rat periodontal pocket.

Gardol is observed to remain at clinically effective levels in the GCF of the periodontal pockets for a prolonged period (several days). The depot system is completely degraded by enzymes within 7 to 10 days and did not need to be removed.

Example 27: Adhesion of the formulation to high energy surfaces.

In order to treat perimplantitis, adhesion not only to biological surfaces but also to high energy surfaces such as a gold or titanium implant is important. It is also important that the formulation adheres to ceramic and plastic surfaces.

A formulation (PC/GDO/EtOH (36/54/10)) as prepared in Example 1 was applied to various surfaces in the oral cavity. The composition showed excellent adhesion to ceramic, plastic, gold, as well as to a normal tooth surface and could not be rinsed away by excess aqueous fluid. The depot resulting from the composition stayed at the site in the oral cavity where it was applied for at least 6h.

Example 28: Bioadhesive sustained release formulation of sodium fluoride for use on the teeth.

Fluoride containing compounds are often needed to oppose caries attack and a bioadhesive formulation precursor with depot effect was prepared as indicated in Example 1 from a mixture of PC/GDO/EtOH/sodium fluoride (35/53/10/2). The formulation was a dispersion of sodium fluoride since it could not be dissolved in the precursor. The liquid formulation was applied to the teeth with the aid of a brush. By uptake of saliva the formulation solidified and formed a depot providing sustained release of sodium fluoride for an extended period (several hours).

Example 29: Oral Cavity Spray Depot Composition

To be suitable as a topical depot system in the oral cavity the mechanical properties of the system was adjusted by decreasing the PC/GDO ratio.

A mixture containing PC/GDO/EtOH (27/63/10) was prepared according to Example 1. A drop of patent blue was added to visualize the formulation after application. About 300µl of the formulation was sprayed into the oral cavity with pump spray bottle. Shortly after application the formulation viscosified/solidified since it underwent a phase transformation by uptake of aqueous fluid (saliva) and loss of solvent (EtOH). The formulation had excellent bioadhesion to keritinized surfaces such as the hard palate and the gum. Here the film lasted for several hours despite saliva secretion and mechanical wear by the tongue. At soft mucosal surfaces the duration was much shorter (minutes).

Example 30: Oral Cavity Liquid Depot Composition

To be suitable for application with a pipette to the oral cavity the solidification/ viscosification of the formulation has to be delayed relative to the spray formulation. This is to allow the formulation to be conveniently distributed with the tongue to a thin film in the oral cavity after application.

Propylene glycol (PG) and EtOH were added to a formulation prepared as in Example 1, to the final composition PC/GDO/EtOH/PG (24/56/10/10). 300µl of the formulation was conveniently applied with a pipette to the oral cavity and distributed with the tongue to a thin film in the oral cavity. After about 20 seconds the viscosification of the formulation started since it underwent a phase transformation by uptake of aqueous fluid (saliva) and loss of solvent (EtOH and PG). After about one minute the solidification/viscosification appeared to be

finished. The formulation had excellent bioadhesion to keritinized surfaces such as the hard palate and the gum. Here the film lasted for several hours despite saliva secretion and mechanical wear by the tongue. At soft mucosal surfaces the duration was much shorter (minutes).

Example 31 - Bioadhesive depot for nails

The mixture in Example 29 was sprayed to the nail bed and in between the toes. The formulation solidifies/viscosifies slowly by uptake of aqueous fluids (cf. sweat). The solidification can be speeded up by adding water after spray application. The formulation had excellent bioadhesive properties and had a duration for several hours.

Eample 32: Loading capacity of the bioactive agent benzydamine in the formulation precursors.

Formulations with compositions as specified in Table 7 were prepared using the method in Example 1. An excess amount of benzydamine (50mg) was added to 0.5 g of the formulations. The vials were placed on a shaker at 15 °C for three days after which the solutions were filtered through a filter (0.45μm) to get rid of crystals of undissolved benzydamine. The benzydamine concentration in each formulation was determined with reversed phase gradient HPLC and UV detection at 306nm and the results are given in Table 7.

Table 7

Composition GDO/PC(Lipoid S100)/EtOH	Benzydamine concentration in formulation
67.5/22.5/10	3.4%
63/27/10	3.2%
58.5/31.5/10	3.3%
60/20/20	4.0%
56/24/20	4.5%
52/28/20	4.3%

Example 33: Compositions containing PC and tocopherol

Depot precursor formulations were prepared with several different PC/α-tocopherol compositions using the method of Example 1 (PC was first dissolved in the appropriate amount of EtOH and thereafter α-tocopherol was added to give clear homogenous solutions).

Each formulation was injected in a vial and equilibrated with excess water. The phase behaviour was evaluated visually and between crossed polarizes at 25°C. Results are presented in Table 8.

Table 8

α-tocopherol	PC	Ethanol	Phase in excess H_2O
2.25g	2.25g	0.5g	H_{II}
2.7g	1.8g	0.5g	H_{II}/I_2
3.15g	1.35g	0.5g	I_2
3.6g	0.9g	0.5g	I_2/L_2

Example 34: Composition containing octreotide

60mg octreotide was dissolved in 0.1g EtOH. 0.25g PC and 0.59g α-tocopherol were subsequently dissolved in this solution and a depot formulation precursor was obtained. Injecting the formulation precursor into excess aqueous solution (phosphate buffered saline - PBS) resulted in a monolithic liquid crystalline phase (I_2 structure) i.e. octreotide (6.0%) did not change monolith formation and phase behaviour after exposure to an aqueous environment.

The octreotide depot precursor formulation in this Example was tested for stability against crystallization during storage. The formulation was stable at 4-8°C for at least two weeks.

Example 35: In vitro release of water-soluble disodium fluorescein

A water-soluble colorant, disodium fluorescein (Fluo), was dissolved in a formulation containing PC/α-tocopherol/Ethanol (27/63/10 wt%) to a concentration

of 5 mg Fluo/g formulation. When 0.1 g of the formulation was injected in 2 ml of phosphate buffered saline (PBS) a reversed micellar (I_2) phase was formed. The absorbency of Fluo released to the aqueous phase was followed at 490 nm over a period of 3 days. The release study was performed in a 3 mL vial capped with an aluminium fully tear off cap at 37°C. The vial was placed on a shaking table at 150 rpm.

The release of Fluo from the PC/α-tocopherol formulation (see Table 9) indicates that this (and similar) formulations are promising depot systems. Furthermore, the absence of a burst effect is noteworthy, and the release indicates that the substance can be released for several weeks to months; only about 0.4% of Fluo is released after 3 days.

Table 9

Formulation	% release (37°C)	
	24 h	72 h
PC/α-tocopherol/EtOH: 27/63/10 wt%	< 0.1*	0.43

* Release below detection limit of the absorbance assay

Example 36: **Formulations of the analgesic/antiinflammatory benzydamine**

Formulations were prepared as in Example 1 by mixing benzydamine with a mixture of GDO, PC, ethanol and optionally PG/AP in the following proportions.

Formulation	BZD	GDO	PC	EtOH	PG	AP
1	3.0	53.3	28.7	10.0	5.0	0.01
2	3.0	53.3	28.7	15.0	0	0.01
3	3.0	57.4	24.6	10.0	5.0	0.01
4	3.0	49.2	32.8	10.0	5.0	0.01

where BZD is benzydamine, EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, PG is propylene glycol, and AP is ascorbyl palmitate.

All formulations are low viscosity liquids which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 37: **Fentanyl nasal formulation**

Formulations were prepared as in Example 1 by mixing the narcotic analgesic fentanyl with a mixture of GDO, PC, ethanol and optionally PG in the following proportions.

Formulation	Fentanyl	PC	GDO	EtOH	PG
1	0.05	34	51	10	5
2	0.05	36	54	10	-
3	0.05	42	43	10	5
4	0.05	45	45	10	-
5	0.15	34	51	10	5
6	0.15	36	54	10	-
7	0.05	30	45	15	10
8	0.15	30	45	15	10

where EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, and PG is propylene glycol

All formulations are low viscosity liquids suitable for administration by nasal spray, which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 38: **Diazepam nasal formulation**

Formulations were prepared as in previous examples by mixing the benzodiazepine antianxiety agent diazepam with a mixture of GDO, PC, ethanol and optionally PG in the following proportions.

Formulation	Diazepam	PC	GDO	EtOH	PG
1	5	32	48	10	5
2	5	34	51	10	-
3	10	37	38	10	5
4	10	40	40	10	-
5	10	30	45	10	5
6	10	32	48	10	-
7	10	26	39	15	10
8	10	30	45	15	-

where EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, and PG is propylene glycol

All formulations are low viscosity liquids suitable for administration by nasal spray, which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 39: **Interferon Alpha-2a**

Interferons (IFNs) are used as a treatment for many types of systemic cancer, often in combination with chemotherapy or radiation. Recent data suggest that IFN Alpha is a multifunctional immunomodulatory cytokine with profound effects on the cytokine cascade including several anti-inflammatory properties. These newly identified immunoregulatory and anti-inflammatory functions may also be of importance in treatment of diseases such as chronic viral hepatitis and help to explain some of the IFN mechanisms.

A non-aqueous precursor formulation was formed by dissolving PC (360 mg) and GDO (540 mg) in EtOH (100 mg). Interferon Alpha-2a (4 mg) was dissolved in water (76 mg) and this solution was thereafter added to the non-aqueous precursor formulation to form a depot formulation precursor of low viscosity.

Injecting the depot precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase (I_2 structure).

Example 40 **Leuprorelin (Leuprolide)**

Leuprorelin acetate (or leuprolide acetate) is a synthetic nonapeptide analogue of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously (e.g. as a depot formulation), inhibits pituitary gonadotropin secretion and suppresses testicular and ovarion steroidogenesis. Leuprorelin is used for the treatment of advanced prostate cancer.

A depot formulation precursor was formed by sequentially dissolving 22.5 mg leuprorelin acetate and 360 mg PC in 100 mg of NMP. 540 mg of GDO was added to the mixture yielding a molecular solution depot formulation precursor of low viscosity. Injecting the formulation precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase (I_2 structure).

Example 41: **Alendronate**

Bisphosphonates are structural analogues of pyrophosphates and have pharmacologic activity specific for bone due to the strong affinity of bisphosphonates for hydroxyapatite, a major inorganic component of bone. The compounds are used to treat postmenopausal osteoporosis, hypercalcemia of malignancy and metastatic bone disease (MBD).

A non-aqueous precursor formulation was formed by dissolving PC (360 mg) and GDO (540 mg) in EtOH (100 mg). Alendronate (12 mg) was dissolved in water (80 mg) and this solution was thereafter added to the non-aqueous precursor formulation to form a depot formulation precursor of low viscosity. Injecting the depot precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase (I_2 structure).

Example 42: **Olanzapine**

Olanzapine is a low molecular weight drug used for the treatment of patients with schizophrenia.

A depot formulation precursor was formed by sequentially mixing 50 mg olanzapine, 360 mg PC and 100 mg of EtOH. 540 mg of GDO was added to the mixture resulting in the final depot formulation precursor.

Injecting the formulation precursor into excess water (syringe 23 G; 0.6mm x 30 mm) resulted in a monolithic liquid crystalline phase (I_2 structure).

Example 43: **Acne formulations with Clindamycin**

Formulations were prepared as in previous examples by mixing the semisynthetic antibiotic clindamycin (free base or salt) with a mixture of GDO, PC, ethanol and PG in the following proportions (by weight).

Formulation	Clindamycin HCl	PC	GDO	EtOH	PG
1	1	30	54	10	5
2	2	29	54	10	5
3	1	34	50	10	5
4	2	33	50	10	5

Formulation	Clindamycin base	PC	GDO	EtOH	PG
5	1	30	54	10	5
6	2	29	54	10	5
7	1	33	54	2	10
8	2	32	54	2	10

The resulting preformulations are low viscosity liquids which, after application resistant to water, sweat, etc. The formulation are applied locally on the skin as a gel or by spraying and are bioadhesive with good film-forming properties.

Example 44: **Further examples of viscosity in PC/GDO mixtures on addition of co-solvent**

Mixtures of PC/GDO and co-solvent were prepared according to the methods of Example 1 and Example 3 in the proportions indicated in the table below. The samples were allowed to equilibrate for several days before viscosity measurements were performed using a Physica UDS 200 rheometer at 25 °C.

Sample	PC/GDO (wt/wt)	EtOH / wt%	Glycerol / wt%	H_2O / wt%	Viscosity / mPas
1	50/50	3	-	-	1900
2	50/50	5	-	-	780
3	50/50	7	-	-	430
4	50/50	8	-	-	300
5	50/50	10	-	-	210
6	50/50	15	-	-	100
7	45/55	3	-	-	1350
8	45/55	5	-	-	540
9	45/55	7	-	-	320
10	45/55	8	-	-	250
11	45/55	10	-	-	150
12	45/55	15	-	-	85
13	40/60	3	-	-	740
14	40/60	5	-	-	400
15	40/60	7	-	-	240
16	40/60	8	-	-	200
17	40/60	10	-	-	130
18	40/60	15	-	-	57
19	40/60	-	10	-	$8*10^6$
20	40/60	-	-	3	$2.5*10^8$
21	40/60	-	-	5	$4*10^7$

This example further illustrates the need for a solvent with viscosity lowering properties in order to obtain injectable formulations. The mixtures containing glycerol (sample 19) or water (samples 20 and 21) are too viscous to be injectable at solvent concentrations equivalent to the samples containing EtOH (compare with samples 13, 14 and 17).

Example 45: **Occtreotide Formulation compositions**

Formulations were prepared as in Example 1 by mixing the peptide active octreotide with a mixture of GDO (at one of several purity levels) or tocopherol, PC, ethanol and optionally dioleoyl PG in the following proportions (by weight)

Formulation	OCT	EtOH	PC	GDO1	GDO2	GDO3	TP	DOPG
E	2	10	35.2	-	-	52.8	-	-
F	2	10	35.2	52.8	-	-	-	-
G	2	10	35.2	-	52.8	-	-	-
H	2	10	26.4	-	-	-	61.6	-
I	1	10	35.6	53.4	-	-	-	-
J	2	5	37.2	-	-	55.8	-	-
K	3	5	36.8	-	-	55.2	-	-
L	6	5	35.6	-	-	53.5	-	-
M	3	5	35.8	-	-	55.2	-	1
N	3	5	33.8	-	-	55.2	-	3
O	3	5	30.8	-	-	55.2	-	6
P	3	5	46	-	-	46	-	-
Q	3	10	43.5	-	-	43.5	-	-
R	6	10	42	-	-	42	-	-
S	3	7	45	-	-	45	-	-
T	6	7	43.5	-	-	43.5	-	-

where OCT is octreotide, EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, TP is α-tocopherol, DOPG is dioleoyl phosphatidylglycerol

GDO quality (according to AC)

	Monoglycerides	Diglycerides	Triglycerides
GDO1	10.9%	87.5%	1.4%
GDO2	4.2%	92.1%	3.5%
GDO3	0.5%	95.3%	4.0%

Formulation P (for composition see above) was administered by s.c.injection in the rat at a level of 1 ml formulation per kg body weight, corresponding to 30 mg/kg of octreotide.

Octreotide plasma levels after administration were monitored for 5 days to examine any burst profile. It was observed that the highest plasma concentration was less than three fold greater than the average plasa concentration over the first 5 days.

The results of the study are shown in Figure 6

Example 46: ***Sunscreen formulations***

Formulations were prepared as in Example 1 by mixing each of several UV absorbing/scattering agents with a mixture of GDO, PC, and ethanol in the following proportions (by weight)

Formulation	PC	GDO	EtOH	Tioveil CM	Spectraveil FIN	Solaveil CT-100	Tioveil 50 MOTG
1	38	42	5	-	-	-	15
2	38	42	5	-	-	15	-
3	37	38	5	15	5	-	-

Where TIOVEIL CM (Uniqema) comprises Cyclomethicone (and) Titanium Dioxide (and) Dimethicone Copolyol (and) Aluminium Stearate (and) Alumina, SPECTRAVEIL FIN(Uniqema) comprises Zinc Oxide (and) C12-15 Alkyl Benzoate (and) Polyhydroxystearic Acid, SOLAVEIL CT-100 (Uniqema) comprises C12-15 Alkyl Benzoate (and) Titanium Dioxide (and) Polyhydroxystearic Acid (and) Aluminum Stearate (and) Alumina, and TIOVEIL 50 MOTG (Uniqema) comprises Titanium Dioxide (and) Caprylic/Capric Triglyceride (and) Mineral Oil (and) Polyhydroxystearic Acid (and) Aluminum Stearate (and) Alumina.

The resulting formulation precursors show low viscosity upon formulation and are readily applied by pump spray. Upon contact with body surfaces a resilient UV protective layer is formed.

Example 47: **Chlorhexidine periodontal depots.**

Formulations were prepared as in Example 1 by mixing the antiinfective agent chlorhexidine digluconate with a mixture of GDO, PC, and ethanol in the following proportions (by weight)

Table. Chlorhexidine digluconate depot formulation compositions.

Formulation	Chlorhexidine digluconate	PC	GDO	EtOH
A	5	34	51	10
B	5	36	54	5
C	7	33	50	10
D	10	32	48	10
E	15	30	45	10

The chlorhexidine depot preformulations have low viscosity and are easily administered to the periodontal pocket. The compositions provide better distribution and spreading of the active substance throughout the periodontal pocket when compared to current products, such as Periochip®.

The depot formed after application gives protection against re-infection of the pocket. The depot also has excellent bioadhesive properties and sticks to mucosal, teeth and bone surfaces.

Release of chlorhexidine digluconate from 250 mg Formulation A (see above) in 0.9% aqueous NaCl (500 ml) was studdied. The formulation was held in a cylindrical metal cup which was placed in a teflon holder at the bottom of a standard

USP release bath. The contact area between the formulation and surrounding saline solution was 2.4 cm^2, and the solution was stirred by paddle at 100 rpm.

The release curve shown in Figure 7 demonstrates the sustained and essentially uniform release of chlorhexidine from the formulation over a period of 24 hours.

Claims:

1) A pre-formulation comprising a low viscosity, non-liquid crystalline, mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture and wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid.

2) A pre-formulation as claimed in claim 1 wherein said liquid crystalline phase structure is bioadhesive.

3) A pre-formulation as claimed in claim 1 or claim 2 wherein component a) consists essentially of diacyl glycerols, especially glycerol dioleate.

4) A pre-formulation as claimed in claim 1 or claim 2 wherein component a) consists essentially of at least one tocopherol.

5) A pre-formulation as claimed in claim 1 or claim 2 wherein component a) consists essentially of a mixture of GDO and tocopherol.

6) A pre-formulation as claimed in any of claims 1 to 5 wherein component b) is selected from phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines, phosphatidylinositols and mixtures thereof.

7) A preformulation as claimed in any of claims 1 to 6 having a viscosity of 0.1 to 5000 mPas.

8) A preformulation as claimed in any of claims 1 to 7 having a molecular solution, L_2 and/or L_3 phase structure.

9) A preformulation as claimed in any of claims 1 to 8 having a ratio of a) to b) of between 95:5 and 5:95 by weight.

10) A preformulation as claimed in any of claims 1 to 9 having 0.5 to 50% component c) by weight of components a) + b) + c).

11) A preformulation as claimed in any of claims 1 to 10 wherein component c) is selected from alcohols, ketones, esters , ethers, amides, sulphoxides and mixtures thereof.

12) A preformulation as claimed in any of claims 1 to 11 additionally comprising up to 10% by weight of a)+b) of a charged amphiphile.

13) A preformulation as claimed in any of claims 1 to 12 wherein said active agent is selected from drugs, antigens, nutrients, cosmetics, fragrances, flavourings, diagnostic agents, vitamins, dietary supplements and mixtures thereof.

14) A preformulation as claimed in calim 13 wherein said drus is selected from hydrophilic small molecule drugs, lipophilic small molecule drugs, amphiphilic small molecule drugs, peptides, proteins, oligonucleotids and mixtures thereof.

15) A preformulation as claimed in claim 13 wherein said drug is selected from somatostatin related peptides, interferons, glucagon-like peptides 1 and 2, GnRH agonists, GnRH antagonists, bisphosponates, chlorhexidine and mixtures thereof.

16) A preformulation as claimed in any of claims 1 to 15 which is administrable by injection.

17) A preformulation as claimed in any of claims 1 to 15 which is administrable by spraying, dipping, rinsing, application from a pad or ball roller, painting, dropping, aerosol spraying or pump spraying.

18) An injectable preformulation as claimed in any of claims 1 to 16 which forms a depot providing continuous release of active agent for at least two weeks, wherein said active agent comprises at least one selected from

i. octreotide
ii. human growth hormone
iii. interferon alpha
iv. leuprolide

19) An injectable preformulation as claimed in any of claims 1 to 16 which forms a depot providing continuous release of active agent for at least two weeks, wherein said active agent comprises at least one selected from

i. risperidone
ii. olanzapine
iii. testosterone undecanoate

20) A topical formulation as claimed in any of claims 1 to 15 for intraoral administration which forms a bioadhesive, controlled release product, wherein said active agent comprises at least one selected from

i. benzydamine
ii. tramadol

21) A topical preformulation as claimed in any of claims 1 to 15 suitable for intraoral administration for treatment of periodontal and topical infections, wherein the active agent is chlorhexidine gluconate, and where the preformulation is applied as a liquid product which forms a surface gel *in situ* between 1 second. and 5 min after application.

22) A non-parenteral formulation as claimed in any of claims 1 to 15 for intranasal spray administration which forms a bioadhesive, controlled release product, wherein said active agent comprises at least one selected from

i. fentanyl
ii. diazepam

23) A topical formulation as claimed in any of claims 1 to 15 suitable for ocular administration, wherein said active agent comprises at least one selected from diclofenac, pilocarpine, levocabastine hydrochloride, ketotifen fumarate, timolol, betaxolol, carteolol, levobunolol, dorzolamide, brinzolamide, epinephrine, dipivefrin, clonidine, apraclonidine, brimonidine, pilocarpine, atanoprost, travoprost, bimatoprost, unoprostone, pilocarpine hydrochloride, dexamethasone, chloramphenicol, and indomethacin.

24) A non-parenteral formulation as claimed in any of claims 1 to 15 for dermatological administration which forms a bioadhesive, controlled release product, wherein the active agent is selected from;

i. acyclovir

ii. testosterone undecanoate.

25) A topical formulation as claimed in any of claims 1 to 15 for dermatological administration which forms a bioadhesive, controlled release product, wherein the active agent is selected from cosmetic agents, fragrances, flavourings, essential oils UV absorbing agents and mixtures thereof.

26) A method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising administering a pre-formulation comprising a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and at least one bioactive agent is dissolved or dispersed in the low viscosity mixture, whereby to form at least one liquid crystalline phase structure upon contact with an aqueous fluid *in vivo* following administration.

27) A method as claimed in claim 26 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

28) The method as claimed in claim 26 or claim 27 wherein said pre-formulation is administered by a method selected from subcutaneous injection, intramuscular injection, intra-cavity injection through tissue, intra-cavity injection into an open cavity without tissue penetration, spraying, rolling, wiping, dabbing, painting, rinsing, or dropping.

29) A method for the preparation of a liquid crystalline composition comprising exposing a pre-formulation comprising a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and at least one bioactive agent dissolved or dispersed in the low viscosity mixture, to an aqueous fluid *in vivo*.

30) A method as claimed in claim 29 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

31) A process for the formation of a pre-formulation suitable for the administration of a bioactive agent to a (preferably mammalian) subject, said process comprising forming a non-liquid crystalline, low viscosity mixture of

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing low viscosity, organic solvent;

and dissolving or dispersing at least one bioactive agent in the low viscosity mixture, or in at least one of components a, b or c prior to forming the low viscosity mixture.

32) A process as claimed in claim 31 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

33) The use of a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained administration of said active agent, wherein said pre-formulation is capable of forming at least one liquid crystalline phase structure upon contact with an aqueous fluid.

34) The use as claimed in claim 33 wherein said preformulation is a preformulation as claimed in any of claims 1 to 25.

35) A method of treatment or prophylaxis of a human or non-human animal subject comprising administration of a preformulation as claimed in any of claims 1 to 25.

36) The method of claim 35 for the treatment of a condition selected from bacterial infection, fungal infection, skin soreness, eye conditions, genital soreness, infections and conditions for the finger and/or toe nails, travel sickness, addiction including nicotine addiction, periodontal infection, conjunctivitis, glaucoma and hormone deficiency or imbalance.

37) The method of claim 35 for prophylaxis against at least one condition selected from infection during surgery, infection during implantation, sunburn, infection at the site of burns, cuts or abrasions, oral infections, genital infections and infections resulting from activities resulting in exposure to infective agents.

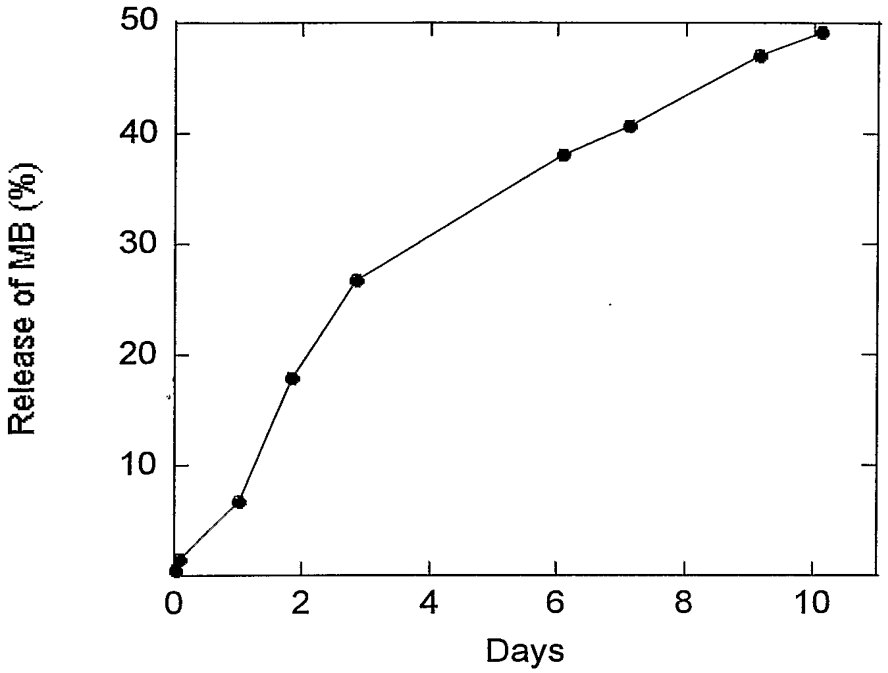


Figure 1. Cumulative release of MB from a depot forming a reversed hexagonal H_{II} phase.

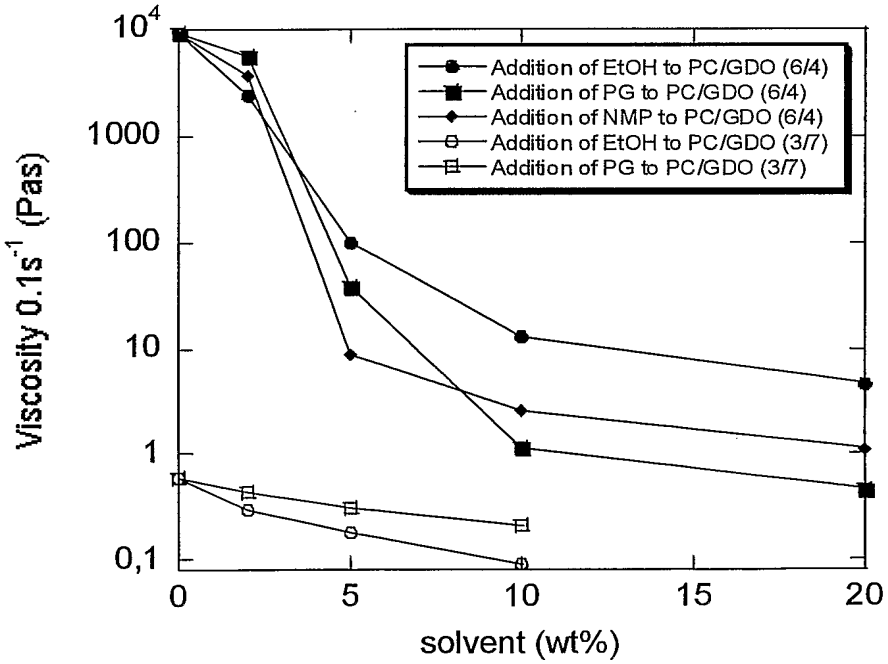


Figure 2. Decrease in viscosity of the depot precursor on addition of solvents. PC/GDO (6/4) is a precursor to a reversed hexagonal H_{II} phase and PC/GDO (3/7) is a precursor to a reversed cubic I_2 phase.

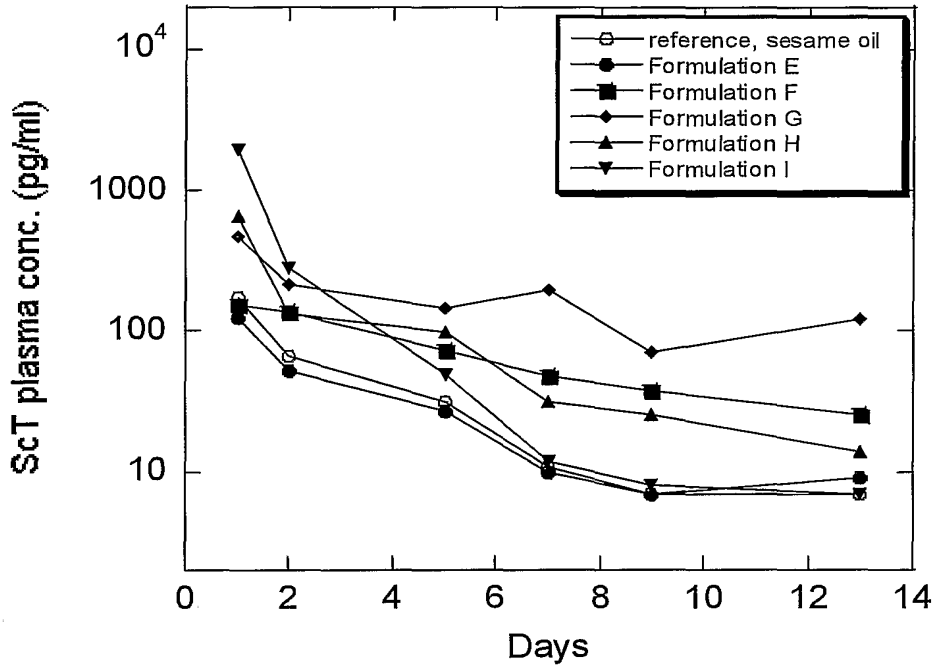


Figure 3. Plasma concentrations in the rat model after subcutaneous administration of formulations E to I. A depot based on sesame oil was used as reference.

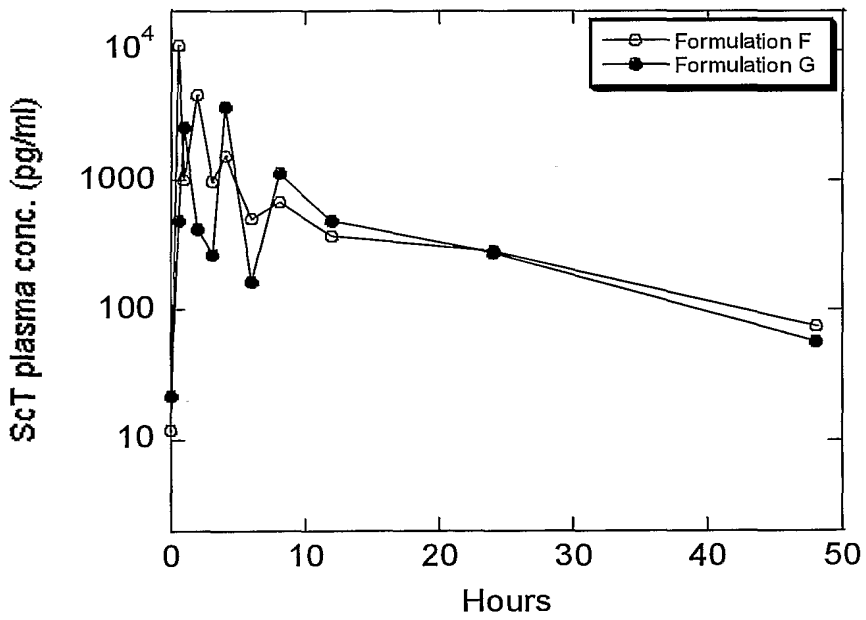


Figure 4. Plasma concentrations in the rat model after subcutaneous administration of formulations F and G.

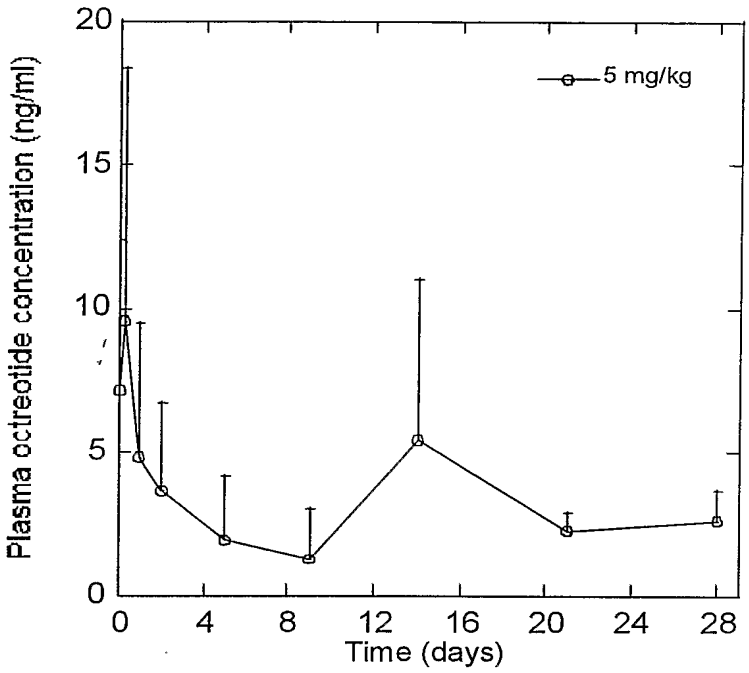


Figure 5: Octreotide plasma levels in the rat model following administration of octreotide formulation precursor (0.5% by weight octreotide).

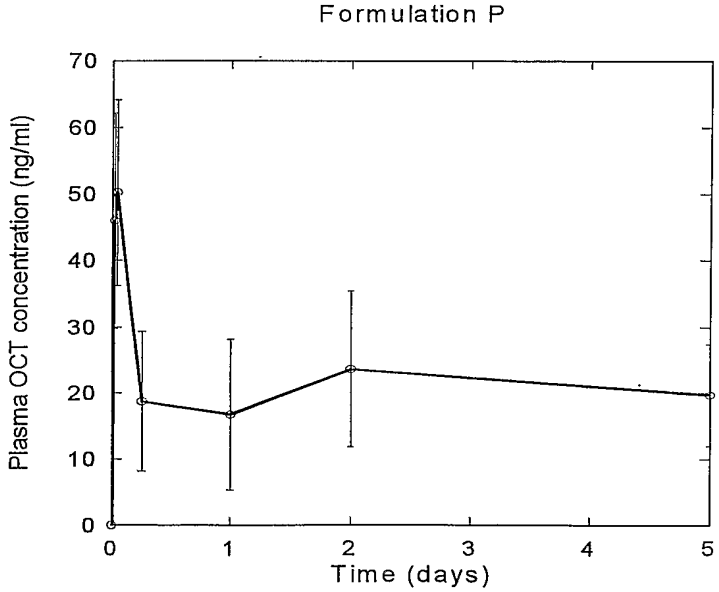


Figure 6: Octreotide plasma levels in the rat model following administration of octreotide formulation P, see Example 45.

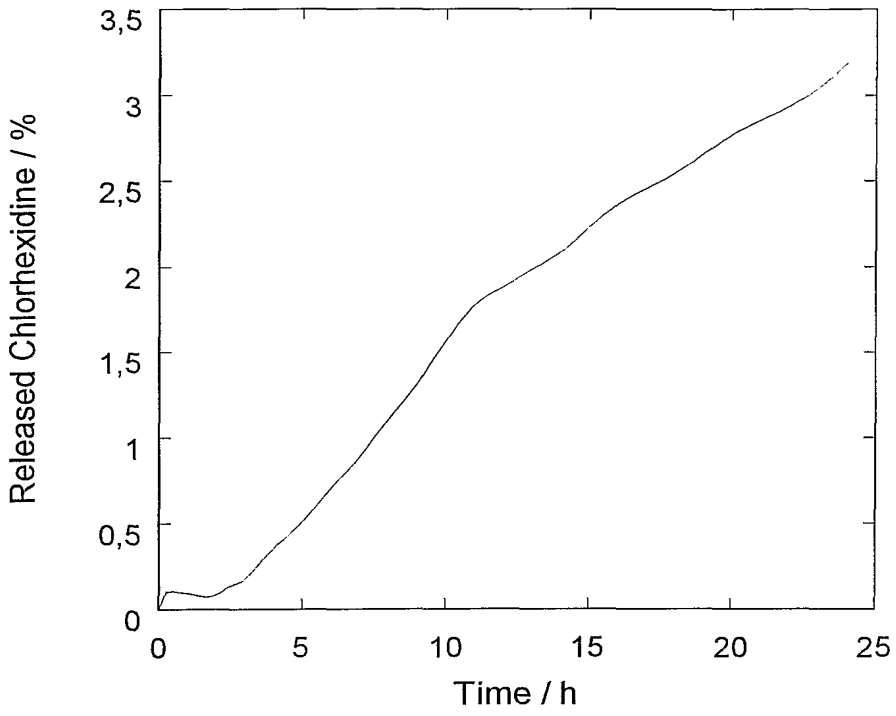


Figure 7: Release of Chlorhexidine from formulation A, see Example 47.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002217

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/10 A61K9/06 A61K9/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/046642 A (CAMURUS AB; JOABSSON, FREDRIK; TIBERG, FREDRIK; GODDARD, CHRISTOPHER) 26 May 2005 (2005-05-26) page 13, last paragraph page 27, paragraph 3 - page 28, paragraph 3 examples 5,6	1-37
X	US 5 807 573 A (LJUSBERG-WAHREN ET AL) 15 September 1998 (1998-09-15) cited in the application column 2, line 60 - line 64 column 4, line 4 - line 62 examples 1,3	1-37

-/--

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2005	19/10/2005

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

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002217

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/13528 A (DUMEX-ALPHARMA A/S; NIELSEN, LISE, SYLVEST; HANSEN, JENS) 17 April 1997 (1997-04-17) page 2, paragraph 2 page 11, paragraph 4 page 58, line 25 - line 27 page 61, paragraph 2	1-37
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A	SHAH JAYMIN C ET AL: "Cubic phase gels as drug delivery systems" ADVANCED DRUG DELIVERY REVIEWS, AMSTERDAM, NL, vol. 47, no. 2-3, 25 April 2001 (2001-04-25), pages 229-250, XP002320651 ISSN: 0169-409X the whole document	1-37

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/002217

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 26-28, 35-37
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-28 and 35-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002217

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TOPICAL BIOADHESIVE FORMULATIONS

(57) Abstract: The present invention relates to topical bioadhesive formulations comprising low viscosity, non-liquid crystalline, mixtures of: a) at least one neutral diacyl lipid and/or at least one tocopherol; b) at least one phospholipid; c) at least one biocompatible, oxygen containing, low viscosity organic solvent; wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture and wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid. The invention additionally relates to a method of delivery of an active agent comprising administration of a preformulation of the invention, a method of treatment comprising administration of a preformulation of the invention and the use of a preformulation of the invention in a method for the manufacture of a medicament.

WO 2006/075123 A1

Topical Bioadhesive Formulations

The present invention relates to formulation precursors (pre-formulations) for the *in situ* generation of controlled release lipid compositions. In particular, the invention relates to pre-formulations in the form of low viscosity mixtures (such as molecular solutions) of amphiphilic components and optionally at least one bioactive agent which undergo at least one phase transition upon exposure to aqueous fluids, such as body fluids, thereby forming a bioadhesive matrix.

Many bioactive agents including pharmaceuticals, nutrients, vitamins and so forth have a "functional window". That is to say that there is a range of concentrations over which these agents can be observed to provide some biological effect. Where the concentration in the appropriate part of the body (e.g. locally or as demonstrated by serum concentration) falls below a certain level, no beneficial effect can be attributed to the agent. Similarly, there is generally an upper concentration level above which no further benefit is derived by increasing the concentration. In some cases increasing the concentration above a particular level results in undesirable or even dangerous effects.

Some bioactive agents have a long biological half-life and/or a wide functional window and thus may be administered occasionally, maintaining a functional biological concentration over a substantial period of time (e.g. 6 hours to several days). In other cases the rate of clearance is high and/or the functional window is narrow and thus to maintain a biological concentration within this window regular (or even continuous) doses of a small amount are required. This can be particularly difficult where non-oral routes of administration (e.g. parenteral administration) are desirable. Furthermore, in some circumstances, such as in the fitting of implants (e.g. joint replacements or oral implants) the area of desired action may not remain accessible for repeated administration. In such cases a single administration must provide active agent at a therapeutic level over the whole period during which activity is needed.

Similarly, where the effect of a bioactive agent is required locally, it may be difficulty or undesirable to administer sufficient of that agent to achieve the effective level throughout the body of the subject. This may be due to undesirable effects of the agent itself (e.g. for steroid anti-inflammatory), or may be because the agent is

used to locally counter an undesirable feature of a systemic treatment (such as chemotherapy) but would undermine that primary treatment if used broadly.

A major difficulty with topically applied compositions is, however, their duration of action. These composition are, by their nature, applied to body surfaces which may be prone to abrasion, washing and flushing with bodily or applied fluids, such as tears, sweat or mucous. A particularly difficult situation for the use of topical preparations is in body cavities, such as the GI tract. This is because such cavities are typically coated in a mucous membrane which is non-adherent and turned over rapidly. In addition, thick, viscous preparations can be difficult to apply effectively to the mouth/throat or rectally to the lower GI tract and are difficult to manufacture due to high viscosity preventing sterile filtration. Existing compositions, however, are typically either low viscosity and short-lived or longer lived at the price of high viscosity. Furthermore, existing topical compositions are often capable of containing only a low level of active agent, due to poor compatibility between the base composition and the active agent. This results in a composition which rapidly loses effectiveness as it begins to dissipate from the site of action. It would therefore be of considerable value to provide topical formulations which were bioadherant, even to mucousal surfaces, and which could be formulated as a low viscosity preformulation which would become adherent upon contact with the desired surface. Furthermore it would be a significant advantage if the formulation was protective, non-irritant, and showed reasonable resistance to wear and exposure to aqueous ambient.

The present inventors have now established that by providing a pre-formulation comprising certain amphiphilic components, at least one bioactive agent and a biologically tolerable solvent, especially in a low viscosity phase such as molecular solution, the pre-formulation may be generated addressing many of the shortfalls of previous formulations. In particular, the pre-formulation is easy to manufacture, may be sterile-filtered, it has low viscosity (allowing easy and rapid administration), and/or allows a high level of bioactive agent to be incorporated (thus allowing a smaller amount of composition to be used and/or providing a long effective lifetime). The compositions are formed from materials that are non-toxic, biotolerable and biodegradable. They are suited for application at sensitive areas such as sensitive parts of the body and sites of inflammation, and comprising lipids which are part of natural protective surface linings, e.g. phospholipids. Furthermore,

due to the combination of bioadhesive properties and extremely low aqueous solubility of main constituents the compositions, the applied composition of the invention are stable to exposure to aqueous media and wear. The composition furthermore provides sustained release of a wide range of actives with a tuneable window of duration. The pre-formulation is therefore highly suitable for the formation of depot compositions following non-parenteral (e.g. topical) administration to body cavities and/or surfaces of the body or elsewhere and are formed from lipids which may provide inherent benefits in themselves in addition to forming highly effective carriers and topical depots for active agents.

In a first aspect, the present invention thus provides a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, (preferably oxygen containing) organic solvent;

optionally including at least one bioactive agent which is dissolved or dispersed in the low viscosity mixture, wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid and/or body surface.

Generally, the aqueous fluid will be a body fluid such as fluid from a mucosal surface, tears, sweat, saliva, gastro-intestinal fluid, extra-vascular fluid, extracellular fluid, interstitial fluid or plasma, and the pre-formulation will form a liquid crystalline phase structure when contacted with a body surface, area or cavity (e.g. *in vivo*) upon contact with the aqueous body fluid. The pre-formulation of the invention will generally not contain any significant quantity of water prior to administration.

In a second aspect of the invention, there is also provided a method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising topically administering a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, (preferably oxygen containing) organic solvent;

and including at least one bioactive agent dissolved or dispersed in the low viscosity mixture; whereby to form at least one liquid crystalline phase structure upon contact with an aqueous fluid at a body surface following administration. Preferably, the pre-formulation administered in such a method is a pre-formulation of the invention as described herein.

The method of administration suitable for the above method of the invention will be a method appropriate for the condition to be treated and the bioactive agent used. A bioadhesive non-parenteral (e.g. topical) depot composition may be formed by administration to the surface of skin, mucous membranes and/or nails, to opthalmological, nasal, oral or internal surfaces or to cavities such as nasal, rectal, vaginal or buccal cavities, the periodontal pocket or cavities formed following extraction of a natural or implanted structure or prior to insertion of an implant (e.g a joint, stent, cosmetic implant, tooth, tooth filling or other implant).

In a further aspect, the present invention also provides a method for the preparation of a liquid crystalline composition (especially a depot composition) comprising exposing a pre-formulation comprising a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

and optionally at least one bioactive agent dissolved or dispersed in the low viscosity mixture, to an aqueous fluid at a body surface. Preferably the pre-formulation administered is a pre-formulation of the present invention as described herein. The exposure to a fluid may be internally within at an internal surface of a body cavity, or may be at an external body surface such as a skin surface, depending upon the nature of the composition and any active agent.

The liquid crystalline composition formed in this method is bioadhesive as described herein.

In a still further aspect the present invention provides a process for the formation of a pre-formulation suitable for the administration of a bioactive agent to a surface of a (preferably mammalian) subject, said process comprising forming a low viscosity mixture of

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

and optionally dissolving or dispersing at least one bioactive agent in the low viscosity mixture, or in at least one of components a, b or c prior to forming the low viscosity mixture. Preferably the pre-formulation so-formed is a formulation of the invention as described herein.

In a yet still further aspect the present invention provides the use of a low viscosity mixture of:

a) at least one neutral diacyl lipid and/or a tocopherol;

b) at least one phospholipid;

c) at least one biocompatible (preferably oxygen containing), organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained local administration of said active agent, wherein said pre-formulation is capable of forming at least one liquid crystalline phase structure upon contact with an aqueous fluid.

In a further aspect, the present invention provides a method for the treatment of a human or animal subject comprising administration of a composition of the present invention, optionally including an active agent. In this aspect, the method of treatment is in particular a method for the treatment of inflammation and/or irritation, especially at a body surface and/or in a body cavity such as the gastrointestinal tract.

In a still further aspect, the present invention provides for the use of a composition of the present invention in therapy, and in particularly for the use of a composition of the present invention, optionally including an active agent, in the manufacture of a medicament for the treatment of inflammation and/or irritation, especially at a body surface and/or in a body cavity such as the gastrointestinal tract.

The use of non-lamellar phase structures (such as liquid crystalline phases) in the delivery of bioactive agents is now relatively well established. Such structures form when an amphiphilic compound is exposed to a solvent because the amphiphile has both polar and apolar groups which cluster to form polar and apolar regions. These regions can effectively solubilise both polar and apolar compounds. In addition,

many of the structures formed by amphiphiles in polar and/or apolar solvents have a very considerable area of polar/apolar boundary at which other amphiphilic compounds can be adsorbed and stabilised. Amphiphiles can also be formulated to protect active agents, to at least some extent, from aggressive biological environments, including enzymes, and thereby provide advantageous control over active agent stability and release.

The formation of non-lamellar regions in the amphiphile/water, amphiphile/oil and amphiphile/oil/water phase diagrams is a well known phenomenon. Such phases include liquid crystalline phases such as the cubic P, cubic D, cubic G and hexagonal phases, which are fluid at the molecular level but show significant long-range order, and the L3 phase which comprises a multiply interconnected bi-continuous network of bilayer sheets which are non-lamellar but lack the long-range order of the liquid crystalline phases. Depending upon their curvature of the amphiphile sheets, these phases may be described as normal (mean curvature towards the apolar region) or reversed (mean curvature towards the polar region).

The non-lamellar liquid crystalline and L3 phases are thermodynamically stable systems. That is to say, they are not simply a meta-stable state that will separate and/or reform into layers, lamellar phases or the like, but are the stable thermodynamic form of the lipid/solvent mixture.

As used herein, the term "low viscosity mixture" is used to indicate a mixture which may be readily administered to a subject and in particular readily administered by means of a standard syringe and needle or pump/aerosol spray arrangement. This may be indicated, for example by the ability to be dispensed from a 1 ml disposable syringe through a 22 awg (or a 23 gauge) needle by manual pressure. In a particularly preferred embodiment, the low viscosity mixture should be a mixture capable of passing through a standard sterile filtration membrane such as a 0.22 μm syringe filter. In other preferred embodiments, a similar functional definition of a suitable viscosity can be defined as the viscosity of a pre-formulation that can be sprayed using a compression pump or pressurized spray device using conventional spray equipment. A typical range of suitable viscosities would be, for example, 0.1 to 5000 mPas, preferably 1 to 1000 mPas at 20°C.

It has been observed that by the addition of small amounts of low viscosity solvent, as indicated herein, a very significant change in viscosity can be provided. As indicated in Figure 2, for example, the addition of only 5% solvent can reduce viscosity 100-fold and addition of 10% may reduce the viscosity up to 10,000 fold. In order to achieve this non-linear, synergistic effect, in lowering viscosity it is important that a solvent of appropriately low viscosity and suitable polarity be employed. Such solvents include those described herein infra.

Particularly preferred examples of low viscosity mixtures are molecular solutions and/or isotropic phases such as L2 and/or L3 phases. As describe above, the L3 is a non-lamellar phase of interconnected sheets which has some phase structure but lacks the long-range order of a liquid crystalline phase. Unlike liquid crystalline phases, which are generally highly viscous, L3 phases are of lower viscosity. Obviously, mixtures of L3 phase and molecular solution and/or particles of L3 phase suspended in a bulk molecular solution of one or more components are also suitable. The L2 phase is the so-called "reversed micellar" phase or microemulsion. Most preferred low viscosity mixtures are molecular solutions, L3 phases and mixtures thereof. L2 phases are less preferred, except in the case of swollen L_2 phases as described below.

The present invention provides a pre-formulation comprising components a, b, c and optionally and preferably at least one bioactive agent as indicated herein. One of the considerable advantages of the pre-formulations of the invention is that components a and b may be formulated in a wide range of proportions. In particular, it is possible to prepare and use pre-formulations of the present invention having a much greater proportion of phospholipid to neutral, diacyl lipid and/or tocopherol than was previously achievable without risking phase separation and/or unacceptably high viscosities in the pre-formulation. The weight ratios of components a:b may thus be anything from 5:95 right up to 95:5. Preferred ratios would generally be from 90:10 to 20:80 and more preferably from 85:15 to 30:70. In one preferred embodiment of the invention, there is a greater proportion of component b than component a. That is, the weight ratio a:b is below 50:50, e.g. 48:52 to 2:98, preferably, 40:60 to 10:90 and more preferably 35:65 to 20:80.

The amount of component c in the pre-formulations of the invention will be at least sufficient to provide a low viscosity mixture (e.g. a molecular solution, see above)

of components a, b and c and will be easily determined for any particular combination of components by standard methods. The phase behaviour itself may be analysed by techniques such as visual observation in combination with polarized light microscopy, nuclear magnetic resonance, and cryo-transmission electron microscopy (cryo-TEM) to look for solutions, L2 or L3phases, or liquid crystalline phases. Viscosity may be measured directly by standard means. As described above, an appropriate practical viscosity is that which can effectively be syringed and particularly sterile filtered and/or sprayed from a pump or pressurised spray. This will be assessed easily as indicated herein. The maximum amount of component c to be included will depend upon the exact application of the pre-formulation but generally the desired properties will be provided by any amount forming a low viscosity mixture (e.g. a molecular solution, see above) and/or a solution with sufficiently low viscosity.

Since the administration of unnecessarily large amounts of solvent to a subject is generally undesirable the amount of component c may, in one embodiment, be limited to no more than ten times (e.g. three times) the minimum amount required to form a low viscosity mixture, preferably no more than five times and most preferably no more than twice this amount.

Higher proportions of solvent may also be used for the non-parenteral (e.g. topical) applications of the invention, however, especially when applied to external body surfaces, where the solvent will be lost by evaporation rather than absorbed into the body. For such applications up to 100 times the minimum amount of solvent may be used (e.g. up to 95% by weight of the composition, preferably up to 80% by weight and more preferably up to 50% by weight), especially where a very thin layer of the resulting non-parenteral depot is desired.

Where the compositions of the invention are formulated as aerosol spray compositions (e.g. for topical or delivery of an active), the composition may also comprise a propellant. Such compositions may also include a high proportion of solvent component c), as considered above, since much of the solvent will evaporate when the composition is dispensed, particularly under the influence of the propellant.

Suitable propellants are volatile compounds which will mix with the composition of the invention under the pressure of the spray dispenser, without generating high

viscosity mixtures. They should evidently have acceptable biocompatibility. Suitable propellants will readily be identified by simple testing and examples include hydrocarbons (especially C_1 to C_4 hydrocarbons), carbon dioxide and nitrogen. Volatile hydrofluorocarbons such as HFCs 134, 134a, 227ea and/or 152a may also be suitable.

As a general guide, the weight of component c will typically be around 0.5 to 50% of the total weight of the a-b-c solution. This proportion may be limited to 2 to 30% or 5 to 20% by weight. As indicated above; however, in case of a spray composition, especially with a propellant, the amount of c may exceed 50%.

The formulations of the invention may additionally contain small proportions of other agent, such as polymers which are soluble in the precursor. Such polymers may act as a reinforcement of the swollen liquid crystalline phase so that a film attached to a mucosal surface is more strongly attached. A "reinforcement" along the same principle could also be obtained by soaking a matrix (paper, polymer net, or similar) with the precursor. Upon applying this "patch" to the skin the formulation may by itself act as the glue. In contrast to conventional adhesives for coating damaged tissue, whoever, the formulations of the invention are adhesive even to mucous membranes and are not irritant. In many cases, they are in fact soothing in themselves, as described herein, and may contain suitable active agent.

Component "a" as indicated herein is a neutral lipid component comprising a polar "head" group and also non-polar "tail" groups. Generally the head and tail portions of the lipid will be joined by an ester moiety but this attachment may be by means of an ether, an amide, a carbon-carbon bond or other attachment. Preferred polar head groups are non-ionic and include polyols such as glycerol, diglycerol and sugar moieties (such as inositol and glucosyl based moieties); and esters of polyols, such as acetate or succinate esters. Preferred polar groups are glycerol and diglycerol, especially glycerol.

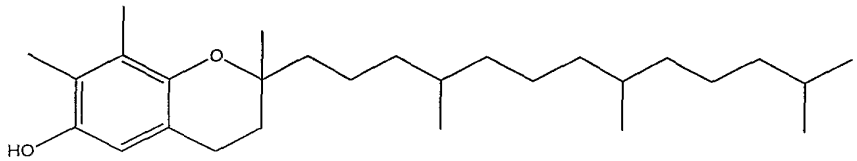
In one preferred aspect, component a is a diacyl lipid in that it has two non-polar "tail" groups. This is generally preferable to the use of mono-acyl ("lyso") lipids because these are typically less well tolerated *in vivo*. The two non-polar groups may have the same or a differing number of carbon atoms and may each independently be saturated or unsaturated. Examples of non-polar groups include

C_6-C_{32} alkyl and alkenyl groups, which are typically present as the esters of long chain carboxylic acids. These are often described by reference to the number of carbon atoms and the number of unsaturations in the carbon chain. Thus, CX:Z indicates a hydrocarbon chain having X carbon atoms and Z unsaturations. Examples particularly include caproyl (C6:0), capryloyl (C8:0), capryl (C10:0), lauroyl (C12:0), myristoyl (C14:0), palmitoyl (C16:0), phytanoly (C16:0), palmitoleoyl (C16:1), stearoyl (C18:0), oleoyl (C18:1), elaidoyl (C18:1), linoleoyl (C18:2), linolenoyl (C18:3), arachidonoyl (C20:4), behenoyl (C22:0) and lignoceroyl (C24:9) groups. Thus, typical non-polar chains are based on the fatty acids of natural ester lipids, including caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, or the corresponding alcohols. Preferable non-polar chains are palmitic, stearic, oleic and linoleic acids, particularly oleic acid.

The diacyl lipid, when used as all or part of component "a", may be synthetic or may be derived from a purified and/or chemically modified natural sources such as vegetable oils. Mixtures of any number of diacyl lipids may be used as component a. Most preferably this component will include at least a portion of diacyl glycerol (DAG), especially glycerol dioleate (GDO). In one favoured embodiment, component a consists of DAGs. These may be a single DAG or a mixture of DAGs. A highly preferred example is DAG comprising at least 50%, preferably at least 80% and even comprising substantially 100% GDO.

An alternative or additional highly preferred class of compounds for use as all or part of component a are tocopherols. As used herein, the term "a tocopherol" is used to indicate the non-ionic lipid tocopherol, often known as vitamin E, and/or any suitable salts and/or analogues thereof. Suitable analogues will be those providing the phase-behaviour, lack of toxicity, and phase change upon exposure to aqueous fluids, which characterise the compositions of the present invention. Such analogues will generally not form liquid crystalline phase structures as a pure compound in water. The most preferred of the tocopherols is tocopherol itself, having the structure below. Evidently, particularly where this is purified from a natural source, there may be a small proportion of non-tocopherol "contaminant" but this will not be sufficient to alter the advantageous phase-behaviour or lack of toxicity. Typically, a tocopherol will contain no more than 10% of non-tocopherol-

analogue compounds, preferably no more than 5% and most preferably no more than 2% by weight.



Tocopherol

In a further advantageous embodiment of the invention, component a) consists essentially of tocopherols, in particular tocopherol as shown above.

A preferred combination of constituents for component a) is a mixture of at least one DAG (e.g. GDO) with at least one tocopherol. Such mixtures include 2:98 to 98:2 by weight tocopherol:GDO, e.g.10:90 to 90:10 tocopherol:GDO and especially 20:80 to 80:20 of these compounds. Similar mixtures of tocopherol with other DAGs are also suitable.

Component "b" in the present invention is at least one phospholipid. As with component a, this component comprises a polar head group and at least one non-polar tail group. The difference between components a and b lies principally in the polar group. The non-polar portions may thus suitably be derived from the fatty acids or corresponding alcohols considered above for component a. It will typically be the case that the phospholipid will contain two non-polar groups, although one or more constituents of this component may have one non-polar moiety. Where more than one non-polar group is present these may be the same or different.

Preferred phospholipid polar "head" groups include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol. Most preferred is phosphatidylcholine (PC). In a preferred embodiment, component b) thus consists of at least 50% PC, preferably at least 70% PC and most preferably at least 80% PC. Component b) may consist essentially of PC.

The phospholipid portion, even more suitably than any diacyl lipid portion, may be derived from a natural source. Suitable sources of phospholipids include egg, heart (e.g. bovine), brain, liver (e.g. bovine) and plant sources including soybean. Such

sources may provide one or more constituents of component b, which may comprise any mixture of phospholipids.

Since the pre-formulations of the invention may be administered to a subject for the controlled release of an active agent, it is preferable that the components a and b are biocompatible. In this regard, it is preferable to use, for example, diacyl lipids and phospholipids rather than mono-acyl (lyso) compounds. A notable exception to this is tocopherol, as described above. Although having only one alkyl chain, this is not a "lyso" lipid in the convention sense. The nature of tocopherol as a well tolerated essential vitamin evidently makes it highly suitable in biocompatibility.

The nature of the compositions of the invention as being suitable for soothing and healing irritation and inflammation at a body surface makes the need to well tolerated lipids highly important. In particular, the lipid composition will be present at high concentration in contact with tissue which may be damaged or inflamed. As a result, the very high level of compatibility of, for example, the diacyl lipids of the present invention, is significant in comparison with less well tolerated components such as mono-acyl lipids.

It is furthermore most preferable that the lipids and phospholipids of components a and b are naturally occurring (whether they are derived from a natural source or are of synthetic origin). Naturally occurring lipids tend to cause lesser amounts of inflammation and reaction from the body of the subject. Not only is this more comfortable for the subject but it may increase the residence time of the resulting depot composition, since less immune system activity is recruited to the administration site and there is less tendency for the subject to disturb the area. In certain cases it may, however, be desirable to include a portion of a non-naturally-occurring lipid in components a and/or b. This might be, for example an "ether lipid" in which the head and tail groups are joined by an ether bond rather than an ester. Such non-naturally-occurring lipids may be used, for example, to alter the rate of degradation of the resulting depot-composition by having a greater or lesser solubility or vulnerability to breakdown mechanisms present at the site of active agent release. Although all proportions fall within the scope of the present invention, generally, at least 50% of each of components a and b will be naturally occurring lipids. This will preferably be at least 75% and may be up to substantially 100%.

Two particularly preferred combinations of components a and b are GDO with PC and tocopherol with PC, especially in the region 30-90wt% GDO/tocopherol, 10-60 wt% PC and 1-30% solvent (especially ethanol, NMP and/or ispropanol). Most preferred combinations are 35-60% (e.g. 40-55) GDO with 20 to 50% (e.g. 25 to 45%) PC. These are especially suitable in combination with ethanol, particularly at 5 to 25% (e.g. 7 to 19%).

In addition to amphiphilic components a and b, the pre-formulations of the invention may also contain additional amphiphilic components at relatively low levels. In one embodiment of the invention, the pre-formulation contains up to 10% (by weight of components a and b) of a charged amphiphile, particularly an anionic amphiphile such as a fatty acid. Preferred fatty acids for this purpose include caproic, caprylic, capric, lauric, myristic, palmitic, phytanic, palmitolic, stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids, or the corresponding alcohols. Preferable fatty acids are palmitic, stearic, oleic and linoleic acids, particularly oleic acid. It is particularly advantageous that this component be used in combination with a cationic peptide active agent (see below). The combination of an anionic lipid and a cationic peptide is believed to provide a sustained release composition of particular value. This may in part be due to increased protection of the peptide from the degradative enzymes present in vivo.

Component "c" of the pre-formulations of the invention is an oxygen containing organic solvent. Since the pre-formulation is to generate a depot/bioadhesive composition following administration (e.g. *in vivo),* upon contact with an aqueous fluid, it is desirable that this solvent be tolerable to the subject and be capable of mixing with the aqueous fluid, and/or diffusing or dissolving out of the pre-formulation into the aqueous fluid. Solvents having at least moderate water solubility are thus preferred.

A special case is where the composition of the invention is formulated as aerosol spray compositions. Here component c may be seen to comprise the propellant, having a low aqueous solubility. All mixing ratios from essentially pure propellant to mainly oxygen containing organic solvents may be considered. When dispensing the formulation the propellant will to a large degree evaporate. When c mainly constitutes propellant an instant increase of viscosity may be observed after spraying

the formulation. This is due to rapid evaporation of the propellant and may have the advantage of a more effective initial retention at the application site, and the potential disadvantage that the formulation has a low viscosity during "curing" (uptake of water and phase transformation to a liquid crystalline phase with high viscosity) is circumvented.

In a preferred version, the solvent is such that a relatively small addition to the composition comprising a and b, i.e. below 20%, or more preferably below 16%, e.g. up to 10% or even below give a large viscosity reductions of one order of magnitude or more., As described herein, the addition of 10% solvent can give a reduction of two, three or even four orders of magnitude in viscosity over the solvent-free composition, even if that composition is a solution or L_2 phase containing no solvent, or an unsuitable solvent such as water (subject to the special case considered below), or glycerol.

Typical solvents suitable for use as component c include at least one solvent selected from alcohols, ketones, esters (including lactones), ethers, amides and sulphoxides. Examples of suitable alcohols include ethanol, isopropanol and glycerol formal. Monools are preferred to diols and polyols. Where diols or polyols are used, this is preferably in combination with an at least equal amount of monool or other preferred solvent. Examples of ketones include acetone, n-methyl pyrrolidone (NMP), 2-pyrrolidone, and propylene carbonate. Suitable ethers include diethylether, glycofurol, diethylene glycol monoethyl ether, dimethylisobarbide, and polyethylene glycols. Suitable esters include ethyl acetate and isopropyl acetate and dimethyl sulphide is as suitable sulphide solvent. Suitable amides and sulphoxides include dimethylacetamide (DMA) and dimethylsulphoxide (DMSO), respectively. Less preferred solvents include dimethyl isosorbide, tetrahydrofurfuryl alcohol, diglyme and ethyl lactate. The most preferred solvent comprises ethanol and in particular consists of at least 80% ethanol, preferably at least 90% ethanol.

Since the pre-formulations are to be administered to a living subject, it is necessary that the solvent component c is sufficiently biocompatible. The degree of this biocompatibility will depend upon the application method and since component c may be any mixture of solvents, a certain amount of a solvent that would not be acceptable in large quantities may evidently be present. Overall, however, the solvent or mixture forming component c must not provoke unacceptable reactions

from the subject upon administration. Generally such solvents will be hydrocarbons or preferably oxygen containing hydrocarbons, both optionally with other substituents such as nitrogen containing groups. It is preferable that little or none of component c contains halogen substituted hydrocarbons since these tend to have lower biocompatibility. Where a portion of halogenated solvent such as dichloromethane or chloroform is necessary, this proportion will generally be minimised. Evidently, the range of suitable solvents will be greater in formulations for application to sound, external surfaces than to internal, sensitive and/or damaged surfaces, where only the most biocompatible will typically be acceptable. In addition, in the case of aerosol spray compositions also halogenated hydrocarbons may be considered as propellant, since it will evaporate to a large degree during dispensing.

Component c as used herein may be a single solvent or a mixture of suitable solvents but will generally be of low viscosity. This is important because one of the key aspects of the present invention is that it provides preformulations that are of low viscosity and a primary role of a suitable solvent is to reduce this viscosity. This reduction will be a combination of the effect of the lower viscosity of the solvent and the effect of the molecular interactions between solvent and lipid composition. One observation of the present inventors is that the oxygen-containing solvents of low viscosity described herein have highly advantageous and unexpected molecular interactions with the lipid parts of the composition, thereby providing a non-linear reduction in viscosity with the addition of a small volume of solvent.

The viscosity of the "low viscosity" solvent component c (single solvent or mixture) should typically be no more than 18 mPas at 20°C. This is preferably no more than 15 mPas, more preferably no more than 10 mPas and most preferably no more than 7 mPas at 20°C.

The solvent component c will generally be at least partially lost upon formation of the depot/bioadhesive composition on contact with a surface (e.g. a body surface or the surface of an implant), or diluted by absorption of water from the surrounding air and/or tissue. It is preferable, therefore, that component c be at least to some extent water miscible and/or dispersible and at least should not repel water to the extent that water absorption is prevented. In this respect also, oxygen containing solvents with relatively small numbers of carbon atoms (for example up to 10 carbons,

preferably up to 8 carbons) are preferred. Obviously, where more oxygens are present a solvent will tend to remain soluble in water with a larger number of carbon atoms. The carbon to heteroatom (e.g. N, O, preferably oxygen) ratio will thus often be around 1:1 to 6:1, preferably 2:1 to 4:1. Where a solvent with a ratio outside one of these preferred ranges is used then this will preferably be no more than 75%, preferably no more than 50%, in combination with a preferred solvent (such as ethanol). This may be used, for example to decrease the rate of evaporation of the solvent from the pre-formulation in order to control the rate of liquid crystalline depot formation.

A further advantage of the present pre-formulations is that a higher level of bioactive agent may be incorporated into the system. In particular, by appropriate choice of components a-c (especially c), high levels of active agent may be dissolved or suspended in the pre-formulations. Generally, the lipid components in the absence of water are relatively poorly solubilising but in the presence of water form phases too viscous to administer easily. Higher proportions of bioactive agent may be included by use of appropriate solvents as component c and this level will either dissolve in the depot composition as it forms *in situ* or may form microdrops or microcrystals which will gradually dissolve and release active agent. A suitable choice of solvent will be possible by routine experimentation within the guidelines presented herein. In particular, the present inventors have established that the combination of a low molecular weight alcohol solvent (such as ethanol or isopropanol) with the lipid components of the present invention is unexpectedly effective in solubilising a wide range of drugs and other active molecules.

The pre-formulations of the present invention typically do not contain significant amounts of water. Since it is essentially impossible to remove every trace of water from a lipid composition, this is to be taken as indicating that only such minimal trace of water exists as cannot readily be removed. Such an amount will generally be less than 1% by weight, preferably less that 0.5% by the weight of the pre-formulation. In one preferred aspect, the pre-formulations of the invention do not contain glycerol, ethylene glycol or propylene glycol and contain no more than a trace of water, as just described.

In some cases the composition may contain a trace of water (or a polar solvent with similar properties) such that it forms a rather low viscous L2 (reversed micellar)

phase. This can also help to solubilise certain actives in the formulation, particularly those which are only soluble in water.

There is, however, a certain embodiment of the present invention in which higher proportions of water may be tolerated. This is where water is present as a part of the solvent component in combination with an additional water-miscible component c (single solvent or mixture). In this embodiment, up to 10 wt% water may be present providing that at least 3 wt%, preferably at least 5% and more preferably at least 7 wt% component c is also present, that component c is water miscible, and that the resulting preformulation remains non-viscous and thus does not form a liquid crystalline phase. Generally there will be a greater amount of component c) by weight than the weight of water included in the preformulation. Most suitable solvents of use with water in this aspect of the invention include ethanol, isopropyl alcohol, NMP, acetone and ethyl acetate.

The pre-formulations of the present invention contain one or more bioactive agents (described equivalently as "active agents" herein). Active agents may be any compound having a desired biological or physiological effect, such as a protein, drug, antigen, nutrient, cosmetic, fragrance, flavouring, diagnostic, pharmaceutical, vitamin, or dietary agent and will be formulated at a level sufficient to provide an *in vivo* concentration at a functional level (this generally being a local concentration for topical compositions).

Drug agents that may be delivered by the present invention include drugs which act on cells and receptors, such as peripheral nerves, adrenergic receptors, and cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulation system, endocrine and hormone system, blood circulatory system, synoptic sites, neuroeffector junctional sites, the immunological system, the reproductive system, the skeletal system, autacoid system, the alimentary and excretory systems, the histamine system, and the central nervous system. Drug agents intended for local stimulatory or inhibitory effects on enzymes or proteins can also be delivered by the present invention. The effect of the delivered drug agent may also be associated with direct effects on DNA and/or RNA synthesis, such as on transcription, translation, or post-translational modification. Also these effects may be both stimulatory and inhibitory.

Examples of drugs which may be delivered by the composition of the present invention include, but are not limited to, antibacterial agents such as β-lactams or macrocyclic peptide antibiotics, anti fungal agents such as polyene macrolides (e.g. amphotericin B) or azole antifungals, anticancer and/or anti viral drugs such as nucleoside analogues, paclitaxel and derivatives thereof, anti inflammatorys, such as non-steroidal anti inflammatory drugs and corticosteroids, cardiovascular drugs such as blood-pressure lowing or raising agents (especially locally acting), analgesics, and prostaglandins and derivatives. Diagnostic agents include radionuclide labelled compounds and contrast agents including X-ray, ultrasound and MRI contrast enhancing agents (especially for application to an internal surface of a body cavity). Nutrients include vitamins, coenzymes, dietary supplements etc which may, for example, be used for local rescue from the effects of a systemic drug, such as rescue by folate from a folate analogue such as methotrexate.

Particularly suitable active agents include those which would normally have a short residence time in the body due to rapid breakdown or excretion and those with poor oral bioavailability, especially where their effect may be provided by topical treatment, thereby bypassing systemic absorption. These include peptide, protein and nucleic acid based active agents, hormones and other naturally occurring agents in their native or modified forms. By administering such agents in the form of a bioadhesive depot composition formed from the pre-formulation of the present invention, the agents are provided at a sustained level for an extended length of time in spite of having rapid systemic clearance rates. This offers obvious advantages in terms of stability and patient compliance over dosing multiple times each day for the same period. In one preferred embodiment, the active agent thus has a biological half life (upon entry into the blood stream) of less than 1 day, preferably less than 12 hours and more preferably less than 6 hours. In some cases this may be as low as 1-3 hours or less. Suitable agents are also those with poor oral bioavailability relative to that achieved by injection, for where the active agent also or alternatively has a bioavailability of below 0.1%, especially below 0.05% in oral formulations. Similarly, certain agents would be unsuitable or undesirable when administered sytemically but may be administered locally, particularly to external surfaces.

Peptide and protein based active agents are highly suitable for inclusion in the surface-applied depot compositions of the invention. Such agents may be included for their local effect, or may be applied at a surface for systemic action. Suitable

actives for local or systemic effect include human and veterinary drugs selected from the group consisting of adrenocorticotropic hormone (ACTH) and its fragments, angiotensin and its related peptides, antibodies and their fragments, antigens and their fragments, atrial natriuretic peptides, bioadhesive peptides, Bradykinins and their related peptides, calcitonins and their related peptides, cell surface receptor protein fragments, chemotactic peptides, cyclosporins, cytokines, Dynorphins and their related peptides, endorphins and P-lidotropin fragments, enkephalin and their related proteins, enzyme inhibitors, immunostimulating peptides and polyaminoacids, fibronectin fragments and their related peptides, gastrointestinal peptides, gonadotrophin-releasing hormone (GnRH) agonists and antagonist, glucagons like peptides, growth hormone releasing peptides, immunostimulating peptides, insulins and insulin-like growth factors, interleukins, luthenizing hormone releasing hormones (LHRH) and their related peptides, melanocyte stimulating hormones and their related peptides, nuclear localization signal related peptides, neurotensins and their related peptides, neurotransmitter peptides, opioid peptides, oxytocins, vasopressins and their related peptides, parathyroid hormone and its fragments, protein kinases and their related peptides, somatostatins and their related peptides, substance P and its related peptides, transforming growth factors (TGF) and their related peptides, tumor necrosis factor fragments, toxins and toxoids and functional peptides such as anticancer peptides including angiostatins, antihypertension peptides, anti-blood clotting peptides, and antimicrobial peptides; selected from the group consisting of proteins such as immunoglobulins, angiogenins, bone morphogenic proteins, chemokines, colony stimulating factors (CSF), cytokines, growth factors, interferons (Type I and II), interleukins, leptins, leukaemia inhibitory factors, stem cell factors, transforming growth factors and tumor necrosis factors.

A further considerable advantage of the depot compositions of the present invention is that active agents are released gradually over long periods without the need for repeated dosing. The composition are thus highly suitable for children or people who's lifestyle is incompatible with a reliable or repeated dosing regime. Also for "lifestyle" actives where the inconvenience of repeated dosing might outweigh the benefit of the active.

Cationic peptides are particularly suitable for use where a portion of the pre-formulation comprises an anionic amphiphile such as a fatty acid. In this

embodiment, preferred peptides include octreotide, lanreotide, calcitonin, oxytocin, interferon-beta and -gamma, interleukins 4, 5, 7 and 8 and other peptides having an isoelectric point above pH 7, especially above pH 8.

In one preferred aspect of the present invention, the composition of the invention is such that an I_2 phase, or a mixed phase including I_2 phase is formed upon exposure to aqueous fluids and a polar active agent is included in the composition. Particularly suitable polar active agents include peptide and protein actives, oligo nucleotides, and small water soluble actives, including those listed above. Of particular interest in this aspect are the peptide octreotide and other somatostatin related peptides, interferons alpha and beta, glucagon-like peptides 1 and 2 and their receptor agonists, luprorelin and other GnRH agonist, abarelix and other GnRH antagonists, interferon alpha and beta, zolendronate and ibandronate and other bisphosponates, and polar active chlorhexidine (e.g. chlorhexidine digluconate or chlorhexidine dihydrochloride). Consider to exclude. Most of those listed here as particularly interesting are for parenteral dosing, except chlorhexidine!

The amount of bioactive agent to be formulated with the pre-formulations of the present invention will depend upon the functional dose and the period during which the depot composition formed upon administration is to provide sustained release. Typically, the dose formulated for a particular agent will be around the equivalent of the normal single dose multiplied by the number times greater the expected duration of action the formulation is to provide. Evidently this amount will need to be tailored to take into account any adverse effects of a large dose at the beginning of treatment and so this will generally be the maximum dose used. The precise amount suitable in any case will readily be determined by suitable experimentation.

The formulations of the present invention may form non-parenteral depots where the active agent is slowly released at a body surface. It is particularly significant that the compositions generated from the preformulations are bioadhesive because this allows local release of the active agent over a sustained period. That is to say that the compositions should coat the surface to which they are applied and/or upon which they form as appropriate and should remain even when this surface is subject to a flow of air or liquid and/or rubbing. It is particularly preferable that the liquid crystalline depot compositions formed should be stable to rinsing with water. For example, a small volume (e.g. 100 µl) of depot precursor may be applied to a body

surface and be exposed to a flow of five hundred times its own volume of water per minute for 5 minutes. After this treatment, the composition can be considered bioadhesive if less than 50% of the composition or bioactive agent has been lost. Preferably this level of loss will be matched when water equalling 1000 times and more preferably 10 000 times the volume of the composition is flowed past per minute for five, or preferably 10, minutes.

Another advantageous property of the compositions of the invention is that the film generated following administration may not only act as a depot system. This film may also have the advantage of lowering evaporation of water from damaged areas or areas afflicted by a medical condition (where barrier properties of the skin is reduced). Thus, the compositions may have further advantageous properties in themselves and show additive and/or synergistic advantages in combination with active agents, for instance for the prophylaxis of inflammatory or allergic dermatoses and for the care and restoration of sensitive or stressed skin.

Although the non-parenteral depot compositions of the present invention may absorb some or all of the water needed to form a liquid crystalline phase structure from the biological surfaces with which they are contacted, some additional water may also be absorbed from the surrounding air. In particular, where a thin layer of high surface area is formed then the affinity of the composition for water may be sufficient for it to form a liquid crystalline phase structure by contact with the water in the air. The "aqueous fluid" referred to herein is thus, at least partially, air containing some moisture in this embodiment.

Non-parenteral depot compositions will typically be generated by applying the pre-formulation topically to a body surface (external or within a natural or artificially generated body cavity) and/or to the surface of an implant. This application may be by direct application of liquid such as by spraying, dipping, rinsing, application from a pad or ball roller, intra-cavity injection (e.g to an open cavity with or without the use of a needle), painting, dropping (especially into the eyes), applying in the form of a patch, and similar methods. A highly effective method is aerosol or pump spraying and evidently this requires that the viscosity of the pre-formulation be as low as possible and is thus highly suited to the compositions of the invention. Non-parenteral depots may, however, be used to administer systemic agents e.g. transmucosally or transdermally.

Where the formulation is administered in the form of a patch, this may rely on the "glue" function of the composition. This "glue property" may be beneficial for the tissue contacted by the formulation as the compositions can be soothing and rehydrating, as indicted herein. This is in contrast to previously known patches, where the adhesive is typically inert at best.

Conditions particularly suitable for causative or symptomatic treatment by topical bioadhesive depot compositions of the present invention include skin conditions (such as soreness resulting from any cause including chapping, scratching and skin conditions including eczema and herpes) eye conditions, genital soreness (including that due to genital infection such as genital herpes), infections and conditions for the finger and/or toe nails (such as bacterial or fungal infections of the nails such as onychomycosis or poronychia) and in particular imflammation and/or irritation at any body surface. Two particularly suitable conditions which may be improved by use of the compositions of the invention are oral mucositis and inflammatory bowel disease (e.g. crohn's disease or ulcerative collitus). Topical-type bioadhesive formulations may also be used to administer systemic active agents (e.g. medication), particularly by skin adsorption, oral, transdermal or rectal routes. Travel sickness medication is a preferred example, as is nicotine (e.g. in anti-smoking aids). Where context permits, "topical application" as referred to herein includes systemic agents applied non-parenterally to a specific region of the body.

Periodontal infections are particularly suitable for treatment by the compositions of the present invention. In particular, known compositions for treating periodontal infection are difficult to apply or are generally ineffective. The most widely used periodontal depot composition comprises insertion of a collagen "chip" into the periodontal space, from which an anti-infective agent is released. This chip is difficult to insert and does not form to match the shape and volume of the periodontal space, so that pockets of infection may remain untreated. In contrast to this, the compositions of the present invention, applied as a low viscosity preformulation, can be easily and quickly injected into the periodontal space and will flow to conform exactly to that space and fill the available volume. The compositions then quickly absorb water to form a robust gel which is resistant to aqueous conditions of the mouth. The only known previous attempt at such an injectible periodontal treatment relied on dispersions of relatively high viscosity

which were difficult to apply and were subject to undesirable phase separation. All of these drawbacks are now addressed in the compositions of the present invention as described herein. Highly suitable actives for periodontal administration are anti-antibacterial, antibiotic, anti-inflammatory, and local analgesic agents, in particular benzdamine, tramadol and particularly chlorhexidine.

Non-parenteral depot compositions are also of significant benefit in combination with non-pharmaceutical active agents, such as cosmetic actives, fragrances, essential oils etc. Such non-pharmaceutical depots will maintain the important aspects of bioadhesion and sustained release to provide prolonged cosmetic effects, but may easily be applied by spraying or wiping. This additionally applies to agents which have both cosmetic and medical (especially prophylactic) benefits such as sun-protective agents. Since the topical depot compositions provide robust, water resistant barriers which can solubilise high levels of actives, they are especially suitable for sunscreens and sunblocks in combination with ultra violet light (UV, e.g. UVa, UVb and/or UVc) absorbing and/or scattering agents, particularly where high levels of protection is desirable. The compositions are furthermore highly biocompatible and may act to moisten and soothe the skin during sun exposure. Compositions of the invention containing soothing agents such as aloe vera are also highly suitable for soothing and moistening application after exposure to sunlight, or to skin which is dry, inflamed or damaged due to, for example irritation, burning or abrasion.

Active agents particularly suited to non-parenteral (e.g. topical) depot administration, which includes intra oral, buccal, nasal, ophthalmic, dermal, rectal and vaginal delivery routes, include antibacterials such as chlorhexidine, chloramphenicol, triclosan, tetracycline, terbinafine, tobramycin, fusidate sodium, butenafine, metronidazole (the latter particularly for the (e.g. symtomatic) treatment of acne rosacea - adult acne or some vaginal infections), antiviral, including acyclovir, anti infectives such as bibrocathol, ciprofloxacin, levofloxacin, local analgesics such as benzydamine, lidocaine, prilocaine, xylocaine, bupivacaine, analgesics such as tramadol, fentanyl, sufentanyl, morphine, hydromorphone, methadone, oxycodone, codeine, asperine, acetaminophen, NSAIDS such as ibuprofen, flurbiprofen, naproxene, ketoprofen, fenoprofen, diclofenac, etodalac, diflunisal, oxaproxin, piroxicam, piroxicam, indomethansine, sulindac, tolmethin,

salysylic acids such as salisylamide and diflunisal, Cox1 or Cox2 inhibitors such as celecoxib, rofecoxib or valdecoxib, corticosteroids, anticancer and immuno stimulating agents (for instance ,metylaminolevulinat hydrocloride, interferon alpha and beta), anticonvulsants (for instance tiagabine topiramate or gabapentin), hormones (such as testosterone, and testosterone undecanoate, medroxyprogesterone, estradiol) growth hormones (like human growth hormone), and growth factors (like granulocyte macrophage colony-stimulating factor), immuno suppressants (cyclosporine, sirolimus, tacrolimus), nicotine and antivirals (e.g. acyclovir), vitamin D3 and derivatives thereof.

Other particularly suitable actives include:
Acetaminophen, Ibuprofen, Propoxyphene, Codeine, Dihydrocodein, Hydrocodone, Oxycodone, Nalbuphine, Meperidine, Leverorphanol, Hydromorphone, Oxymorphone, Alfentanil, Fentanyl and Sefentanil.

Some specific actives found by the inventors to form highly effective depots of the present invention include the following:

For topical bioadhesive, controlled release products for intraoral (including buccal & periodontal) administration;

i. benzydamine (local analgesic, anti inflammatory) or other local analgesic, analgesic, anti inflammatory, anti bacterial, anti fungal or combination thereof. Composition provides sustained effect at intraoral mucosa, in particular damaged, sensitised, infected mucosa e.g. in patients suffering from oral mucositis (induced by e.g. chemo- and radiotherapy). In particular for treatment of oral mucositis.

ii. tramadol (analgesic). Provides a composition with sustained systemic analgesic effect.

iii. chlorhexidine gluconate (antibacterial) for treatment of periodontal and topical infections. Particularly for long acting effect in periodontal pocket. Compositions result in depots releasing chlorhexidine over more than 1h, preferably more than 6h, most preferably more than 24 h when applied as a liquid, forming a bioadhesive gel *in situ.* Surface gel formation time observed to be between 1 second and 5 min.

Depots i to iii formable having high level of active agent incorporation and high degree of resistance to washing away. Preformulations in the form of a liquid administered as spray or liquid wash/rinse for i and ii and gel-forming liquid for iii, wherein liquid is applied to periodontal pocket, e.g. by injection.

For non-parenteral (e.g. topical or systemic) bioadhesive, controlled release products for nasal administration;

i. fentanyl (analgesic) provides rapid onset and sustained duration analgesia when administered as spray to the nasal or oral cavity

ii. diazepam (anti anxiety) provides non-parenteral, nasal or oral cavity depot with systemic effect giving rapid onset and sustained duration. Administered as a spray

For topical bioadhesive, controlled release products for ophthalmic administration;

i. diclofenac (NSAID) with sustained duration. Administered as in situ phase forming liquid

ii. pilocarpine (parasymptomimetic, cholinergic agonist) for treatment of glaucoma.

iii levocabastine hydrochloride, ketotifen fumarate providing liquid for eye-dropping to give long lasting relief from allergic conjunctivitis with long period between reapplication.

iv Pilocarpine hydrochloride for the treatment of Sjögrens syndrome.

v dexamethasone, (corticosteroid)

vi chloramphenicol (primarily bacteriostatic antiinfective)

vii indomethacin (NSAID)

Depots i to vii formulated as liquid spray or more preferably drops for direct application to eye surface and provide *in situ* depot formation with high resistance to washing out by tears and wear from blinking/eye rubbing. Composition of the invention show excellent compatibility ophthalmic application. Safety studies in rabbit models show no irritation and no blurring effects. Appropriate here?

Other actives suitable for ophthalmic compositions include Antihistamines, Mast cell stabilizers, Nonsteroidal anti-inflammatory drugs (NSAIDs), Corticosteroids (e.g. to treat allergic conjunctivitis), Anti-Glaucoma actives including inflow

suppressing/inhibiting agents (beta blocking agents: timolol, betaxolol, carteolol, levobunolol, etc., topical carbonic anhydrase inhibitors: dorzolamide, brinzolamide, sympathomimetics: epinephrine, dipivefrin, clonidine, apraclonidine, brimonidine), outflow facilitating agents (parasympathomimetics (cholinergic agonists): pilocarpine prostaglandin analogues and related compounds: atanoprost, travoprost, bimatoprost, unoprostone)

For non-parenteral (e.g. topical or systemic) bioadhesive, controlled release products for dermatological administration;

i. acyclovir (antiviral). Composition generates a bioadhesive, film forming product with sustained duration. Applied as spray or liquid

ii. testosterone undecanoate or testosterone enantate (hormone deficiency). Bioadhesive, film forming composition with sustained duration. May be applied as aerosol- or pump-spray, or as liquid.

Particularly suitable applications of dermatological formulations are anti-infective dermatological bioadhesive depots for protection in environments where contact with infective agents is likely (e.g. human or veterinary surgery, abattoir work, certain types of cleaning etc.). Bioadhesive depots generated from composition of the invention provide robust and sustained protection for the wearer. The compositions with antiinfective agents may also be used in situations where skin sterility of the wearer is important for the health of others, such as for nurses or doctors visiting multiple patients in hospital, where cross-infection must be avoided. A prior coating with a composition of the present invention may serve to provide resistance against picking up of infectives from one area and thus prevent transmission to another.

In the methods of treatment of the present invention, as well as in the corresponding use in therapy and the manufacture of medicaments, an active agent is not always necessary. In particular, lipids, particularly phospholipids such as PC have been implicated as highly beneficial in themselves for the treatment of certain conditions (including those described herein below). Without being bound by theory, it is believed that suitable lipids, such as those in the formulations of the present invention, are naturally present in the protective layers over and around many structures of the body, such as the linings of many body cavities and the contact surfaces of joints. These layers may serve as protection from adhesion and attack by

a wide variety of chemical and biological agents (such as on gastric surfaces and in the lining of the GI tract), may act as lubricants (particularly in joints but crucially also on the linings and membranes surrounding many internal structures such as heart and lungs), and may additionally contribute to cell wall repair by allowing lipid exchange and dilution of undesirable membrane-bound and membrane-soluble agents. The lipid nature of the compositions also forms a harmless substrate for unwanted inflammatory lipase enzymes including phospholipases such as phospholipase A_2 (PLA_2).

In an alternative embodiment of the methods of treatment and corresponding uses of the present invention, suitable actives may be included, either as the sole beneficial agent, or to complement the effect of suitable lipid components. Such actives will typically be suited for the treatment of inflammation and/or irritation, such as steroidal and non-steroidal anti-inflammatory drugs and local immune modulators. Examples of such agents are well known and many are mentioned herein elsewhere. They include, cis-urocanic acid, corticosteroids such as prednisone methylprednisolone and hydrocortisone, and derivatives of nonsteroidal anti-inflammatory compounds such as benzydamine, paracetamol, ibuprofen and salicylic acid derivatives including acetyl salicylate and 5-amino salicylates. Local inhibitors of inflammatory pathways are also suitable, including the antigen recognition suppressors methotrexate, azathioprine or 6-mercaptopurine and phospholipase inhibitors, such as PLA_2 inhibitors.

The pre-formulations of the present invention provide non-lamellar liquid crystalline depot compositions upon exposure to aqueous fluids, especially in contact with body surfaces. As used herein, the term "non-lamellar" is used to indicate a normal or reversed liquid crystalline phase (such as a cubic or hexagonal phase) or the L3 phase or any combination thereof. The term liquid crystalline indicates all hexagonal liquid crystalline phases, all cubic liquid crystalline phases and/or all mixtures thereof. Hexagonal as used herein indicates "normal" or "reversed" hexagonal (preferably reversed) and "cubic" indicates any cubic liquid crystalline phase unless specified otherwise. By use of the pre-formulations of the present invention it is possible to generate any phase structure present in the phase-diagram of components a and b with water. This is because the pre-formulations can be generated with a wider range of relative component concentrations than previous lipid depot systems without risking phase separation or resulting in highly viscous

solutions for injection. In particular, the present invention provides for the use of phospholipid concentrations above 50% relative to the total amphiphile content. This allows access to phases only seen at high phospholipid concentrations, particularly the hexagonal liquid crystalline phases.

For many combinations of lipids, only certain non-lamellar phases exist, or exist in any stable state. It is a surprising feature of the present invention that compositions as described herein frequently exhibit non-lamellar phases which are not present with many other combinations of components. In one particularly advantageous embodiment, therefore, the present invention relates to compositions having a combination of components for which an I_2 and/or L_2 phase region exists when diluted with aqueous solvent. The presence or absence of such regions can be tested easily for any particular combination by simple dilution of the composition with aqueous solvent and study of the resulting phase structures by the methods described herein.

In a highly advantageous embodiment, the compositions of the invention may form an I_2 phase, or a mixed phase including I_2 phase upon contact with water. The I_2 phase is a reversed cubic liquid crystalline phase having discontinuous aqueous regions. This phase is of particular advantage in the controlled release of active agents and especially in combination with polar active agents, such as water soluble actives because the discontinuous polar domains prevent rapid diffusion of the actives. Depot precursors in the L_2 phase are highly effective in combination with an I_2 phase depot formation. This is because the L_2 phase is a so-called "reversed micellar" phase having a continuous hydrophobic region surrounding discrete polar cores. L_2 thus has similar advantages with hydrophilic actives.

In transient stages after contact with body fluid the composition can comprise multiple phases since the formation of an initial surface phase will retard the passage of solvent into the core of the depot. Without being bound by theory, it is believed that this transient formation of a surface phase, especially a liquid crystalline surface phase, serves to dramatically reduce the "burst/lag" profile of the present compositions by immediately restricting the rate of exchange between the composition and the surroundings. Transient phases may include (generally in order from the outside towards the centre of the depot): H_{II} or L_α, I_2, L_2, and liquid (solution). It is highly preferred that the composition of the invention is capable

forming at least two and more preferably at least three of these phases simultaneously at transient stages after contact with water at physiological temperatures. In particular, it is highly preferred that one of the phases formed, at least transiently, is the I_2 phase.

It is important to appreciate that the preformulations of the present invention are of low viscosity. As a result, these preformulations must not be in any bulk liquid crystalline phase since all liquid crystalline phases have a viscosity significantly higher than could be administered by syringe or spray dispenser. The preformulations of the present invention will thus be in a non-liquid crystalline state, such as a solution, L_2 or L_3 phase, particularly solution or L_2. The L_2 phase as used herein throughout is preferably a "swollen" L_2 phase containing around 10 wt% or greater of solvent (component c) having a viscosity reducing effect. This is in contrast to a "concentrated" or "unswollen" L_2 phase containing no solvent, or a lesser amount of solvent, or containing a solvent (or mixture) which does not provide the decrease in viscosity associated with the oxygen-containing, low viscosity solvents specified herein.

In one embodiment, a small proportion (e.g.less than 5% by weight) of a reinforcing polymer may be added to the formulation.

Upon administration, the pre-formulations of the present invention undergo a phase structure transition from a low viscosity mixture to a high viscosity (tissue adherent) depot composition. Generally this will be a transition from a molecular mixture, swollen L_2 and/or L3 phase to one or more (high viscosity) liquid crystalline phases such as normal or reversed hexagonal or cubic liquid crystalline phases or mixtures thereof. As indicated above, further phase transitions may also take place following administration. Obviously, complete phase transition is not necessary for the functioning of the invention but at least a surface layer of the administered mixture will form a liquid crystalline structure. Generally this transition will be rapid for at least the surface region of the administered formulation (that part in direct contact with air, body surfaces and/or body fluids). This will most preferably be over a few seconds or minutes (e.g. up to 30 minutes, preferably up to 10 minutes, more preferably 5 minutes of less). The remainder of the composition may change phase to a liquid crystalline phase more slowly by diffusion and/or as the surface region disperses.

In one preferred embodiment, the present invention thus provides a pre-formulation as described herein of which at least a portion forms a hexagonal liquid crystalline phase upon contact with an aqueous fluid. The thus-formed hexagonal phase may gradually disperse, releasing the active agent, or may subsequently convert to a cubic liquid crystalline phase, which in turn then gradually disperses. It is believed that the hexagonal phase will provide a more rapid release of active agent, in particular of hydrophilic active agent, than the cubic phase structure, especially the I_2 and L_2 phase. Thus, where the hexagonal phase forms prior to the cubic phase, this will result in an initial release of active agent to bring the concentration up to an effective level rapidly, followed by the gradual release of a "maintenance dose" as the cubic phase degrades. In this way, the release profile may be controlled.

Without being bound by theory, it is believed that upon exposure (e.g. to body fluids), the pre-formulations of the invention lose some or all of the organic solvent included therein (e.g. by diffusion and/or evaporation) and take in aqueous fluid from the bodily environment (e.g. moist air close to the body or the *in vivo* environment) such that at least a part of the formulation generates a non-lamellar, particularly liquid crystalline phase structure. In most cases these non-lamellar structures are highly viscous and are not easily dissolved or dispersed into the *in vivo* environment and are bioadhesive and thus not easily rinsed or washed away. Furthermore, because the non-lamellar structure has large polar, apolar and boundary regions, it is highly effective in solubilising and stabilising many types of active agents and protecting these from degradation mechanisms. As the depot composition formed from the pre-formulation gradually degrades over a period of hours or days, or even weeks or months (depending upon the nature and site of application), the active agent is gradually released and/or diffuses out from the composition. Since the environment within the depot composition is relatively protected, the pre-formulations of the invention are highly suitable for active agents with a relatively low biological half-life (see above).

In an additional aspect of the invention, the topical compositions may be used to provide a physical barrier on body surfaces, in the absence of any active agent. In particular, because of the very high bioadherance of the compositions, "barrier" coatings formed by spraying or application of liquid may be formed from the present compositions so as to reduce contact with potential infective or irritant agents or to

reduce soiling of the body surfaces. The robust nature of the compositions and resistance to washing provide advantageous characteristics for such barriers, which could conveniently be applied as a liquid or by spraying. Without being bound to theory it is believed that the stability and wear resistance of applied topical compositions is due to the particular phase transitions of the composition on exposure to aqueous fluid/moisture and the bioadhesion thereof, in combination with the low aqueous solubility of the diacyl lipid building blocks.

The formulations, compositions and methods of the invention relating to the treatment of inflammation or irritation, are particularly suitable for addressing inflammation and/or irritation in a body cavity. Administration to a body cavity is thus highly suitable in this aspect and will be carried out by a method suitable for the cavity being treated. Mouthwashes, for example, may be suitable for oral or buccal cavities, while other parts of the GI tract may be suitably treated by oral formulations, including dispersions and dry pre-formulations, and rectal formulations such as enemas or suppositories. Rinses and pesseries are similarly suitable for vaginal delivery.

The compositions of the present invention are highly suitable for treating inflammation in a body cavity because of the highly bioadhesive nature of the non-lamellar phase and the resulting long-lasting effects. The inherently soothing and highly biocompatible nature of the constituents is also important and may pay a passive or active role in the treatment of inflammation.

The methods of treatment and corresponding uses of the present invention are thus most applicable to inflammatory diseases and inflammation caused by, for example, wounding, abrasion, or reaction to aggressive therapies such as irradiation and/or chemotherapy. Especially suitable are inflammatory diseases affecting at least one body cavity. Diseases of the GI tract are highly suitable for treatment with the compositions of the present invention, particularly inflammatory bowel disease including Crohn's disease and ulcerative collitus and oral inflammation such as oral mucositis. Similarly, application to a body cavity during surgery may also be used to take advantage of the properties of the formulations. They may thus be directly applied, for example by spraying or painting, to sooth inflammation resulting from or exposed during surgery and also to reduce the tendency of surgically manipulated tissue to "stick" and/or form adhesions/bridges at unwanted sites.

The invention thus particularly provides for a method of treatment of an inflammatory disease (e.g. Crohn's disease, ulcerative collitus or oral mucositis), said method comprising the administration of a preformulation of the present invention either in the absence of an active agent, or comprising at least one anti-inflammatory or anti-infective active agent such as one selected from corticosteroids such as prednisone methylprednisolone and hydrocortisone, and derivatives of nonsteroidal anti-inflammatory compounds such as benzydamine, paracetamol, ibuprofen and salicylic acid derivatives including acetyl salicylate and 5-amino salicylates. Local inhibitors of inflammatory pathways are also suitable, including the antigen recognition suppressors methotrexate, azathioprine or 6-mercaptopurine and phospholipase inhibitors, such as PLA_2 inhibitors. Other sutable actives include glutamine, antioxidants such as ascorbate, beta-carrotine, vitamin E, oxypentifylline, Azelastine hydrochloride, allopurinol, chlorhexadine, povidone iodine, nystatin, clotrimazole, polymixin E, tobramycin, amphotericin B, acyclovir, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage stimulating factor (GM-CSF), cytokines and cytokine inducers/supressors.

A particularly preferred method and corresponding use is a method for the treatment of oral mucositis in a human or animal subject (especially one in need thereof) by a composition of the present invention (especially comprising preferred combinations of components a), b) and c)) comprising at least one local analgesics or anti-inflammatory agent, especially benzydamine or a derivative thereof. Optionally these may be combined with one or more of the actives indicated above for the treatment of inflammation, and/or with a topical anaesthetic such as lignocaine, cocaine, diphendramine, or particularly dyclonine HCl.

The Invention will now be further illustrated by reference to the following non-limiting Examples and the attached Figures, in which;

Figure 1 shows the cumulative release of methylene blue (MB) from a depot formulation comprising PC/GDO/EtOH (45/45/10 wt%) when injected into excess water;

Figure 2 demonstrates the non-linear decrease of pre-formulation viscosity upon addition of N-methyl pyrolidinone (NMP) and EtOH;

Figure 3 displays the *in vitro* release in excess aqueous phase of chlorhexidine from a depot formulation comprising PC/GDO/EtOH (36/54/10 wt%) containing 50 mg chlorhexidine / g of formulation, corresponding to 5% drug load.

Examples:

Example 1

Availability of various liquid crystalline phases in the depot by choice of composition

Injectable formulations containing different proportions of phosphatidyl choline ("PC" - Epikuron 200) and glycerol dioleate (GDO) and with EtOH as solvent were prepared to illustrate that various liquid crystalline phases can be accessed after equilibrating the depot precursor formulation with excess water.

Appropriate amounts of PC and EtOH were weighed in glass vials and the mixture was placed on a shaker until the PC completely dissolved to form a clear liquid solution. GDO was then added to form an injectable homogenous solution.

Each formulation was injected in a vial and equilibrated with excess water. The phase behaviour was evaluated visually and between crossed polarizes at 25°C. Results are presented in Table 1.

TABLE 1

Formulation	PC (wt%)	GDO (wt%)	EtOH (wt%)	Phase in H_2O
A	22.5	67.5	10.0	L_2
B	28.8	61.2	10.0	I_2
C	45.0	45.0	10.0	H_{II}
D	63.0	27.0	10.0	H_{II}/L_α

L_2 = reversed micellar phase

I_2 = reversed cubic liquid crystalline phase

H_{II} = reversed hexagonal liquid crystalline phase

L_α = lamellar phase

Example 2

In vitro release of a water-soluble substance

A water-soluble colorant, methylene blue (MB) was dispersed in formulation C (see Example 1) to a concentration of 11 mg/g formulation. When 0.5 g of the formulation was injected in 100 ml water a stiff reversed hexagonal H_{II} phase was formed. The absorbency of MB released to the aqueous phase was followed at 664 nm over a period of 10 days. The release study was performed in an Erlenmeyer flask at 37°C and with low magnetic stirring.

The release profile of MB (see Figure 1) from the hexagonal phase indicates that this (and similar) formulations are promising depot systems. Furthermore, the formulation seems to give a low initial burst, and the release profile indicates that the substance can be released for several weeks; only about 50% of MB is released after 10 days.

Example 3

Viscosity in PC/GDO (6:4) or PC/GDO (3:7) on addition of solvent (EtOH, PG and NMP)

A mixture of PC/GDO/EtOH was manufactured according to the method in Example 1. All, or nearly all, of the EtOH was removed from the mixture with a rotary evaporator (vacuum, 40°C, 1h) and the resulting solid mixture were weighed in glass vial after which 2, 5, 10 or 20% of a solvent (EtOH, propylene glycol (PG) or n-methyl pyrrolidone (NMP)) was added. The samples were allowed to equilibrate several days before the viscosity was measured at a shear rate of $0.1s^{-1}$ with a Physica UDS 200 rheometer at 25°C.

This example clearly illustrates the need for solvent with certain depot precursors in order to obtain an injectable formulation (see Figure 2). The viscosity of solvent-free PC/GDO mixtures increases with increasing ratio of PC. Systems with low PC/GDO ratio (more GDO) are injectable with a lower concentration of solvent.

Example 4

Composition and in vitro phase study

The formulations were manufactured according to the method described in Example 1 with compositions according to Table 2. An active substance (peptide), salmon calcitonin (sCT), was added to each formulation to a concentration of 500 μg sCT/g formulation. The formulations were designed as homogenous suspensions for parenteral administration (mixing required shortly prior to use since the drug is not completely dissolved in the PC/GDO/EtOH system).

The phase study in this example is performed in excess of rat serum at 37°C in order to simulate an *in vivo* situation. Table 2 shows that the same phases as those in water are formed (compare Table 1).

TABLE 2

Formulation	PC (wt%)	GDO (wt%)	OA (wt%)	EtOH (wt%)	Phase in rat serum
E	18	72	-	10	L_2
F	36	54	-	10	I_2
G	34	51	5	10	I_2
H	54	36	-	10	H_{II}
I	72	18	-	10	H_{II}/L_α

OA = Oleic Acid

Example 5

Sterile filtration of formulations with reduced viscosity

To lower the viscosity with various solvents is sometimes necessary in order to obtain an injectable formulation and to be able to administrate the system with a regular syringe (see Example 3). Another important effect from the viscosity-lowering solvent is that the formulations can be sterile filtrated.

Formulations E to I in Example 4 were studied in a sterile filtration test by using a 0.22μm filter (before addition of the active substance). Formulations E to H were

successfully filtrated, but formulation I failed since the viscosity was too high. An aseptic manufacturing procedure was therefore needed for this formulation.

Example 6: Preparation of depot precursor compositions with various solvents.

Depending on composition of the formulation and the nature and concentration of active substance certain solvents may be preferable.

Depot precursor formulations (PC/GDO/solvent (36/54/10)) were prepared by with various solvents; NMP, PG, PEG400, glycerol/EtOH (90/10) by the method of Example 1. All depot precursor compositions were homogeneous one phase solutions with a viscosity that enabled injection through a syringe (23G - i.e. 23 gauge needle; 0.6mm x 30mm). After injecting formulation precursors into excess water a liquid crystalline phase in the form of a high viscous monolith rapidly formed with NMP and PG containing precursors. The liquid crystalline phase had a reversed cubic micellar (I_2) structure. With PEG400, glycerol/EtOH (90/10) the viscosification/solidification process was much slower and initially the liquid precursor transformed to a soft somewhat sticky piece. The difference in appearance probably reflects the slower dissolution of PEG400 and glycerol towards the excess aqueous phase as compared to that of EtOH, NMP and PG.

Example 7: Preparation of depot composition containing benzydamine.

Benzydamine is a non-steroidal antiinflammatory drug and is extensively used as a topical drug in inflammatory conditions.

1g of a depot formulation containing 1.5mg benzydamine was prepared by dissolving the active substance in a mixture of PC/GDO/EtOH (36/54/10) prepared as described in Example 1. The depot composition was stable against crystallization during storage at 25°C for at least two weeks. Equilibration of the formulation precursor with excess water resulted in a high viscous monolithic liquid crystalline phase (I_2 structure).

Example 8: Robustness of the behaviour of the formulation against variations in the excipient quality.

Depot precursor formulations were prepared with several different GDO qualities (supplied by Danisco, Dk), Table 3, using the method of Example 1. The final depot precursors contained 36%wt PC, 54%wt GDO, and 10%wt EtOH. The appearance of the depot precursors was insensitive to variation in the quality used, and after contact with excess water a monolith was formed with a reversed micellar cubic phase behaviour (I_2 structure).

Table 3. Tested qualities of GDO.

GDO quality	Monoglyceride (%wt)	Diglyceride (%wt)	Triglyceride (%wt)
A	10.9	87.5	1.6
B	4.8	93.6	1.6
C	1.0	97.3	1.7
D	10.1	80.8	10.1
E	2.9	88.9	8.2
F	0.9	89.0	10.1

Example 9: Preparation of depot composition containing saturated PC (Epikuron 200SH).

Depot precursor formulations were prepared with various amounts PC comprising saturated hydrocarbon chains by addition of Epikuron 200SH directly to a mixture of PC/GDO/EtOH, prepared as for Example 1. The formulations are shown in Table 4. All precursor formulations were homogenous one phase samples in RT, while they became more viscous with increasing amount Epikuron 200SH. Injecting the depot precursor into excess water gave a monolith comprising a reversed miceller cubic (I_2) structure. Monoliths formed from samples containing higher amounts of Epikuron 200SH became turbid, possibly indicating segregation between Epikuron 200SH and the other components upon exposure to water and formation of the I2 phase.

Table 4. Depot composition containing saturated PC

Formulation	Saturated PC, Epikuron 200SH (%wt)	PC (%wt)	GDO (%wt)	EtOH (%wt)
G1	3.9	34.6	51.9	9.6
G2	7.0	33.5	50.2	9.3
G3	14.3	30.8	46.3	8.6

Example 10: Bioadhesive spray of depot precursor formulation.

A pump spray bottle was found to be a convenient way to apply the formulation topically, e.g. to the skin or the oral mucosa.

A depot precursor formulation prepared as in Example 1 (36%wt PC, 54%wt GDO, and 10%wt EtOH) was sprayed with a pump spray bottle onto the skin and oral mucosa. A film with solid mechanical properties formed shortly after application.

Example 11: Robustness of a topical film.

After applying the depot precursor formulation, as described in Example 10, (36%wt PC, 54%wt GDO, and 10%wt EtOH) to the skin, the applied formulation was exposed to flushing water (10L/min) for 10 minutes. The formulation showed excellent bioadhesive properties and resistance against rinsing and no loss of the formulation could be discerned.

Example 12: Formation of cubic phase with solid properties after exposure of depot precursor formulation to air.

After exposing a depot precursor formulation prepared as described in Example 1 (36%wt PC, 54%wt GDO, and 10%wt EtOH) to air (RT, relative humidity 40%) for at least 3 hours, a solid cubic phase was formed. This formation of a cubic phase structure demonstrates that a topical film will acquire bulk non-lamellar depot properties after application without the need for direct exposure to excess aqueous fluid.

Example 13: Formulation to treat periodontitis or perimplantitis.

In order to treat periodontitis or perimplantitis an antibacterial formulation is injected in the periodontal pocket, and a prolonged effect of the formulation is normally desired.

100μL of a formulation as prepared in Example 1, with the addition of the antibiotic chlorohexidine (PC/GDO/EtOH/chlorhexidine (35/53/10/2)), is injected via a syringe into a rat peridontal pocket. The injected composition is observed to

transform from the low viscous formulation, and which initially spreads out to fill voids, to form a solid mass by uptake of gingival fluids. An antibacterial depot system is thus provided.

Chlorhexidine remains at clinically effective levels (MIC 125μg/ml) in the GCF of the periodontal pockets for over 1 week. The depot system is completely degraded by enzymes within 7 to 10 days and does not need to be removed.

Example 14: Alternate antibacterial formulation to treat periodontitis or perimplantitis.

An alternate antibacterial formulation was provided by a formulation prepared as described in Example 1 and containing the antibacterial detergent Gardol (Glycine, N-methyl-N-(1-oxododecyl)-, sodium salt) (PC/GDO/EtOH/Gardol (34/51/10/5)). This formulation is injected into the rat periodontal pocket.

Gardol is observed to remain at clinically effective levels in the GCF of the periodontal pockets for a prolonged period (several days). The depot system is completely degraded by enzymes within 7 to 10 days and did not need to be removed.

Example 15: Adhesion of the formulation to high energy surfaces.

In order to treat perimplantitis, adhesion not only to biological surfaces but also to high energy surfaces such as a gold or titanium implant is important. It is also important that the formulation adheres to ceramic and plastic surfaces.

A formulation (PC/GDO/EtOH (36/54/10)) as prepared in Example 1 was applied to various surfaces in the oral cavity. The composition showed excellent adhesion to ceramic, plastic, gold, as well as to a normal tooth surface and could not be rinsed away by excess aqueous fluid. The depot resulting from the composition stayed at the site in the oral cavity where it was applied for at least 6h.

Example 16: Bioadhesive sustained release formulation of sodium fluoride for use on the teeth.

Fluoride containing compounds are often needed to oppose caries attack and a bioadhesive formulation precursor with depot effect was prepared as indicated in Example 1 from a mixture of PC/GDO/EtOH/sodium fluoride (35/53/10/2). The formulation was a dispersion of sodium fluoride since it could not be dissolved in the precursor. The liquid formulation was applied to the teeth with the aid of a brush. By uptake of saliva the formulation solidified and formed a depot providing sustained release of sodium fluoride for an extended period (several hours).

Example 17: Oral Cavity Spray Depot Composition

To be suitable as a topical depot system in the oral cavity the mechanical properties of the system was adjusted by decreasing the PC/GDO ratio.

A mixture containing PC/GDO/EtOH (27/63/10) was prepared according to Example 1. A drop of patent blue was added to visualize the formulation after application. About 300µl of the formulation was sprayed into the oral cavity with pump spray bottle. Shortly after application the formulation viscosified/solidified since it underwent a phase transformation by uptake of aqueous fluid (saliva) and loss of solvent (EtOH). The formulation had excellent bioadhesion to keritinized surfaces such as the hard palate and the gum. Here the film lasted for several hours despite saliva secretion and mechanical wear by the tongue. At soft mucosal surfaces the duration was much shorter (minutes).

Example 18: Oral Cavity Liquid Depot Composition

To be suitable for application with a pipette to the oral cavity the solidification/ viscosification of the formulation has to be delayed relative to the spray formulation. This is to allow the formulation to be conveniently distributed with the tongue to a thin film in the oral cavity after application.

Propylene glycol (PG) and EtOH were added to a formulation prepared as in Example 1, to the final composition PC/GDO/EtOH/PG (24/56/10/10). 300µl of the formulation was conveniently applied with a pipette to the oral cavity and distributed with the tongue to a thin film in the oral cavity. After about 20 seconds the viscosification of the formulation started since it underwent a phase transformation by uptake of aqueous fluid (saliva) and loss of solvent (EtOH and PG). After about one minute the solidification/viscosification appeared to be

finished. The formulation had excellent bioadhesion to keritinized surfaces such as the hard palate and the gum. Here the film lasted for several hours despite saliva secretion and mechanical wear by the tongue. At soft mucosal surfaces the duration was much shorter (minutes).

Example 19 - Bioadhesive depot for nails

The mixture in Example 18 was sprayed to the nail bed and in between the toes. The formulation solidifies/viscosifies slowly by uptake of aqueous fluids (cf. sweat). The solidification can be speeded up by adding water after spray application. The formulation had excellent bioadhesive properties and had a duration for several hours.

Eample 20: Loading capacity of the bioactive agent benzydamine in the formulation precursors.

Formulations with compositions as specified in Table 5 were prepared using the method in Example 1. An excess amount of benzydamine (50mg) was added to 0.5 g of the formulations. The vials were placed on a shaker at 15 °C for three days after which the solutions were filtered through a filter (0.45μm) to get rid of crystals of undissolved benzydamine. The benzydamine concentration in each formulation was determined with reversed phase gradient HPLC and UV detection at 306nm and the results are given in Table 5.

Table 5

Composition GDO/PC(Lipoid S100)/EtOH	Benzydamine concentration in formulation
67.5/22.5/10	3.4%
63/27/10	3.2%
58.5/31.5/10	3.3%
60/20/20	4.0%
56/24/20	4.5%
52/28/20	4.3%

Example 21: Compositions containing PC and tocopherol

Depot precursor formulations were prepared with several different PC/α-tocopherol compositions using the method of Example 1 (PC was first dissolved in the appropriate amount of EtOH and thereafter α-tocopherol was added to give clear homogenous solutions).

Each formulation was injected in a vial and equilibrated with excess water. The phase behaviour was evaluated visually and between crossed polarizes at 25°C. Results are presented in Table 6.

Table 6

α-tocopherol	PC	Ethanol	Phase in excess H_2O
2.25g	2.25g	0.5g	H_{II}
2.7g	1.8g	0.5g	H_{II}/I_2
3.15g	1.35g	0.5g	I_2
3.6g	0.9g	0.5g	I_2/L_2

Example 22: In vitro release of water-soluble disodium fluorescein

A water-soluble colorant, disodium fluorescein (Fluo), was dissolved in a formulation containing PC/α-tocopherol/Ethanol (27/63/10 wt%) to a concentration of 5 mg Fluo/g formulation. When 0.1 g of the formulation was injected in 2 ml of phosphate buffered saline (PBS) a reversed micellar (I_2) phase was formed. The absorbency of Fluo released to the aqueous phase was followed at 490 nm over a period of 3 days. The release study was performed in a 3 mL vial capped with an aluminium fully tear off cap at 37°C. The vial was placed on a shaking table at 150 rpm.

The release of Fluo from the PC/α-tocopherol formulation (see Table 7) indicates that this (and similar) formulations are promising depot systems. Furthermore, the absence of a burst effect is noteworthy, and the release indicates that the substance can be released for several weeks to months; only about 0.4% of Fluo is released after 3 days.

Table 7

Formulation	% release (37°C)	
	24 h	72 h
PC/α-tocopherol/EtOH: 27/63/10 wt%	< 0.1*	0.43

* Release below detection limit of the absorbance assay

Example 23: Formulations of the analgesic/antiinflammatory benzydamine

Formulations were prepared as in Example 1 by mixing benzydamine with a mixture of GDO, PC, ethanol and optionally PG/AP in the following proportions.

Formulation	BZD	GDO	PC	EtOH	PG	AP
1	3.0	53.3	28.7	10.0	5.0	0.01
2	3.0	53.3	28.7	15.0	0	0.01
3	3.0	57.4	24.6	10.0	5.0	0.01
4	3.0	49.2	32.8	10.0	5.0	0.01

where BZD is benzydamine, EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, PG is propylene glycol, and AP is ascorbyl palmitate.

All formulations are low viscosity liquids which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 24: Fentanyl nasal formulation

Formulations were prepared as in Example 1 by mixing the narcotic analgesic fentanyl with a mixture of GDO, PC, ethanol and optionally PG in the following proportions.

Formulation	Fentanyl	PC	GDO	EtOH	PG
1	0.05	34	51	10	5
2	0.05	36	54	10	-
3	0.05	42	43	10	5
4	0.05	45	45	10	-
5	0.15	34	51	10	5
6	0.15	36	54	10	-
7	0.05	30	45	15	10

8	0.15	30	45	15	10

where EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, and PG is propylene glycol

All formulations are low viscosity liquids suitable for administration by nasal spray, which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 25: Diazepam nasal formulation

Formulations were prepared as in previous examples by mixing the benzodiazepine antianxiety agent diazepam with a mixture of GDO, PC, ethanol and optionally PG in the following proportions.

Formulation	Diazepam	PC	GDO	EtOH	PG
1	5	32	48	10	5
2	5	34	51	10	-
3	10	37	38	10	5
4	10	40	40	10	-
5	10	30	45	10	5
6	10	32	48	10	-
7	10	26	39	15	10
8	10	30	45	15	-

where EtOH is ethanol, PC is LIPOID S100 soybean phosphatidylcholine, GDO is glycerol dioleate, and PG is propylene glycol

All formulations are low viscosity liquids suitable for administration by nasal spray, which generate liquid crystalline phase compositions upon exposure to aqueous conditions.

Example 26: Acne formulations with Clindamycin

Formulations were prepared as in previous examples by mixing the semisynthetic antibiotic clindamycin (free base or salt) with a mixture of GDO, PC, ethanol and PG in the following proportions (by weight).

Formulation	Clindamycin HCl	PC	GDO	EtOH	PG
1	1	30	54	10	5
2	2	29	54	10	5
3	1	34	50	10	5
4	2	33	50	10	5

Formulation	Clindamycin base	PC	GDO	EtOH	PG
5	1	30	54	10	5
6	2	29	54	10	5
7	1	33	54	2	10
8	2	32	54	2	10

The resulting preformulations are low viscosity liquids which, after application resistant to water, sweat, etc. The formulation are applied locally on the skin as a gel or by spraying and are bioadhesive with good film-forming properties.

Example 27: Further examples of viscosity in PC/GDO mixtures on addition of co-solvent

Mixtures of PC/GDO and co-solvent were prepared according to the methods of Example 1 and Example 3 in the proportions indicated in the table below. The samples were allowed to equilibrate for several days before viscosity measurements were performed using a Physica UDS 200 rheometer at 25°C.

Sample	PC/GDO (wt/wt)	EtOH / wt%	Glycerol / wt%	H_2O / wt%	Viscosity / mPas
1	50/50	3	-	-	1900
2	50/50	5	-	-	780
3	50/50	7	-	-	430
4	50/50	8	-	-	300
5	50/50	10	-	-	210
6	50/50	15	-	-	100
7	45/55	3	-	-	1350
8	45/55	5	-	-	540
9	45/55	7	-	-	320
10	45/55	8	-	-	250
11	45/55	10	-	-	150
12	45/55	15	-	-	85
13	40/60	3	-	-	740
14	40/60	5	-	-	400
15	40/60	7	-	-	240
16	40/60	8	-	-	200
17	40/60	10	-	-	130
18	40/60	15	-	-	57
19	40/60	-	10	-	$8*10^6$
20	40/60	-	-	3	$2.5*10^8$
21	40/60	-	-	5	$4*10^7$

This example further illustrates the need for a solvent with viscosity lowering properties in order to obtain injectable formulations. The mixtures containing glycerol (sample 19) or water (samples 20 and 21) are too viscous to be injectable at solvent concentrations equivalent to the samples containing EtOH (compare with samples 13, 14 and 17).

Example 28: Sunscreen formulations

Formulations were prepared as in Example 1 by mixing each of several UV absorbing/scattering agents with a mixture of GDO, PC, and ethanol in the following proportions (by weight)

Formulation	PC	GDO	EtOH	Tioveil CM	Spectraveil FIN	Solaveil CT-100	Tioveil 50 MOTG
1	38	42	5	-	-	-	15
2	38	42	5	-	-	15	-
3	37	38	5	15	5	-	-

Where TIOVEIL CM (Uniqema) comprises Cyclomethicone (and) Titanium Dioxide (and) Dimethicone Copolyol (and) Aluminium Stearate (and) Alumina, SPECTRAVEIL FIN (Uniqema) comprises Zinc Oxide (and) C12-15 Alkyl Benzoate (and) Polyhydroxystearic Acid, SOLAVEIL CT-100 (Uniqema) comprises C12-15 Alkyl Benzoate (and) Titanium Dioxide (and) Polyhydroxystearic Acid (and) Aluminum Stearate (and) Alumina, and TIOVEIL 50 MOTG (Uniqema) comprises Titanium Dioxide (and) Caprylic/Capric Triglyceride (and) Mineral Oil (and) Polyhydroxystearic Acid (and) Aluminum Stearate (and) Alumina.

The resulting formulation precursors show low viscosity upon formulation and are readily applied by pump spray. Upon contact with body surfaces a resilient UV protective layer is formed.

Example 29: Chlorhexidine periodontal depots.

Formulations were prepared as in Example 1 by mixing the antiinfective agent chlorhexidine digluconate with a mixture of GDO, PC, and ethanol in the following proportions (by weight)

Table. Chlorhexidine digluconate depot formulation compositions.

Formulation	Chlorhexidine digluconate	PC	GDO	EtOH
A	5	34	51	10
B	5	36	54	5
C	7	33	50	10
D	10	32	48	10
E	15	30	45	10

The chlorhexidine depot preformulations have low viscosity and are easily administered to the periodontal pocket. The compositions provide better distribution and spreading of the active substance throughout the periodontal pocket when compared to current products, such as Periochip®.

The depot formed after application gives protection against re-infection of the pocket. The depot also has excellent bioadhesive properties and sticks to mucosal, teeth and bone surfaces.

Release of chlorhexidine digluconate from 250 mg Formulation A (see above) in 0.9% aqueous NaCl (500 ml) was studied. The formulation was held in a cylindrical metal cup which was placed in a teflon holder at the bottom of a standard USP release bath. The contact area between the formulation and surrounding saline solution was 2.4 cm^2, and the solution was stirred by paddle at 100 rpm.

The release curve shown in Figure 3 demonstrates the sustained and essentially uniform release of chlorhexidine from the formulation over a period of 24 hours.

Example 30, topical formulation with a NSAID

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). It belongs to the phenylacetic acid group and is used in inflammatory conditions of various etiologies, degenerative joint disease and many other painful conditions.
A formulation for topical administration containing diclofenac sodium was prepared by first preparing a placebo formulation.

Composition of placebo formulation

Excipient	Abbreviation	Concentration (%)
Phosphatidyl choline (from soy bean)	SPC	45.0
Glycerol dioleate	GDO	45.0
Etanol 99,5 %	EtOH	10.0

Diclofenac sodium to a concentration of 5% was dissolved in the placebo formulation. The resulting oily liquid was slightly yellowish, transparent, and had a low viscosity.

Example 31, formation of liquid crystalline phase

One drop of the diclofenac sodium containing formulation in Example 30 was added to 3 ml aqueous saline solution with a pipette. A cohesive liquid crystalline phase formed.

Example 32, formation of rigid film *in situ*

One drop of the diclofenac sodium containing formulation in example 30 was applied to the skin on the arm of a healthy volunteer and smeared out to a thin film covering an area of about 2-4 cm^2. Shortly after application the liquid formulation

transformed to a much more rigid film by uptake of small amounts of water from the skin and/or the air.

Example 33, improving spray pattern by lowering viscosity
A placebo formulation with the composition as given in the Table in Example 30 was filled in a standard pump-spray bottle. After priming the pump with formulation the formulation could be applied to the skin with a sub-optimal spray-pattern. By diluting the formulation further with EtOH the viscosity of the formulation decreased and at an EtOH concentration corresponding to about 25% the formulation could be applied as a mist to the skin. Spaying the formulation to the skin on the arm of a healthy volunteer resulted in formation of a rigid film after evaporation of EtOH and uptake of small amounts of water from the skin and/or the air.

Example 34, improving spray pattern by using a compression pump device
A placebo formulation with the composition as given in the Table in Example 30 was filled in a standard compression pump bottle. This device gave a good mist/aerosol and spray pattern. Spaying the formulation to the skin on the arm of a healthy volunteer resulted in formation of a rigid film after uptake of small amounts of water from the skin and/or the air.

Example 35, use of pressure driven device
A placebo formulation with the composition as given in the Table in Example 30 was filled in a pressure driven spray-device either with a hydrocarbon propellant or with HFC-134a as propellant, respectively. Both propellants were found to form low-viscous homogeneous mixtures with the formulation. Spaying the formulation to the skin on the arm of a healthy volunteer resulted in rapid formation of a rigid film after uptake of small amounts of water from the skin and/or the air.

Example 36, spraying formulation with very low concentration of EtOH
A formulation with the composition as given in the table below was prepared by evaporating EtOH from the placebo formulation with the composition as given in the Table in Example 30 with the aid of a rotary evaporator (vacuum, 40°C). The resulting formulation had a high viscosity but when mixed with propellant (hydrocarbon propellant or HFC-134a) and filled in a spray bottle the formulation could be sprayed to the skin on the arm of a healthy volunteer where a rigid film formed after uptake of small amounts of water from the skin and/or the air.

Composition of placebo formulation

Excipient	Abbreviation	Concentration (%)
Phosphatidyl choline (from soy bean)	SPC	49.0
Glycerol dioleate	GDO	49.0
Etanol 99,5 %	EtOH	2.0

Example 37, targeting to different surfaces by varying the composition of the formulation

By varying the PC/GDO ratio in the formulation duration of the formulation at different places in the oral cavity could be adjusted. A formulation with the composition PC/GDO/EtOH (36/54/10) has a preference for adherance to hard surfaces, such as teeth, while a formulation with the composition PC/GDO/EtOH (27/63/10) was found to be better suited for the upper palate.

Example 38, formation of a liquid crystalline phase from precursors with various solvent mixtures

To improve solubility of active substance in the precursors it may be useful to change solvent in the formulation. A number of different solvent mixtures were used in the formulation precursors (see Table) and their ability to form a liquid crystalline phase after contacting them with excess aqueous solution was investigated. One drop of each formulation was added to 3 ml aqueous saline solution with a pipette. Independent of the solvent (mixture) used a cohesive liquid crystalline phase formed.

Composition of formulations

Excipients	Composition (wt%)
PC/GDO/EtOH	45/45/10
PC/GDO/EtOH/NMP	45/45/5/5
PC/GDO/EtOH/propylene-carbonate	45/45/5/5
PC/GDO/EtOH/dimethyl-isosorbide	45/45/5/5
PC/GDO/EtOH/dimethyl- acetamide	45/45/5/5
PC/GDO/EtOH/ethyl-acetate	45/45/5/5

Example 39 - topical formulation with testosterone enanthate

A topical formulation containing 2% testosterone enanthate was prepared by mixing the components in the Table below. Shortly after applying the liquid formulation to the skin it transformed to a much more rigid film by uptake of small amounts of water from the skin and/or the air.

Composition of topical formulation with testosterone enanthate

Component	Amount (g)	Composition (wt%)
Testosterone enanthate	0.060	2.00
Soy Phosphatidyl Choline	1.323	44.10
Glycerol Dioleate	1.323	44.10
Ethanol	0.294	9.80

Legends to Figures:

Figure 1. Cumulative release of MB from a depot forming a reversed hexagonal H_{II} phase.

Figure 2. Decrease in viscosity of the depot precursor on addition of solvents. PC/GDO (6/4) is a precursor to a reversed hexagonal H_{II} phase and PC/GDO (3/7) is a precursor to a reversed cubic I2 phase.

Figure 3: Release of Chlorhexidine from formulation A, see Example 33.

Claims:

1) a pre-formulation comprising a low viscosity mixture of:
a) at least one neutral diacyl lipid and/or a tocopherol;
b) at least one phospholipid;
c) at least one biocompatible, (preferably oxygen containing) organic solvent;
optionally including at least one bioactive agent is dissolved or dispersed in the low viscosity mixture, wherein the pre-formulation forms, or is capable of forming, at least one liquid crystalline phase structure upon contact with an aqueous fluid and/or body surface.

2) A pre-formulation as claimed in claim 1 wherein said liquid crystalline phase structure is bioadhesive.

3) A pre-formulation as claimed in claim 1 or claim 2 wherein component a) consists essentially of diacyl glycerols, especially glycerol dioleate.

4) A pre-formulation as claimed in any of claims 1 to 3 wherein component b) is phosphatidylcholine.

5) A preformulation as claimed in any of claims 1 to 4 having a viscosity of 0.1 to 5000 mPas.

6) A preformulation as claimed in any of claims 1 to 5 having a molecular solution, L_2 and/or L_3 phase structure.

7) A preformulation as claimed in any of claims 1 to 6 having 35 to 60% by weight a), 20 to 50% by weight b) and 10 to 20% by weight c).

8) A preformulation as claimed in any of claims 1 to 10 wherein component c) is an alcohol.

9) A preformulation as claimed in any of claims 1 to 8 additionally comprising up to 10% by weight of a)+b) of a charged amphiphile.

10) A preformulation as claimed in any of claims 1 to 9 wherein said active agent is selected from corticosteroids nonsteroidal anti-inflammatory compounds, local inhibitors of inflammatory pathways phospholipase inhibitors, antioxidants, antiinfectives, cytokines and cytokine inducers/supressors.

11) A preformulation as claimed in any of claims 1 to 10 which is administrable by rinsing, spraying, gargling, as a patch, by suppository or by enema.

12) A preformulation as claimed in claim 11 comprising bezydamine

13) A topical formulation as claimed in any of claims 1 to 11 for intraoral administration which forms a bioadhesive, controlled release product, wherein said active agent comprises at least one selected from; benzydamine, tramadol, Acetaminophen, Ibuprofen, Propoxyphene, Codeine, Dihydrocodein, Hydrocodone, Oxycodone, Nalbuphine, Meperidine, Leverorphanol, Hydromorphone, Oxymorphone, Alfentanil, Fentanyl and Sefentanil.

14) A topical preformulation as claimed in any of claims 1 to 11 suitable for intraoral administration for treatment of periodontal and topical infections, wherein the active agent is chlorhexidine gluconate, and where the preformulation is applied as a liquid product which forms a surface gel *in situ* between 1 second. and 5 min after application.

15) A topical formulation as claimed in any of claims 1 to 11 suitable for ocular administration, wherein said active agent comprises at least one selected from diclofenac, pilocarpine, levocabastine hydrochloride, ketotifen fumarate, timolol, betaxolol, carteolol, levobunolol, dorzolamide, brinzolamide, epinephrine, dipivefrin, clonidine, apraclonidine, brimonidine, pilocarpine, atanoprost, travoprost, bimatoprost, unoprostone, pilocarpine hydrochloride, dexamethasone, chloramphenicol, and indomethacin.

16) A topical formulation as claimed in any of claims 1 to 11 for dermatological administration which forms a bioadhesive, controlled release product, wherein the active agent is selected from cosmetic agents, fragrances, flavourings, essential oils UV absorbing agents and mixtures thereof.

17) A method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising administering a pre-formulation comprising a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and at least one bioactive agent is dissolved or dispersed in the low viscosity mixture, whereby to form at least one liquid crystalline phase structure upon contact with an aqueous fluid *in vivo* following administration.

18) A method as claimed in claim 17 wherein said preformulation is a preformulation as claimed in any of claims 1 to 16.

19) The use of a non-liquid crystalline, low viscosity mixture of:

a) at least one neutral diacyl lipid and/or at least one tocopherol;

b) at least one phospholipid;

c) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained local administration of said active agent, wherein said pre-formulation is capable of forming at least one liquid crystalline phase structure upon contact with an aqueous fluid.

20) The use as claimed in claim 19 wherein said preformulation is a preformulation as claimed in any of claims 1 to 16.

21) A method of treatment or prophylaxis of a human or non-human animal subject comprising administration of a preformulation as claimed in any of claims 1 to 16.

22) A method for the treatment of a human or animal subject comprising administration of a preformulation as claimed in any of claims 1 to 16.

23) A method as claimed in claim 22 for the treatment of inflammation and/or irritation at a body surface and/or in a body cavity.

24) The method as claimed in claim 23 wherein said inflammation is caused by Crohn's disease, ulcerative collitus or oral mucositis.

25) Use of a composition as claimed in any of claims 1 to 16 in the manufacture of a medicament for the treatment of inflammation and/or irritation at a body surface and/or in a body cavity.

26) Method for the treatment of oral mucositis in a human or animal subject comprising administration of a preformulation as claimed in claim 1, said composition comprising 40 to 60 wt% GDO, 20 to 35% PC, 5 to 25% ethanol, and 1 to 8% bezydamine, or a derivative thereof.

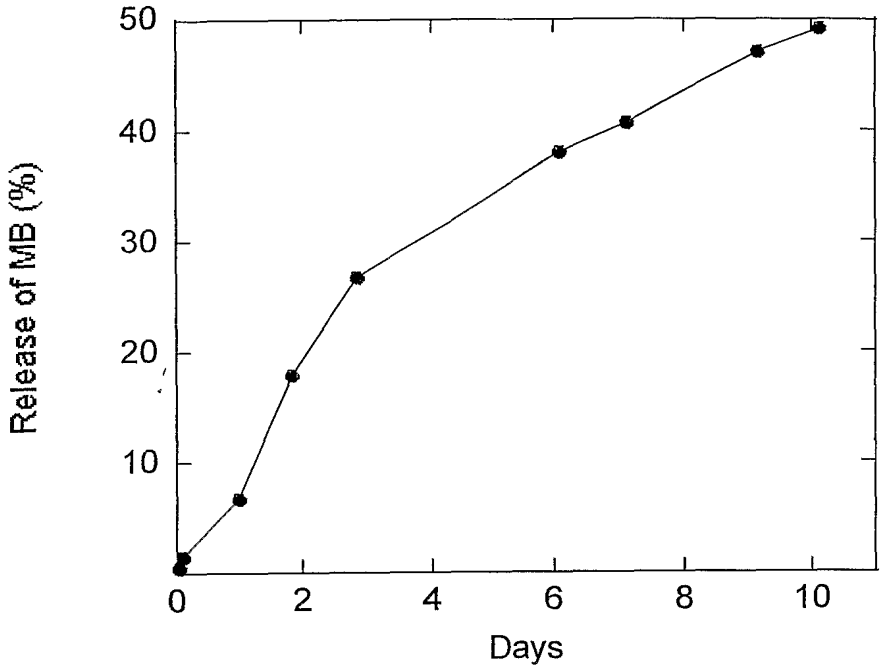


Figure 1. of MB from a depot forming a reversed hexagonal H_{II} phase.

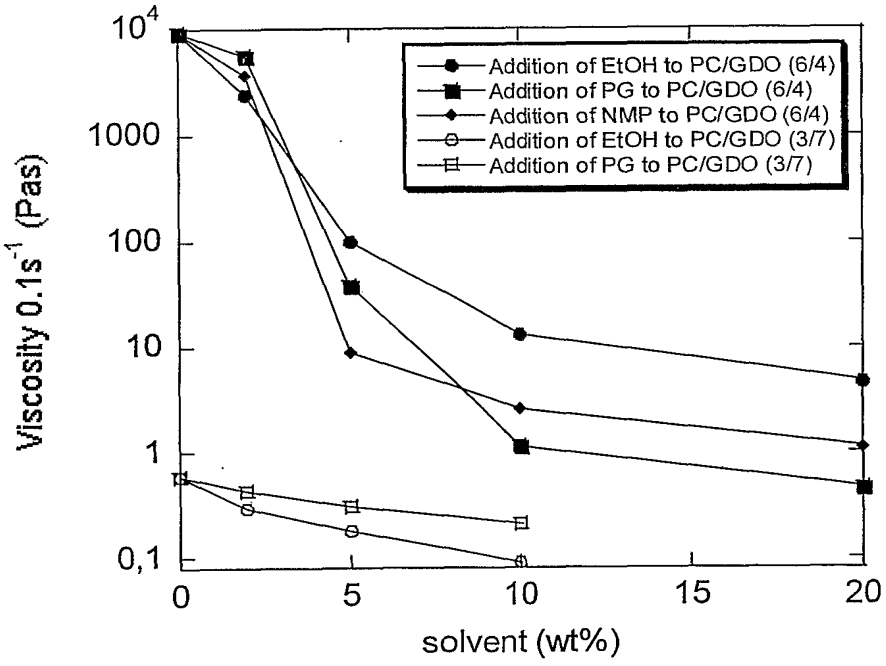


Figure 2.

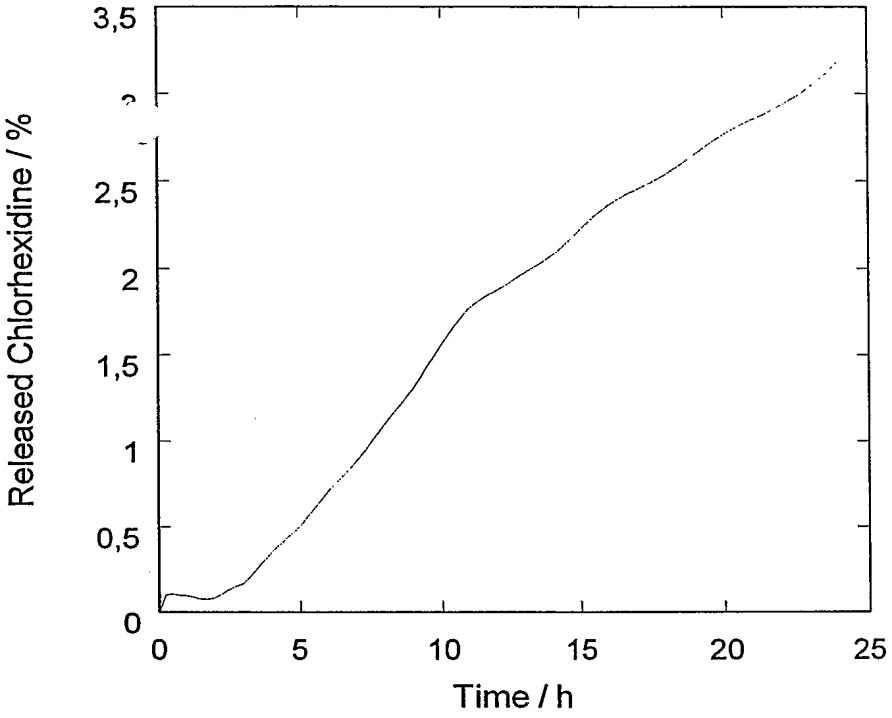


Figure 3

INTERNATIONAL SEARCH REPORT

Inter nal application No
PCT/GB2005/004746

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/10 A61K9/06 A61K9/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/046642 A (CAMURUS AB; JOABSSON, FREDRIK; TIBERG, FREDRIK; GODDARD, CHRISTOPHER) 26 May 2005 (2005-05-26) page 13, last paragraph page 27, paragraph 3 - page 28, paragraph 3 examples 5,6 page 20	1-26
X	US 5 807 573 A (LJUSBERG-WAHREN ET AL) 15 September 1998 (1998-09-15) column 2, line 60 - line 64 column 4, line 4 - line 62 examples 1,3	1-26

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2006	16/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Giménez Miralles, J

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Inter ıal application No
PCT/GB2005/004746

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/068562 A (THE PROCTER & GAMBLE COMPANY) 6 September 2002 (2002-09-06) page 10, last paragraph page 14	1-26
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Y	WO 98/47487 A (DUMEX-ALPHARMA A/S; NIELSEN, LISE, SYLVEST) 29 October 1998 (1998-10-29) the whole document	1-26
Y	US 6 464 987 B1 (FANARA DOMENICO ET AL) 15 October 2002 (2002-10-15) column 4, line 52 - line 65 claim 10 column 3	1-26
A	SHAH JAYMIN C ET AL: "Cubic phase gels as drug delivery systems" ADVANCED DRUG DELIVERY REVIEWS, AMSTERDAM, NL, vol. 47, no. 2-3, 25 April 2001 (2001-04-25), pages 229-250, XP002320651 ISSN: 0169-409X the whole document	1-26

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004746

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17,18,21-24,26
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17, 18, 21-24 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ıal application No
PCT/GB2005/004746

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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Information on patent family members

Inter nal application No
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WO 2007/043057 A2

(54) Title: COMPOSITIONS FOR NASAL DELIVERY

(57) Abstract: Use of phospholipids, one or more C2-C4 alcohols and water in the preparation of a vesicular composition adapted for intranasal administration of an active agent, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

Compositions for Nasal Delivery

Nasal drug delivery is a popular way to treat local/respiratory ailments which has traditionally been restricted to administer drugs for sinus conditions, such as congestion and allergies. Recently, however, there has been increased interest in the nose as an alternative to oral and parenteral delivery for many systemic drugs and vaccines. The vastly vascularised and immunogenic nasal mucosa present potential benefits for systemic absorption in terms of quick action, avoidance of any degradation and/or unwanted entero-hepatic metabolism of the drug (improved bio-availability) and patient compliance as well as improved immune response for vaccines. The nasal route could also provide an attractive needle-free alternative for currently injectable drugs which may improve patient compliance and allow extended use of self-medication for many chronic diseases/acute conditions or vaccinations. Some systemically-acting drugs for the treatment of osteporosis, cardiovascular medications and painkillers are already on the market in nasal formulations.

However, although this route is beginning to be explored for systemic delivery of drugs the major limitation in nasal delivery is the insufficient permeation of drugs across the nasal mucosa. Furthermore, the anatomical and physiological features of the nose are not ideal for drug administration, since a relatively small surface area (150 cm^2) puts considerable constraints on formulations and drug candidates. Only very potent molecules can be used in this route. For example, for peptides there is the inverse relationship between bioavailability and molecular weight of the peptide which points toward, that

those peptides with more than 30-40 amino acids require penetration enhancers for attaining a sufficient bioavailability (in the range of 10%). There are two main pathways for absorption of the molecule from the nasal cavity: paracellular (driven by passive diffusion) or transcellular (driven by carrier or receptor mediated active transport). In the absence of active transport components, most peptides cross the nasal epithelium by the paracellular route, driven by passive diffusion. Due to hydrophilicity of peptides the transcellular route is mainly relevant for transport processes or for transcytosis. Both transcellular routes are energy dependent and are therefore designated as active transport processes.

The issue of improving nasal absorption is important. Several strategies have been investigated in the past decade such as chelators of calcium (EDTA), inhibition of nasal enzymes (boro-leucin, aprotinin), inhibition of muco-ciliar clearance (preservatives), solubilisation of nasal membrane (cyclodextrin, fatty acids, surfactants) and formation of micelles (surfactants). Many surfactants such as bile acids, Laureth 9 and taurodehydrofusidate (STDHF) turned out to be quite effective in enhancing nasal absorption, but caused local cytotoxic effects on ciliated cells. Therefore, enhancers with an acceptable safety profile under chronic treatment are still to be discovered. A greater permeability of drug through nasal mucosa has the potential to overcome the limitations of oral route and to approach the benefits of intravenous infusion. Safe and efficacious enhancers will be necessary for commercially successful products.

The delivery of biologically active materials to the skin and cell membranes by means of an aqueous vehicle that comprises the combination of lipid vesicles and water miscible organic solvents has been described in the art.

For example, an aqueous carrier system containing phospholipids and ethanol was described in EP 158441, with the weight ratio between the aforementioned components being from 40:1 to 1:20.

US 5,711,965 describes a solution comprising phospholipids, ethanol and water in a weight ratio of 10:16:74, respectively.

US 5,540,934, US 5,716,638 and WO 03/000174 describe an aqueous composition containing vesicles (ethosomes) in the presence of ethanol.

US 6,627,211 describes a carrier suitable for the administration of an anti-convulsive agent to the nasal mucous membranes. It appears that the content of organic solvents in said carrier is relatively high (30% to 60% ethanol and 30 to 60% propylene glycol).

It has now been found that an aqueous composition which contains phospholipids in a concentration of 0.2 to 10% by weight, in combination with one or more short chain alcohols, wherein the weight concentration of water is not less than 30% by weight and the weight concentration of said alcohol(s) is in the range between 12 to 30% by weight, may be adapted for use as an intranasal drug delivery vehicle.

Accordingly, in a first aspect, the present invention provides the use of phospholipid, one or more C2-C4 alcohols and water in the preparation of a vesicular composition adapted for intranasal administration of an active agent, wherein the concentrations of said phospholipid and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, and the water content of said composition is not less than 30% by weight.

Preferably, the water content in the composition is not less than 35%, and more preferably not less than 45%. The weight ratio between the alcohol(s) and the phospholipids is not less than 2:1, and more preferably not less than 5:1.

Phospholipids suitable for use in the preparation of the composition according to the present invention include phosphatidylcholine (PC), hydrogenated phosphatidylcholine, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG) and phosphatidylinositol (PL). The chemical structure of phospholipids that may be used according to the present invention is described in US 4,614,730, which is incorporated herein by reference. Preferably, the phospholipids are present in the composition of the invention at a concentration of 0.5 to 5% by weight.

The term C2-C4 alcohols, as used herein, refers to alkanols containing two, three or four carbon atoms. The alcohols to be used according to the present invention

specifically include ethanol, 1-propanol, isopropyl alcohol and *tert*-butyl alcohol, with the former being especially preferred. The concentration of ethanol in the composition contemplated by the present invention for use as an intranasal drug delivery vehicle is preferably in the range of 15 to 27% by weight.

According to a particularly preferred embodiment of the invention, the composition further comprises one or more water miscible polyols, and especially glycols (1,2-diols, such as ethylene glycol and propylene glycol, with the latter being especially preferred), at a concentration of 1 to 30% by weight, and preferably 5 to 20 by weight.

The compositions of the present invention may be prepared by mixing together the various components, namely, water, phospholipids, one or more C2-C4 alcohols (and possibly also one or more polyols) and the active ingredient under conditions that allow the formation of vesicles. More specifically, the compositions of the present invention may be conveniently prepared by dissolving the phospholipids in the alcohol (or in the alcohol/glycol mixture), followed by the addition of the active ingredient, either in the form of an aqueous solution thereof or in a solid form, with a subsequent addition of water. The preparation of the composition is preferably carried out under stirring, typically at room temperature or at an elevated temperature, which is preferably not higher than 50°C.

Alternatively, a dispersion of the phospholipids and the active ingredient in water is prepared, into which the

alcohol, optionally together with polyol (e.g., a mixture of ethanol and propylene glycol) are added with stirring, possibly under heating.

It is also possible to first prepare freeze-dried lipid vesicles having the active ingredient encapsulated therein, and subsequently dispersing the same in a mixture of water, the C2-C4 alcohol and optionally polyol.

As mentioned above, the combination of phospholipids, water, and the water-miscible organic solvents (namely, the alcohol and the polyol) according to the concentrations and weight ratios specified above allows the formation of a non-irritant, vesicular composition, with the vesicles present therein, whose size ranging between 50 nm to few microns, and more specifically, up to 5μm, exhibiting good properties for enhanced nasal absorption. Figure 1 is TE (transmission electron) micrograph of a specific composition according to the present invention (containing insulin as the active agent; the exact composition is given in the Examples below - entry F in table 1A). It may be seen that in this specific system, the vesicular structures are multilamellar. The vesicles were visualized by transmission electron microscopy (TEM) and scanning electron microscopy. TEM analysis was carried out using a Philips TEM CM 12 electron microscope (TEM, Eindhoven, The Netherlands) with an accelerating voltage of 100kV.

Thus, the present invention concerns methods for intranasal administration, and compositions for intranasal administration comprising vesicular systems

formed from at least one active molecule, phospholipid, alcohol (C2-C4) and water. Optionally, the composition further comprises glycol (propylene glycol, transcutol, tetraglycol, etc).

We have found that pharmaceutical formulations including the above ingredients could deliver therapeutic amounts of agents to the systemic circulation or the brain of mammals and have efficient therapeutic or prophylaxis effect. The invention can be used for pharmaceutical, cosmetic, medical, veterinary, diagnostic and research applications. The present invention includes nasally administering to the mammal a therapeutically effective amount of active ingredient by means of compositions described above. The nasal delivery may be either for local purposes (to the mucosa of the nose), for systemic administration through the circulation or for CNS administration for curing brain disease.

It should be noted that the composition according to the present invention may include additional excipients that are well known in the art, such as surfactants, preservatives, thickening agents, co-solvents, adhesives, antioxidants, buffers, viscosity and absorption enhancing agents and agents capable of adjusting the pH and osmolarity of the formulation.

Suitable surfactants that can be used in accordance with the present invention include ionic, nonionic or amphoteric surface active agents. More specifically, hydrophilic surfactants (e.g. Tweens, Tween 80, Myrj, Brjs, Labrasol etc.) or lipophilic surfactants (eg. Span 20, Span 60, Myrj, Arlacel 83 and such) may be suitably

used, preferably at a concentration in the range of 0-25% by weight.

Suitable preservatives that can be used with the present formulations include, for example, benzyl alcohol, parabens, chlorobutanol, benzalkonium salts and combinations thereof. Some examples of antioxidants include tocopherols, butyl hydroxytoluene, sodium metabisulfite, potassium metabisulfite, ascorbyl palmitate and the like. These preservatives and antioxidants may be present in the formulations in a concentration of from about 0.001% up to about 5%w/w.

Regarding buffers, the nasal delivery system may include a buffer for maintaining the formulation at a pH of about 7.0. The particular buffer, of course, can vary depending upon the particular nasal delivery system used, as well as the specific active molecule selected. Buffers that are suitable for use in the present invention include, for example, acetate, citrate, prolamine, carbonate and phosphate buffers and combinations thereof. The pharmaceutical formulations of the present invention may include a pH adjusting agent.

Regarding thickening agents, the viscosity of the formulations of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be added to the compositions of the present invention include for example, methyl cellulose, xanthan gum, tragacanth, adhesives, guar gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans, mucoadhesive polymer-

systems like poly(acrylates), cellulose derivatives, hyaluronic acid, hyaluronic acid derivatives, chitin, collagen, pectin, starch, poly(ethylene glycol), sulfated polysaccharides, carrageenan, Na-alginate, gelatine, pectin and combinations thereof. The desired concentration of the thickening agent will depend upon the agent selected and the viscosity desired.

The compositions may also comprise gel forming or bioadhesive compounds such as carbopols, alginates, scleroglucan, cellulose derivatives, starch, albumin, pluronic gels, diethyl aminoethyl (DEAE)-sephadex, polycarbophil, hyaluronic acid, hyaluronates, starch, gelatin, cholagen and others. Compositions can also be incorporated in the w/o cream, o/w cream, hydrophilic ointment or lipophilic ointment, gels, other semi-solid bases. The compositions could be delivered to the nasal cavity as drops, mists, aerosols, instillations, by use of pipetor, special devices, evaporators, vaporizators and such.

The formulations of the present invention may also include agents such as tolerance enhancers to reduce or prevent drying of the mucus membrane and to prevent irritation thereof.

The compositions according to the present invention may be applied to the nasal cavity as liquids, sprays, aerosols, nebulizaers or semi-solid preparations. Semisolid preparations may be on the base of gels, w/o or o/w creams or hydrophilic/lipophilic ointments. The compositions may contain molecularly dispersed (soluble, solubilized, etc.) active agent or the fine particles/crystals of the active agent. The compositions

could be administered from nasal sprays, metered-dose sprays, squeeze bottles, liquid droppers, disposable one-dose droppers, nebulizers, cartridge systems with unit-dose ampoules, single-dose pumps, bi-dose pumps, multiple-dose pumps or any other device. For example, the compositions of the invention may be stored in/delivered from a spray or aerosol device/container as described in details in Remington's Pharmaceutical Sciences (16th edition, Chapters 83 and 92).

Regarding spray devices, it should be noted that both single (unit) dose or multiple dose systems may be used. Typically, a spray device comprises a bottle and a pump; such devices are commercially available from various sources. Typically, the volume of liquid that is dispensed in a single spray actuation is in the range of from 5 to 250 microlitters/each nostril/single administration and the concentration of the active ingredient in the formulation may be readily adjusted such that one or more spray into the nostrils will comply with the dosage regimen.

The present invention also provides a spray device or a dose cartridge for use in a nasal delivery device loaded with a composition as described above.

In another aspect, the invention provides a method of administering an active pharmaceutical ingredient to a patient in need thereof, which method comprises the intranasal administration of a vesicular composition comprising a therapeutically effective amount of said ingredient, phospholipids, one or more C2-C4 alcohols and water, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in

the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 20%, and preferably not less than 30% by weight.

Mammals include humans, pet animals, laboratory animals, farm animals and wild animals.

The intranasal drug delivery vehicle according to the present invention may be adapted for the administration of active agents that can be used for medical, pharmaceutical, veterinary, research or diagnostic purposes. However, especially preferred active agents to be used according to the present invention include an anti-diabetic agent (e.g., insulin or derivative thereof), an anti-malaria agent (which is most preferably dihydroartemisinin); an anti-anxiety agent and an anticonvulsant (which is most preferably diazepam) and anti-emetic agent (which is most preferably granisetron hydrochloride); an anti-anxiety/anti-depressant (which is most preferably buspirone hydrochloride); an anti-multiple sclerosis agent (which is most preferably glatiramer acetate); an anti-depressant/ an anti-hot flashes agent (which is most preferably paroxetine or a pharmaceutically acid addition salt thereof); an anti-dementia/Alzheimer's agent (which is most preferably rivastigmine); and an anti-obesity agent (which is most preferably sibutramine).

More specifically, it has now been found that the intranasal drug delivery vehicle according to the present invention may be used for the intranasal administration of insulin. The term insulin or derivative thereof, as used herein, encompasses rapid acting (e.g. insulin

aspart, insulin glulisine, insulin lispro), short-acting (regular), intermediate-acting (NPH), intermediate and short acting mixtures and long-acting insulin (e.g. insulin glargine, insuline detemir) (according to FDA classification as appears in www.fda.gov/fdac/features/2002/chrt_insulin.html). Insulin is typically administered at daily dose of 1.5 to 150IU.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of insulin or a derivative thereof together with water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for treating diabetes in a mammal, which method comprises the intranasal administration of the aforementioned insulin-containing composition.

It has now been also found that the intranasal drug delivery vehicle according to the present invention may be used for the intranasal administration of diazepam. Diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzo-diazepin-2-one. A method for the synthesis of

diazepam has been described, for example by Sternbach LH, Reeder E, Keller O, & Metlesics W. [Quinazolines and 1,4-benzodiazepines III substituted 2-amino-5-phenyl-3H-1,4-benzodiazepine 4-oxides. J Org Chem, 26: 4488-4497, 1961]. Diazepam is typically administered at a daily dose of 0.2 to 100 mg.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition, which comprises a therapeutically effective amount of diazepam together with water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for preventing and/or treating epileptic seizures in a mammal, which method comprises the intranasal administration of the aforementioned diazepam-containing composition.

It has now been also found that it is possible to prepare a pharmaceutical composition of Granisetron [an anti-emetic agent, which is chemically named: endo-1-methyl-N-(9-methyl-9-azabicycle[3.3.1]non-3-yl)-1H-indazole-3-carboxamide] that is suitable for the intranasal administration of said drug. Granisetron is described in EP 200444; methods for preparing granisetron are also

described in WO03/080606. Granisetron is typically administered at a daily dose of 0.1 to 10 mg.

Accordingly, in another aspect, the present invention provides a pharmaceutical composition, which comprises a therapeutically effective amount of granisetron or a pharmaceutically acceptable salt thereof together with water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for treating and/or preventing emesis in a mammal, which method comprises the intranasal administration of the aforementioned granisetron-containing composition.

Other compositions for intranasal administration contemplated by the present invention comprise:
(i) a therapeutically effective amount of an a pharmaceutically active ingredient selected from the group consisting of buspirone, glatiramer, paroxetine, rivastigmine and sibutramine and a pharmaceutically acceptable salt thereof, together with:
(ii) water;
(iii) phospholipids; and
(iv) one or more C2-C4 alcohols;
wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and

12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight. Preferably, the composition further comprises a polyol, and more specifically, propylene glycol, at a concentration in the range of 1 to 30% by weight.

In another aspect, the present invention provides a method for preventing and/or treating obesity in a mammal, which method comprises the intranasal administration of the aforementioned sibutramine-containing composition. Sibutramine is typically administered at a daily dose of 1 to 30 mg. Its preparation is described by Jeffery et al., [Synthesis of Sibutramine, A Novel Cyclobutylalkylamine Useful in the Treatment of Obesity and its Major Human Metabolites, J. Chem. Soc. Perkin. Trans. 1, 2583-2589 (1996)] and also in US Patent Nos. 4,746,680; 4,929,629; and 5,436,272.

In another aspect, the present invention provides a method for preventing and/or treating dementia, and specifically, Alzheimer disease in a mammal, which method comprises the intranasal administration of the aforementioned rivastigmine-containing composition. Rivastigmine may be administered as its hydrogen tartrate salt at a daily dose of 1 to 20 mg.

In another aspect, the present invention provides a method for treating multiple sclerosis in a mammal, which method comprises the intranasal administration of the aforementioned glatiramer-containing composition. Glatiramer is typically administered at a daily dose of 1 to 60 mg. Glatiramer acetate is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine

in a molar ratio of approximately 4.6:1.5:3.6:1.0, respectively, which is synthesized by chemically polymerizing the four amino acids, forming products with average molecular weights ranging from about 4000 to about 13,000 daltons. The corresponding molar fractions are approximately 0.427 for alanine, 0.141 for glutamic acid, 0.337 for lysine and 0.093 for tyrosine, and may vary by about +/-10%.

In another aspect, the present invention provides a method for treating depression and/or hot flushes in a mammal, which method comprises the intranasal administration of the aforementioned paroxetine-containing composition. Paroxetine is typically administered at a daily dose of 5 to 100 mg. Its preparation is described, for example, in US 6,956,121 and US 6,686,473.

An especially important aspect of the present invention is related to the treatment of malaria. In malaria prevalent regions of the world, Plasmodium infections is the reason for a very high mortality rates (hundreds of thousands of deaths), especially among children. Many patients with acute malaria are unable to tolerate oral therapy and parenteral treatment, which could only be available at hospitals, is necessary. However, these amenities are usually inaccessible.

It has now been found that anti-malaria drug administered intranasally is effective at least as or even more that i.p. administration. This finding paves the way to the formulation of a pharmaceutical composition for intra-nasal administration comprising a carrier and at least one anti-malaria agent.

Examples of anti-malaria drugs are artemisinin derivatives, dihydroartemisinin, artemotil, chloroquine, primaquine, doxycillin, quinine, aminoquinolines, cinchona alkaloids, antifolates, quinidine, melfoquine, halofantrine, lumefantrine, amodiaquine, pyronaridine, tafenoquine, artesunates, artemether, artemotil, biguanides, proguanil, chloproguanil, diaminopyrimidines, pyremethamine, trimethoprim, dapsone, sulfonamides, atovaquone, sulfadoxine-pyrimethamine, N-acetyl cysteine, piperaquine, DHA-piperaquine, lumefantrine, dermaseptins, bisphosphonates, quercitin etc.

The present invention is thus also concerned with a pharmaceutical composition for intra-nasal administration comprising a carrier and at least one anti-malaria drug, wherein said carrier is most preferably a vesicular carrier (namely, a carrier that contain vesicles suspended therein), and also with the use of an anti-malaria agent in the preparation of a medicament for intra-nasally treating malaria.

The intranasal composition may comprise any carrier or combination of carriers known to be suitable for intranasal administration. Preferably, however, the composition in accordance with this aspect of the invention comprises at least one anti malaria agent in combination with the intranasal drug delivery vehicle as described above, which vehicle comprises not less than 30% by weight water, from 12 to 30% by weight C2-C4 alcohol(s), from 1 to 30% by weight water-miscible polyol(s), from 0.2 to 10% phospholipids arranged in a vesicular structure. Other preferred features of the

anti-malaria composition are as described above in connection with said intranasal drug delivery vehicle.

By another aspect the present invention provides a method for treating malaria (including cerebral malaria) comprising: administering intra-nasally to a subject in need of such treatment a therapeutically effective amount of at least one anti-malaria drug. Preferably, the anti-malaria drug is dihydroartemisinin, which is typically administered at the following dosage regimen:
Adults: 40-120mg/day in divided doses for 6-7 days;
Children: 2-4 mg/kg in a divided loading dose on the first day followed by 1-2 mg/kg daily for 6 days.
Dihydroartemisinin can be prepared by reduction of artemisinin with sodium borohydride; [A. Brossi et al., Arteether, a New Antimalarial Drug: Synthesis and Antimalarial Properties, J. Med. Chem. 31, 645-650 (1988)].

As used herein, nasally administering or nasal administration includes administering the compositions into naristilles of the nose to the mucous membranes of the nasal passage or nasal cavity of the mammal. Such formulations can be administered, for example, as a nasal spray, nasal inhaler, nasal drop, aerosol, propellants, pressured dispersion, aqueous aerosol, nebulizer, nasal suspension, instillation, nasal gel, nasal ointment and nasal cream by aid of any new or old type device. Administration of compositions of the present invention may also take place using a nasal tampon or nasal sponge containing the compositions.

Active ingredient can also be brought into a viscous base by adding to the above delivery systems conventionally used ingredients such as natural gums, cellulose and derivatives, acrylic polymers (eg.carbopol) and vinyl polymers (polyvinylpyrrolidone), scleroglucans, xylan, alginates, calcium alginate, hyaluronates, collagenates, starch gells, gelatine systems, kitosan carriers.

It should be understood that the intranasal drug delivery vehicle according to the present invention is not limited for the administration of the specific active ingredients mentioned above. It should be noted that the active agent can be a chemically defined synthetic molecule, a naturally derived or synthetic peptide, a protein, a polysaccharide, or a nucleic acid such as RNA or DNA. The active agent may also be referred to as active compound, drug, drug substance, medicinal substance, therapeutic agent, and the like. The active agents that could be delivered by means of the above compositions alone or in combinations are without being limited:

-Antimalarial agents (e.g. artemisinin derivatives, dihydroartemisinin, artemotil, chloroquine, primaquine, doxycillin, quinine, aminoquinolines, cinchona alkaloids, antifolates, quinidine, melfoquine, halofantrine, lumefantrine, amodiaquine, pyronaridine, tafenoquine, artesunates, artemether, artemotil, biguanides, proguanil, chloproguanil, diaminopyrimidines, pyremethamine, trimethoprim, dapsone, sulfonamides, atovaquone, sulfadoxine-pyrimethamine, N-acetyl cysteine, piperaquine, DHA-piperaquine, lumefantrine, dermaseptins, bisphosphonates, quercitin etc. The drugs could be used alone or in combinations.)

-OTC drugs (e.g. antipyretics, anesthetics, cough suppressants, etc.)

-Antiinfective agents

Anti-malaria agents (such as dihydroartemisinin, etc.)

-Antibiotics (e.g. penicillins, cephalosporins, macrolids, tetracyclines, aminoglycosides, anti-tuberculosis agents, doxycycline, ciprofloxacine, moxifloxacine, gatifloxacine, carbapenems, azithromycine, clarithromycine, erythromycine, ketolides, penems, tobramyicin, filgrastim, pentamidine, microcidin, clerocidin; amikacine, etc.)

-Antifungal/Antimycotic (metronidazole, ketoconazole, itraconazole, voriconazole, clotrimazole, bifonazole, fluconazole, amphotericine B, natamycine, nystatine, ciclopiroxolamine, etc.)

-Genetic molecules (e.g. Anti-sense oligonucleotides, nucleic acids, oligonucleotides, DNA, RNA,

-Anti-cancer agents (e.g. anti-proliferative agents, anti-vascularization agents, taxol, etopside, cisplatin, etc.)

-Anti-protozoal agents

-Antivirals (e.g. acyclovir, gancyclovir, ribavirin, anti-HIV agents, anti-hepatitis agents, famciclovir, valaciclovir, didanosine, saquinavir, ritonavir, lamivudine, stavudine, zidovudine, etc.)

-Anti-inflammatory drugs (e.g. NSAIDs, steroidal agents, cannabinoids, leukotriene-antagonists, tacrolimus, sirolimus, everolimus, etc.)

-Anti-allergic molecules (e.g. antihistamines, fexofenadine)

-Bronchodilators

-Vaccines and other immunogenic molecules (e.g. tetanus toxoid, reduced diphtheria toxoid, acellular pertussis

vaccine, mums vaccine, smallpox vaccine, anti-HIV vaccines, hepatitis vaccines, pneumonia vaccines, influenza vaccines, TNF-alpha-antibodies etc.)

-Anesthetics, local anesthetics.

-Antipyretics (e.g. paracetamol, ibuprofen, diclofenac, aspirin, etc.)

-Agents for treatment of severe events such cardiovascular attacks, seizures, hypoglycemia, etc.

-Afrodisiacs from plants or synthetics

-Anti-nausea and anti-vomiting.

-Immunomodulators (immunoglobulins, etc.)

-Cardiovascular drugs (e.g. beta-blockers, alpha-blockers, calcium channel blockers, etc.)

-Peptide and steroid hormones (eg. insulin, insulin derivatives, insulin detemir, insulin monomeric, oxytocin, LHRH, LHRH analogues, adreno-corticotropic hormone, somatropin, leuprolide, calcitonin, parathyroid hormone, estrogens, testosterone, adrenal corticosteroids, megestrol, progesterone, sex hormones, growth hormones, growth factors, etc.)

-Peptide and protein related drugs (e.g. amino acids, peptides, polypeptides, proteins)

-Vitamins (e.g. Vit A, Vitamins from B group, folic acid, Vit C, Vit D, Vit E, Vit K, niacin, derivatives of Vit D, etc.)

- Autonomic Nervous System Drugs

-Fertilizing agents

-Antidepressants (e.g. buspirone, venlafaxine, benzodiazepins, selective serotonin reuptake inhibitors (SSRIs), sertraline, citalopram, tricyclic antidepressants, paroxetine, trazodone, lithium, bupropion, sertraline, fluoxetine, etc.)

-Agents for smoking cessation (e.g. bupropion, nicotine, etc.)

-Agents for treating alcoholism and alcohol withdrawal

-Lipid-lowering agents (eg. inhibitors of 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, simvastatin, atrovastatin, etc.)

-Drugs for CNS or spinal cord (benzodiazepines, lorazepam, hydromorphone, midazolam, Acetaminophen, 4'-hydroxyacetanilide, barbiturates, anesthetics, etc.)

- Anti-epilepsic agents (e.g. valproic acid and its derivatives, carbamazepin, etc.)

-Angiotensin antagonists (e.g. valsartan, etc.)

-Anti-psychotic agents and anti-schizophrenic agents (e.g. quetiapine, risperidone)

-Agents for treatment of Parkinsonian syndrome (e.g. L-dopa and its derivatives, trihexyphenidyl, etc.)

-Anti-Alzheimer drugs (e.g. cholinesterase inhibitors, galantamine, rivastigmine, donepezil, tacrine, memantine, N-methyl D-aspartate (NMDA) antagonists).

-Agents for treatment of non-insulin dependent diabetes (e.g. metformine,

-Agents against erectile dysfunction (e.g. sildenafil, tadalafil, papaverine, vardenafil, PGE1, etc.)

-Prostaglandins

-Agents for bladder dysfunction (e.g. oxybutynin, propantheline bromide, trospium, solifenacin succinate etc.)

-Agents for treatment menopausal syndrome (e.g estrogens, non-estrogen compounds, etc.)

-Agents for treatment hot flashes in postmenopausal women

-Agents for treatment primary or secondary hypogonadism (e.g. testosterone, etc.)

-Cytokines (e.g. TNF, interferons, IFN-alpha, IFN-beta, interleukins etc.)

-CNS stimulants

-Muscle relaxants

-Anti paralytic gas agents

-Appetite stimulators/depressors (e.g. cannabinoids, etc.)

-Gastrointesinal absorption modifiers

-Narcotics and Antagonists (e.g. opiates, oxycodone etc.)

-Painkillers (opiates, endorphins, tramadol, codein, NSAIDs, gabapentine etc.)

-Hypnotics (Zolpidem, benzodiazepins, barbiturates, ramelteon, etc.)

-Histamines and Antihistamines

-Antimigraine Drugs (e.g. imipramine, propranolol, sumatriptan, eg.)

-Diagnostic agents (e.g. Phenolsulfonphthalein, Dye T-1824, Vital Dyes, Potassium Ferrocyanide, Secretin, Pentagastrin, Cerulein, etc.)

- Topical decongestants or anti-inflammatory drugs

-Anti-acne agents (e.g. retinoic acid derivatives, doxicillin, minocyclin, etc.)

-ADHD related medication (e.g. methylphenidate, dexmethylphenidate, dextroamphetamine, d- and l-amphetamin racemic mixture, pemoline, etc.)

-Diuretic agents

-Anti-osteoporotic agents (e.g. bisphosphonates, aledronate, pamidronate, tirphostins, etc.)

-Drugs for treatment of asthma

-Anti-Spasmotic agents (e.g. papaverine, etc.)

-Agents for treatment of multiple sclerosis and other neurodegenerative disorders (eg. mitoxantrone, glatiramer acetate, interferon beta-1a, interferon beta-1b, etc.)

-Plant derived agents from leave, root, flower, seed, stem or branches extracts.

In the drawings

Figure 1 is a TE micrograph of insulin vesicles in a Composition F according to the invention.

Figure 2 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin composition G (aqueous control containing 58IU/ml) versus untreated mice.

Figure 3 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of human insulin compositions C (a composition of the invention containing 58IU/ml insulin) and D (placebo) versus untreated mice.

Figure 4 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin composition F (a composition of the invention containing 20IU/ml insulin) versus untreated mice.

Figure 5 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin compositions N and O (compositions of the invention containing 58IU/ml insulin) versus untreated mice.

Figure 6 is a bar diagram showing the results of Writhing test in mice following administration of diazepam

vesicular composition prior to writhing induction with acetic acid versus untreated control.

Figure 7 is a bar diagram showing the results of Writhing test in mice following administration of diazepam vesicular carrier(drug dose 5mg/kg) simultaneously with writhing induction with acetic acid solution versus untreated control.

Figure 8 is a bar diagram showing the results of Writhing test in mice following intranasal (IN) administration of diazepam phospholipid ethanolic vesicles Composition (5mg/kg) and subcutaneous (SC) injection of diazepam simultaneously with writhing induction with acetic acid solution versus untreated control.

Figure 9 is a graph depicting the changes in the weight of rats following administration of ipecac syrup and inducing Pica syndrome on day 3. Animals intranasally treated with granisetron HCl Composition B (IN-GR, 1.5mg drug/kg rat, n=5) versus untreated control (n=5).

Figure 10 is a graph showing the changes in the food consumption in rats following administration of ipecac syrup and inducing Pica syndrome on day 3. Animals intranasally treated with granisetron HCl Composition B (IN-GR, 1.5mg drug/kg rat, n=5) versus untreated control (n=5).

Figure 11 is a graph showing the changes in the kaolin consumption in rats following administration of ipecac syrup and inducing Pica syndrome on day 3. Animals intranasally treated with granisetron HCl Composition B

(IN-GR, 1.5mg drug/kg rat, n=5) versus untreated control (n=5).

Figure 12 is a CLS (confocal laser scanning) micrograph showing the transport of Rhodamine B across the nasal mucosa from the composition of the invention applied for 0.5h to the rat nostril. White means the highest fluorescent intensity.

Figure 13 is a graph showing Blood glucose levels (% of initial) in mice following intranasal administration of 25µL of insulin compositions in a comparative study. The concentration of human insulin in all Compositions is 63 IU/mL. Composition I is a composition of the invention; Composition II is a control composition having only 10% EtOH; Composition III is a liposomal control composition.

Examples

Materials

Insulin solution used for preparation of the Compositions C-V is Biosynthetic Human Insulin aqueous solution 100IU/mL (Actrapid, Novartis).

Example 1

Insulin-containing composition

20 mg of phospholipids (Phospholipon 90, Natterman were dissolved in 0.3g ethanol (J.T. Baker) and to this solution 0.1g propylene glycol was added. The obtained solution was added slowly to the 0.58 g of the aqueous solution of human insulin (100IU/mL) under constant stirring at room temperature. The composition is stirred for additional 5 min. It is also possible to introduce

the aqueous human insulin solution into the phospholipid solution in ethanol and propylene glycol. The final composition contains 58 IU insulin/ g.

Example 2

Insulin-containing composition

15 mg of phospholipids (Phospholipon 90) were dissolved in a mixture of 225mg ethanol and 75mg propylene glycol. To the obtained solution, 685 mg of aqueous solution of insulin (100IU/mL) were added slowly under constant stirring at 40C temperature. The composition is stirred for additional 5 min. The final composition contains 68.5 IU insulin/g. This composition is also prepared at room temperature.

Example 3

Insulin-containing composition

To freeze-dried liposomes containing 40 mg phospholipid and 116 IU human insulin a mixture of 0.6g EtOH, 0.2g PG and 1.16g DDW was added in aliquots under constant stirring at room temperature. The composition is stirred for additional 5 min. The final composition containes 58IU insulin/ g (1.45 IU insulin/25 microliter).

Example 4

Insulin-containing composition

To a liposomal dispersion containing 30mg phospholipid, 137 IU insulin and 685mg DDW, 225mg EtOH and 75mg

Propylene glycol were added under constant stirring at room temperature. The composition is stirred for additional 5 min. The final composition contains 68.5IU insulin/g.

Example 5

Insulin-containing composition

0.05g Carbopol 974P was dispersed in 1mL of insulin aqueous solution (100IU/mL). In a separate container 0.5 g of Phospholipon 90 and 0.15g cholesterol were dissolved in 1.85g ethanol and to this solution 0.95g propylene glycol were added. To this mixture 0.65g Tween 20 were added. To the obtained system 4.8mL of insulin aqueous solution (100IU/mL) were added slowly under constant stirring at room temperature in Heidolph mixer (650rpm). The composition was stirred for additional 5 min. This phase was slowly added to Carbopol dispersion in insulin aqueous solution under constant mixing at 400rpm. To the obtained system 0.05g triethanolamine (TEA) were added slowly under constant mixing at 400rpm.

Example 6

Insulin-containing composition

0.01g Carbopol 974P was dispersed in 1.18 mL of DDW. In a separate container 0.5 g of phospholipids (Phospholipon 90) and 0.02g ceramide were dissolved in 1.48g ethanol and to this solution 1g propylene glycol were added. To the obtained system 5.8mL of insulin aqueous solution (100IU/mL) were added slowly under constant stirring at room temperature in Heidolph mixer (650rpm). The composition was stirred for additional 5 min. This phase

was slowly added to Carbopol dispersion in DDW under constant mixing at 400rpm. To the obtained system 0.01g triethanolamine (TEA) were added slowly under constant mixing at 400rpm.

Example 7

Dihydroartemisinin-containing compositions

Dihydroartemisinin	23-350mg
Phospholipid	70-250mg
Ethanol	750-1050mg
Propylene glycol	350-1000mg
Water to	3.5g

Preparation: Phospholipid was dissolved in ethanol and to this solution propylene glycol was added. To the obtained solution DHA was added and the mixture was left at room temperature for 3-4 days. Then DDW was added to the composition slowly under constant stirring. The composition was stirred for additional 15 min.

Example 8

Diazepam-containing composition

1 g soy phospholipid was dissolved in a mixture of 3 g ethanol and 9.8 g propylene glycol and to this solution 400mg of diazepam and 2.4 g Labrasol was added. Water (3.4 g) preheated to 40C was added slowly with constant stirring in Heidolph mixer (650rpm). The composition is stirred for additional 15min. The final composition contains 2%w/w diazepam.

Example 9

Granisetron HCl-containing composition

50 mg of soy phospholipids were dissolved in 150 mg ethanol. To this solution, 200 mg of propylene glycol and 10mg Labrasol were added and mixed. To the obtained mixture 15 mg of granisetron were added and dissolved. 575 microlitter of DDW (at room temperature) were added very slowly under constant vortexing. The composition is stirred for additional 5 min.

Example 10

Granisetron HCl-containing composition

70mg of Phospholipon 90 were dissolved in 150 mg ethanol. To this solution, 230mg propylene glycol were added and mixed. To the obtained mixture, 20mg of granisetron HCl were added and dissolved. 530 microlitter of DDW (preheated to 40C) were added very slowly under constant vortexing. The composition is stirred for additional 15 min.

Example 11

Hypoglycemic effect (reduced blood glucose levels) by intranasal administration of insulin

Tables IA and IB detail various compositions of human insulin, which were prepared according to the procedures described in Examples 1-6 above.

Table IA

Component, %w/w	*C*	*D*	*E*	*F*	*G*	*H*
Insulin aqueous soln.	58	-	68.5	20	58	58
Phospholipon 90	2	2	1.5	2	-	2
Ethanol	30	30	22.5	30	-	10
Propylene Glycol	10	10	7.5	10	-	10
Water (double distilled)	-	58	-	38	42	20
Final insulin dose administered to mice IU/25µL of Composition	1.45	0	1.71	0.5	1.45	1.45

Table IA (continuation):

Component, %w/w	*H*	*I*	*J*	*K*	*L*	*M*
Insulin aqueous soln.	58	-	58	58	58	58
Phospholipon 90	2	2	1	0.25	0.5	5
Ethanol	12	12	15	15	15	12.5
Propylene Glycol	10	10	5	10	12	5
Water (double distilled)	18	76	21	16.75	14.5	19.5
Final insulin dose administered to mice IU/25µL of Composition	1.45	0	1.45	1.45	1.45	1.45

Table IB

Component, % w/w	*N*	*O*	*P*	*Q*	*R*	*S*	*T*	*U*	*V*
Insulin aqueous soln.	58	58	58	58	58	58	58	58	58
Phospholipon 90	5	2	9	10	8	1	5	5	1
Cholesterol	-	-	1	-	-	0.1	1.5	-	-
Ceramide	-	-	-	1	-	-	-	0.2	-
Tween 20	-	-	-	1.8	-	-	6.5	-	-
Ethanol	15	15	20	20	20	20	18.5	14.8	12
Propylene Glycol	10	10	12	9	10	10	10	10	15
Water (double distilled)	12	15	-	-	3.9	9.8	-	11.9	13.5
Hydroxy-propyl cellulose	-	-	-	0.2	0.1	-	-	-	0.5
Carbopol	-	-	-	-	-	0.1	0.5	0.1	-

The effect of nasal administration of insulin to mice by means of the compositions described in Tables IA and IB was tested as follows.

Experiments were carried out on C75/bl male mice (weight 22-28g). 25 µL of the Compositions (see Figures and Table) were applied to the nasal cavity of the animal under short isofluran anesthesia. The mice have not received food during the experiment. Blood glucose levels were measured by glucose oxidase method using Glucometer Elite (disposable strips). The measurements were performed starting from one hour prior to intranasal administration of Compositions up to a maximum of 8 hours from the administration. Compositions D and I were used as Placebo controls for the Compositions C and H,

respectively. Composition G served as the insulin aqueous solution control.

Figures 2-5 present the Blood Glucose Levels (BGL) profiles following administration of various insulin compositions. Administration of compositions D and I (placebo controls), or composition G (aqueous control) had no effect on BGL (Figures 2 and 3). Compositions C, F, N and O significantly improved intranasal insulin absorption reducing the BGL.

Example 12

Treatment and prophylaxis of malaria by intranasal administration of dihydroartemisinin (DHA)

Table II details compositions of dihydroartemisinin, which were prepared according to the procedure described in Example 7 above.

Table II:

Component, %w/w	*A*	*B*	*C*	*D*	*E*
Dihydroartemisinin (DHA)	0.66	0.66	0.33	0.40	10
Phospholipon 90	2	2	5	2	5
Ethanol	27	20	17	22	28
Propylene Glycol	10	20	20	15	25
Tween 20	-	10	-	5	2
Water (double distilled)	54.34	47.34	57.67	55.6	30

The compositions described in Table II were tested as follows.

Experiments were carried out in vivo in ICR female mice infected with 10^6 erythrocytes parasitized Plasmodium berghei anka, a model of cerebral malaria with striking similarities to the human disease. Infections were monitored using giemsa-stained thin blood smears prepared from tail blood. The animals were treated under isoflurane anesthesia with 10mg DHA/kg/day in a two divided daily doses by two dosage regimens: prophylaxis regimen- starting at 2 days before the infection for a total of 6 days; treatment regimen- starting on day 2 after infection (parasitemia first detected) for a total of 4 days. Mice were either treated by the intranasal administration or by the i.p. injection containing the same DHA doses. Controls included placebo (delivery carrier only) and untreated infected animals. Experiments were conducted in accordance with institutional guidelines for animal care.

Results show that parasites were not detected in the prophylaxis regimen animal group treated with intranasal administration of DHA in the enhancing permeation carrier, but appeared in 74% of mice treated in the same regimen by i.p. DHA injection. In the treatment regimen, 75% of mice which received intranasal DHA survived, in comparison with only 19% in the i.p. treatment group. Isoflurane anesthesia and the administration of the placebo carrier did not affect the development of the disease. All mice in the control groups succumbed to the parasitemia.

In conclusion, it has been shown that DHA intranasal administration from an enhancing permeation carrier, was

effective for prophylaxis and treatment of anemic and cerebral malaria in mice.

Example 13

Intranasal administration of diazepam

The efficacy of the intranasal administration of the diazepam-containing composition prepared according to Example 8 was tested by means of the following experiments.

Experiment 1: The experiments were carried out on Female Balb/c mice (21-26g). Two experimental groups were used: control (untreated) (n=6) and treated group (n=6). The animals in active treatment group were administered with the Diazepam intranasal Phospholipid ethanolic vesicular compositions 2.9µl in each nose (5mg/kg animal). Half an hour after nasal application, each animal in treated and control groups was IP administered with acetic acid 0.6% (10 ml/kg) and individually housed in cage with a smooth flat floor. Antinociception effect was recorded by counting the number of writhes 5 minutes after injection of acetic acid for period of 10 minutes. A writhe is indicated by abdominal constriction and stretching of at least one hind limb.

Figure 6 is a bar diagram illustrating the results obtained, which show that intranasal administration of diazepam from the vesicular composition, 0.5 h before acetic acid injection efficiently prevented writhing episodes.

Experiment 2: The experiment was carried out on Female Balb/c mice (21-26g). Two experimental groups were used: control (untreated) (n=6) and treated group (n=6). The

animals in active treatment group were administered with the Diazepam intranasal vesicular composition 2.9µl in each nose (5mg/kg animal). Immediately after nasal application (t=0), each animal in treated and control groups was IP administered with acetic acid 0.6% (10 ml/kg) and individually housed in cage with a smooth flat floor. Antinociception was recorded by counting the number of writhes 5 minutes after injection of acetic acid for period of 10 minutes.

Figure 7 is a bar diagram illustrating the results obtained, which show that intranasal administration of diazepam from the vesicular composition simultaneously with injection of acetic acid solution was efficient in treating writhing episodes.

Experiment 3: The experiments were carried out on Female Balb/c mice (21-26g). Three experimental groups were used: control (untreated) (n=4), mice intranasally administered with the Diazepam IN vesicular composition (2.8µl in each nostril = diazepam dose of 5mg/kg animal) (n=4) and mice subcutaneously administered with the Diazepam solution 0.125 % at dose of 5mg/kg animal (n=4). The animals in active treatment groups were administered with the Diazepam intranasal composition and subcutaneous diazepam. Simultaneously, each animal in treated and control groups was IP administered with acetic acid 0.6% (10 ml/kg) and individually housed in cage with a smooth flat floor. Antinociception was recorded by counting the number of writhes 5 minutes after injection of acetic acid for period of 10 minutes.

Figure 8 is a bar diagram illustrating the results obtained, which show that intranasal administration of

diazepam from the vesicular composition, was significantly more efficient in treating writhing episodes as compared to the same dose of the drug administered subcutaneously.

Example 14

Intranasal administration of granisetron HCl

Table III details compositions of granisetron, which were prepared according to the procedures described in Examples 9-10 above.

Table III

Component %w/w	*A*	*B*	*C*	*D*	*E*
Granisetron HCL	1.5	1.5	2	3	4
Phospholipon 90	5	5	5	5	2
Ethanol	10	15	18	25	27
Propylene Glycol	20	20	12	5	20
Labrasol	-	1	1	1	1
Water (DDW)	63.5	57.5	62	61	46

Table III (continuation)

Component %w/w	*F*	*G*	*H*	*I*	*J*	*K*
Granisetron HCL	5	1.5	2	1.5	2	1
Phospholipon 90	5	0.5	7	10	5	5
Ethanol	10	10	15	12	10	10
Propylene Glycol	20	20	23	15	20	20
Labrasol	1	1	-	2	12	6
Water (DDW)	59	67	53	59.5	51	58

The compositions detailed in Table III were used for the intranasal administration of granisetron hydrochloride to rats and the pharmacodynamic response thereof was evaluated as follows.

Experiments were carried out on Male SD/H rats weighing 200-240 g. The animals were housed individually in cages (23×23×20 cm) in a room with a 12-h light/12-h dark cycle (lights on between 06:00 and 18:00 h) at a constant temperature (27±1 °C) and humidity (50±5%). Pelleted food and water was available ad libitum. Each cage had a wire-mesh floor to permit collection of spilt kaolin and food. Kaolin pellets were prepared according to the methods described Takeda et al. (1993). Briefly, gum Arabic and hydrated aluminum silicate (kaolin- China clay) were mixed together (1:100 on a weight: weight basis) with distilled water to form a thick paste. Pellets of the resulting kaolin mixture were shaped to resemble the dimensions of the rats' normal laboratory diet. The pellets were dried completely at room temperature.

The kaolin pellets were introduced into the cages 3 days prior to drug administration. They were held in identical stainless-steel containers (7×8×3 cm, attached to the side of the cage) to the food pellets. The kaolin and food containers were removed each day (at 10:00 h) and the spilt kaolin and food collected, to determine the rats' consumption, during each 24-h period, up to a total 72 h observation time. Rat weight was also recorded on a daily basis.

Ipecac syrup 5ml/kg was administrated orally and animals returned to the experiment cages. Rats were administrated

with intranasal Granisetron HCl Composition B (at a dose of 1.5mg granisetron HCl/kg rat). One hour after intranasal administration of granisetron, Ipecac syrup was given orally using a gavage to treated (n=5) and untreated (control, n=5) animals. Immediately after Ipecac syrup, the animals in the treatment group were administered with an additional dose of intranasal Granisetron hydrochloride followed by drug intranasal administration at regular 12-h intervals for additional 2.5 days. Kaolin and food intake as well as rat weights were measured at 24, 48 and 72 h post- Ipecac.

The results collected are represented in Figures 9 to 11. The Results show that intranasal administration of granisetron HCl from composition B, was efficient in preventing weight loss (Fig. 9), stimulating food consumption (Fig. 10) and preventing kaolin consumption (Fig. 11) in rats with Pica syndrome (equivalent to emesis and vomiting in humans).

Example 15

Transport of fluorescent probe across nasal mucosa following in vivo administration

Visualization of Rhodamine B (hydrophilic probe, MW 479) permeation across the nasal mucosa using the composition of the invention (containing 0.05% (0.5mg/mL) Rhodamine B) was carried out as follows.

A stock solution of Rhodamine B (2mg/mL) was prepared in water. 50mg of phospholipid were dissolved in 200 mg ethanol. To this solution 100 mg propylene glycol and 10 mg Labrasol were added and mixed. To the obtained mixture

250 microliter of the aforementioned aqueous Rhodamine B solution (2mg/ml) were added slowly with constant stirring. The residual 390 microlitter of DDW were added slowly to the obtained system with constant vortexing. The composition is stirred for additional 5 min. The composition is described in Table IV.

Table IV

Component	*Rhodamine B composition %w/w*
Rhodamine B stock aqueous soln.	25
Phospholipon 90	5
Ethanol	20
Propylene Glycol	10
Labrasol	1
Water (DDW)	39

The composition was applied intranasally to the right nostril of SD/H male 220-250g rats (application volume 100µL) anesthetized i.p. with Ketamine-Xylazine mixture
The animals were sacrificed 1/2 hour from the application and the nasal septum with the adjunct epithelial membrane from each animal were carefully removed from the bone. The harvested septum was fixed with 3.8% Formalin in PBS (pH 7.4) for 1 hour in room temperature. The untreated epithelia on the left side of the septum were separated from the septum. The septum with right side epithelia was placed on the slide, covered with cover glass, fixed with tape and observed under CLS microscope (10-40X/0.6 plan Neofluor lens, Zeiss LSM 410 confocal system with an Axiovert 135 inverted microscope).

Figure 12 is a photograph showing that the composition of the invention efficiently delivered rhodamine B across the nasal mucosa (White means the highest fluorescent intensity).

Example 16

Granisetron HCL-containing composition in the form of a viscous liquid

700mg of Phospholipon 90 were dissolved in 1500 mg ethanol. To this solution 2300mg of propylene glycol were added and mixed. To the obtained mixture 200mg of granisetron were added and dissolved. 5280 microlitter of DDW (preheated to 40C) were added very slowly under constant mixing in Heidolph mixer (650rpm). The composition was mixed for additional 15 min. To the obtained system 20mg of hydroxypropylcellulose were added slowly and mixed for additional 15 min in Heidolph mixer (650rpm). The resulting composition was left for 30min in room temperature and than mixed for additional 5min.

Example 17

Insulin-containing composition in the form of a semi-solid

0.2 g of phospholipon 90 were dissolved in 3g ethanol and to this solution 0.94g propylene glycol were added. The obtained solution was added slowly to 5.8 mL of the aqueous insulin solution (100IU/mL) under constant stirring at room temperature in Heidolph mixer (650rpm). The composition was stirred for additional 5

min. To the obtained system 60 mg of hydroxypropylcellulose were added slowly and mixed for additional 15 min in Heidolph mixer (650rpm). The resulting composition was left for 30min in room temperature and than mixed for additional 10 min. The final semi-solid composition contains 58IU insulin/ g.

Example 18

Insulin-containing composition in the form of a gel

0.2g of Carbopol 980 was dispersed in 2.48g DDW in Heidolph mixer (400rpm) followed by a slow addition of 0.2 g of TEA. The mixture was left for 10min in room temperature to obtain the gel phase.

In another container 0.2g of Phospholipin 90 were dissolved in 2g EtOH to this solution 1g of propylene glycol and 0.02g of Vitamin E were added and mixed to obtain clear system in Heidolph mixer (700rpm). The obtained system was stirred for additional 5 min and added slowly to the gel phase under constant mixing at 400rpm. To the obtained semi-solid preparation 3.9mL of insulin aqueous solution containing 250 IU/mL (prepared from dissolving 40.6mg of human insulin powder containing 24IU/mg (Sigma) in DDW) was added. The obtained composition was mixed for additional 5 min. It is notable that insulin solution could be added in each stage of the preparation. The final semi-solid composition contains 97.5IU insulin/ g.

Example 19 (comparative)

Insulin-containing compositions were prepared, as described in Table V below:

Table V

	Compositions, , %w/w		
Component	*I*	*II*	*III*
Insulin aqueous solution 100IU/ml	63	63	63
Phospholipon 90	2	2	2
Ethanol	25	10	2
Propylene Glycol	10	-	-
DDW	-	25	33
Final insulin dose administered to mice IU/25µL of Composition	1.575 IU	1.575 IU	1.575 IU

Experimental protocol:

Nasal absorption experiments with insulin compositions I, II (control composition containing 10% EtOH) and III (control liposomal composition containing 2% EtOH) were performed in ICR/male mice (7-10Weeks) obtained from (Harlan/Israel). The animals were fasted 1 h prior to an insulin administration and during the experiment time, with free access to water. Compositions were intranasally administered to the animals (12.5µl in each nostril, a total of 25 µl per animal- each nose side), using a pipette with a disposable plastic tip. The nasal insulin formulations were administered at time=0h following a short isofluran anesthesia. The total amount of insulin delivered nasally to each animal, was 1.575 IU. Blood glucose levels were measured by glucose oxidase method using Glucometer Elite (disposable strips). The

measurements were performed starting from one hour prior to intranasal administration of Compositions up to 6 hours from the administration.

The results presented in Figure 13 show that Composition I efficiently reduced blood glucose levels, while administration of Compositions II and III (controls) had no effect on BGL.

Example 20

Buspirone HCl-containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Buspirone HCL	1	2
Phospholipon 90	2	2
Ethanol	20	25
Propylene Glycol	10	-
Vitamin E	0.2	0.2
Carbopol 980	1	-
Triethanolamine (TEA)	1	-
Water (DDW)	64.8	70.8

Preparation method for Buspirone Composition A:

0.1g of Carbopol 980 was dispersed in 2.48g DDW in Heidolph mixer (400rpm) to this dispersion 1g of EtOH was added under constant mixing followed by a slow addition of 0.1 g of TEA. The mixture was left for 10min in room temperature to obtain the gel phase.

In another container 0.2g of Phospholipin 90 were dissolved in 1g EtOH to this solution 1g of propylene glycol and 0.02g of Vitamin E were added and mixed to obtain clear system. To this system 0.1g of buspirone HCl

dissolved in 4g DDW were slowly added under constant stirring at room temperature in Heidolph mixer (700rpm). The obtained system was stirred for additional 5 min and added slowly to the gel phase under constant mixing at 400rpm. The obtained composition A was mixed for additional 5 min.

Preparation method for Buspirone Composition A:

0.2g of Phospholipin 90 were dissolved in 2.5g EtOH; to this solution 0.02g of Vitamin E were added and mixed to obtain clear system. To this system, 0.2g of buspirone HCl dissolved in 7.08g DDW were slowly added under constant stirring at room temperature in Heidolph mixer (700rpm). The obtained system was stirred for additional 5 min.

Example 21

Insulin-containing composition

0.2g mg of phospholipids (Phospholipon 90) were dissolved in 1.5g ethanol and to this solution 0.5g propylene glycol were added.

Insulin aqueous solution containing 250 IU/mL insulin was prepared by dissolving 81.25mg of human insulin powder containing 24IU/mg (Sigma) in 7.8 mL DDW. The obtained insulin aqueous solution was added slowly under constant stirring at room temperature to the previously prepared phospholipid solution. The composition is stirred for additional 5 min. The final composition contains 195 IU insulin/g.

Example 22

Glatiramer acetate -containing composition

The following compositions were prepared:

Component, %w/w			
	A	*B*	*C*
Glatiramer acetate	1	2	2
Soy phospholipids	2	2	3
Ethanol	20	25	15
Propylene Glycol	10	-	10
Vitamin E	0.2	0.2	0.2
Carbopol 980	1	-	0.1
Triethanolamine (TEA)	1	-	0.1
Water (DDW)	64.8	70.8	69.6

Example 23

Paroxetine -containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Paroxetine	0.5	1
Phosphatydylcholine	2.5	3
Ethanol	23	15
Propylene Glycol	10	15
Vitamin E	0.2	0.2
Labrasol	1	-
Water (DDW)	62.8	65.8

Example 24

Rivastigmine -containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Rivastigmine tartrate	0.5	0.75
Soy Phospholipid	2	5
Ethanol	12	20
Propylene Glycol	10	15
Water (DDW)	75.5	59.25

Example 25

Sibutramine -containing composition

The following compositions were prepared:

Component, %w/w		
	A	*B*
Sibutramine	1	1.5
Phospholipon 90	5	2
Ethanol	14	22
Propylene Glycol	15	-
Vitamin E	0.2	-
Labrasol	1	-
Water (DDW)	63.8	74.5

Claims:

1) Use of phospholipids, one or more C2-C4 alcohols and water in the preparation of a vesicular composition adapted for intranasal administration of an active agent, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

2) Use of phospholipids, one or more C2-C4 alcohols, one or more water-miscible polyols and water in the preparation of a vesicular composition adapted for the intranasal administration of an active agent, wherein the concentrations of said phospholipids, said one or more alcohols and said one or more polyols in said composition are in the ranges of 0.2 to 10%, 12 to 30% and 1 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

3) Use according to claim 2, wherein the C2-C4 alcohol is ethanol and the polyol is propylene glycol.

4) Use of a carrier comprising not less than 30% by weight water, from 12 to 30% by weight C2-C4 alcohol(s), from 1 to 30% by weight water-miscible polyol(s), from 0.2 to 10% phospholipids arranged in a vesicular structure and therapeutically effective amount of a pharmaceutically active ingredient, in the preparation of a pharmaceutical composition suitable for intranasal administration.

5) Use according to any one of claims 1 to 4, wherein the weight ratio between the C2-C4 alcohol and the phospholipids is not less than 2:1.

6) Use according to any one of claims 1 to 5, wherein said composition is a composition for treating and/or preventing emesis, diabetes, malaria, depression, Alzheimer's disease, multiple sclerosis, hot flushes symptoms and obesity.

7) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-emetic agent.

8) Use according to claim 7, wherein the anti-emetic agent is granisetron or a pharmaceutically acceptable salt thereof.

9) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of granisetron or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

10) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-diabetic agent.

11) Use according to claim 10, wherein the anti-diabetic agent is insulin or a derivative thereof.

12) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of insulin or a derivative thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

13) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-malaria agent.

14) Use according to claim 13, wherein the anti-malaria agent is dihydroartemisinin.

15) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of dihydroartemisinin, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

16) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-anxiety and/or anticonvulsant agent.

17) Use according to claim 16, wherein the anti-anxiety and/or anticonvulsant agent is diazepam.

18) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of diazepam, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

19) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-obesity agent.

20) Use according to claim 19, wherein the anti-obesity agent is sibutramine or a pharmaceutically acceptable salt thereof.

21) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of sibutramine or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

22) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an antidepressant or anti-hot flashes agent.

23) Use according to claim 22, wherein the antidepressant or anti-hot flashes agent is paroxetin or a pharmaceutically acceptable salt thereof.

24) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of paroxetine or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

25) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-multiple sclerosis agent.

26) Use according to claim 25, wherein the anti-multiple sclerosis agent is glatiramer acetate.

27) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of glatrimer or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

28) Use according to claim 1 or 4, wherein the composition comprises a therapeutically effective amount of an anti-dementia agent.

29) Use according to claim 28, wherein the anti-dementia agent is rivastigmine or a pharmaceutically acceptable salt thereof.

30) A pharmaceutical composition for intranasal administration, which comprises a therapeutically effective amount of rivastigmine or a pharmaceutically acceptable salt thereof, water, phospholipids and one or more C2-C4 alcohols, wherein the concentrations of said phospholipids and said one or more alcohols are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight.

31) A method of administering an active pharmaceutical ingredient to a patient in need thereof, which method comprises the intranasal administration of a composition comprising a therapeutically effective amount of said ingredient, phospholipids, one or more C2-C4 alcohols and water, wherein the concentrations of said phospholipids and said one or more alcohols in said composition are in the ranges of 0.2 to 10% and 12 to 30% by weight, respectively, with the water content of said composition being not less than 30% by weight, said phospholipids forming vesicles in said composition.

32) A method for preventing and/or treating emesis in a mammal, which method comprises the intranasal

administration of a granisetron-containing composition according to claim 9.

33) A method for treating diabetes in a mammal, which method comprises the intranasal administration of the insulin-containing composition according to claim 12.

34) A method for treating malaria in a mammal, which method comprises the intranasal administration of the dihydroartemisinin-containing composition according to claim 15.

35) A method for treating epileptic seizures in a mammal, which method comprises the intranasal administration of a diazepam-containing composition according to claim 18.

36) A method for preventing and/or treating obesity in a mammal, which method comprises the intranasal administration of a sibutramine-containing composition according to claim 21.

37) A method for treating depression and/or hot flushes in a mammal, which method comprises the intranasal administration of a paroxetine-containing composition according to claim 24.

38) A method for treating multiple sclerosis in a mammal, which method comprises the intranasal administration of a glatiramer acetate-containing composition according to claim 27.

39) A method for preventing and/or treating dementia in a mammal, and specifically, Alzheimer disease, which method comprises the intranasal administration of a rivastigmine-containing composition according to claim 30.

40) Use of an anti-malaria agent and a vesicular carrier in the preparation of a medicament for the intranasal treatment of malaria.

41) A method for preventing and/or treating malaria in a mammal, which method comprises the intranasal administration of a therapeutically effective amount of an anti-malaria drug in a pharmaceutically acceptable carrier.

42) A method according to claim 41, wherein the pharmaceutically acceptable carrier contains vesicles.

43) A method according to claim 42, wherein the carrier comprises not less than 30% by weight water, from 12 to 30% by weight C2-C4 alcohol(s), from 1 to 30% by weight water-miscible polyol(s) and from 0.2 to 10% phospholipids arranged in a vesicular structure.

44) A method according to claim 42, wherein the anti-malaria drug is dihydroartemisinin.

45) A method according to claim 41, wherein the anti-malaria drug is an artemisinin derivative.

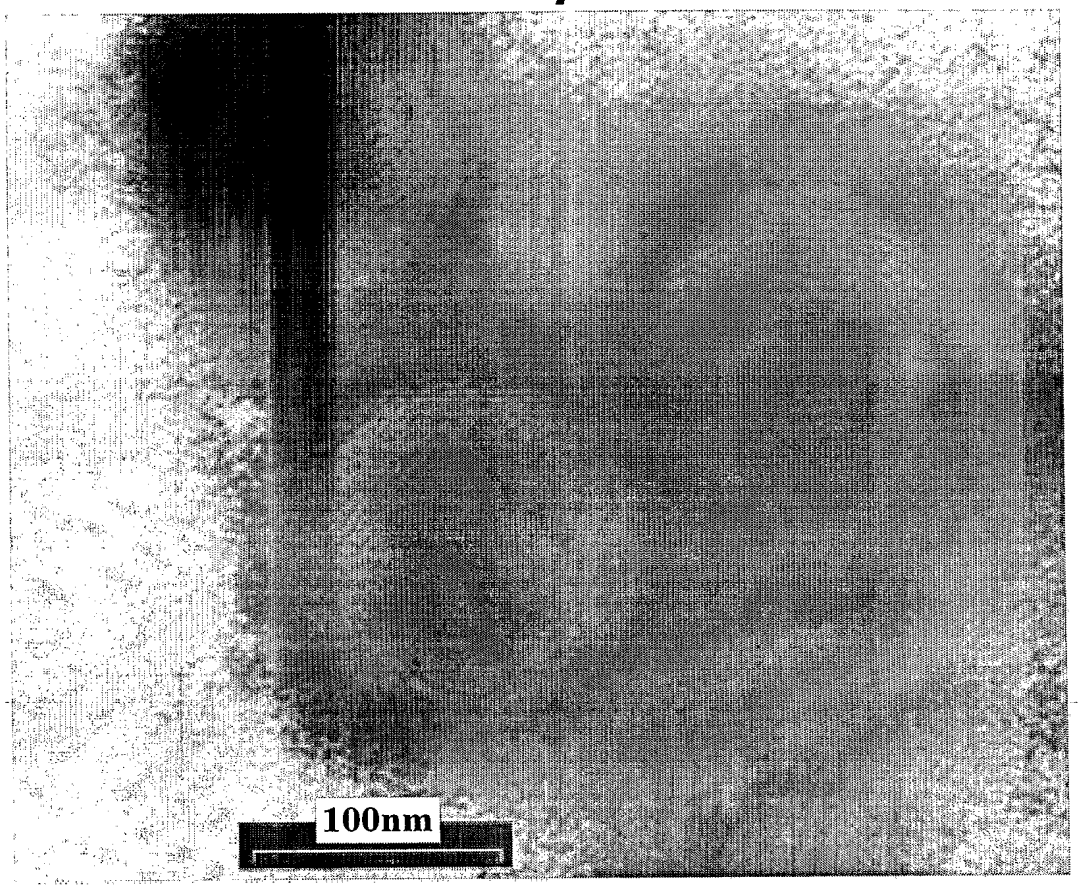
100nm

Fig. 1

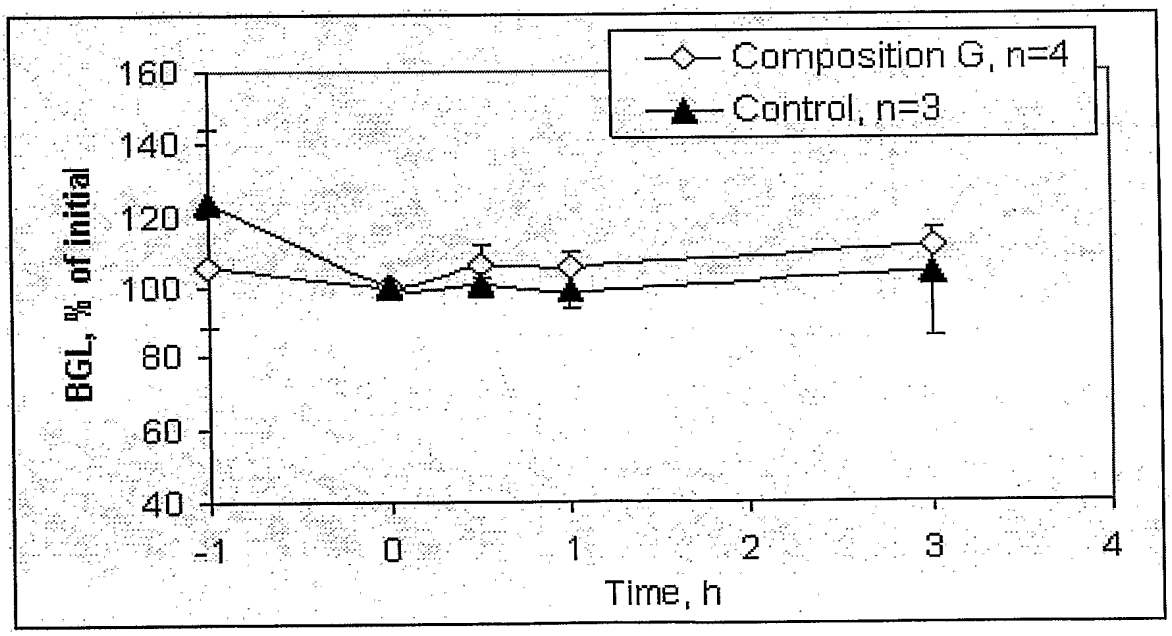
Composition G, n=4
Control, n=3
BGL, % of initial
160
140
120
100
80
60
40
-1
0
1
2
3
4
Time, h

Fig. 2

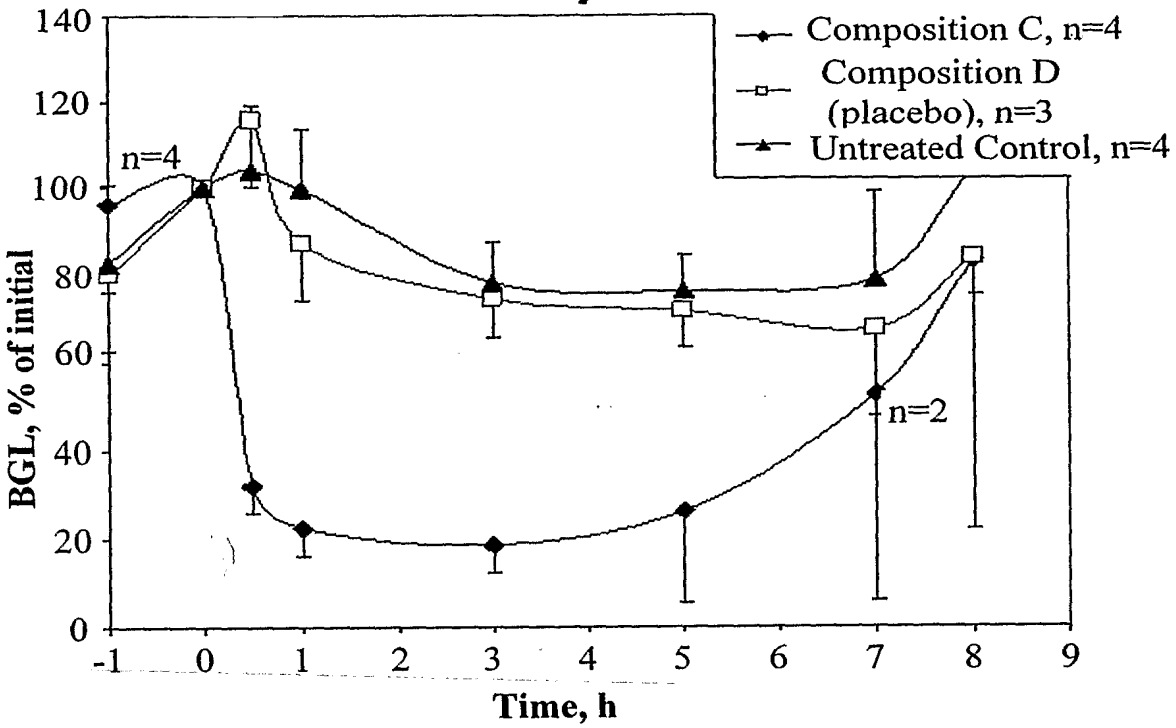
Composition C, n=4
Composition D (placebo), n=3
Untreated Control, n=4
n=4
n=2
BGL, % of initial
Time, h
140
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
6
7
8
9

Fig. 3

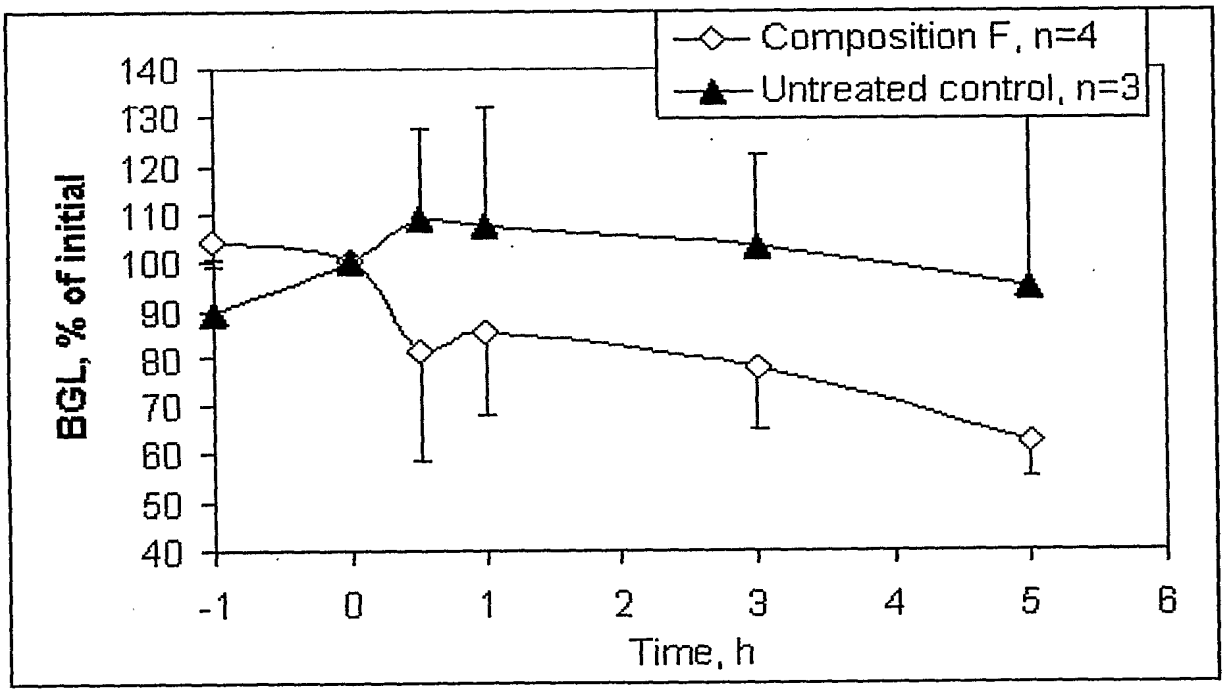
Composition F, n=4
Untreated control, n=3
BGL, % of initial
Time, h
140
130
120
110
100
90
80
70
60
50
40
-1
0
1
2
3
4
5
6

Fig. 4

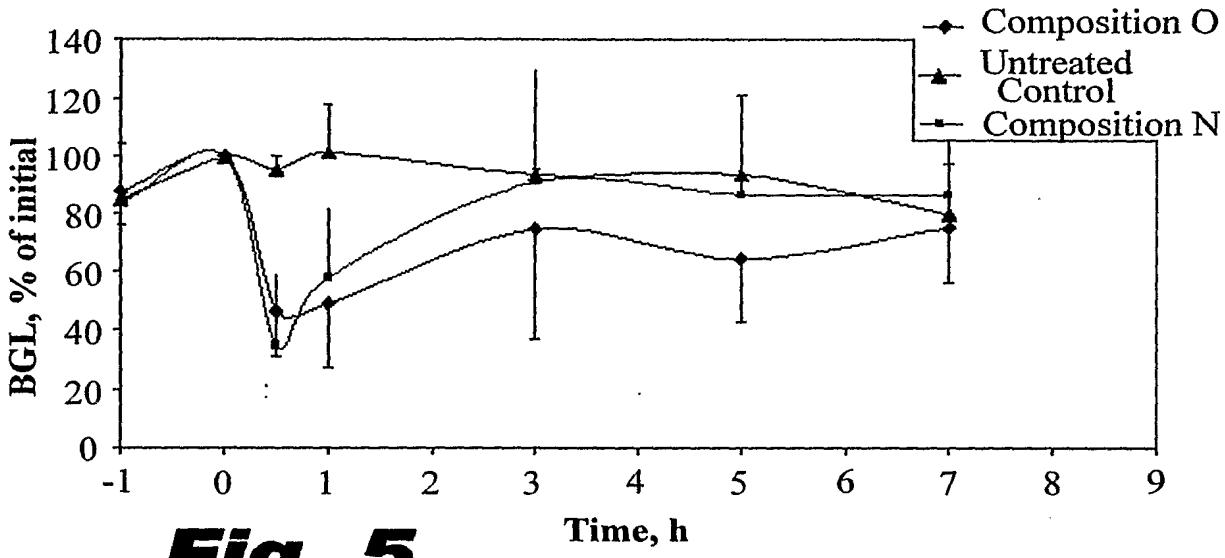
Composition O
Untreated Control
Composition N
BGL, % of initial
140
120
100
80
60
40
20
0
-1
0
1
2
3
4
5
6
7
8
9
Time, h

Fig. 5

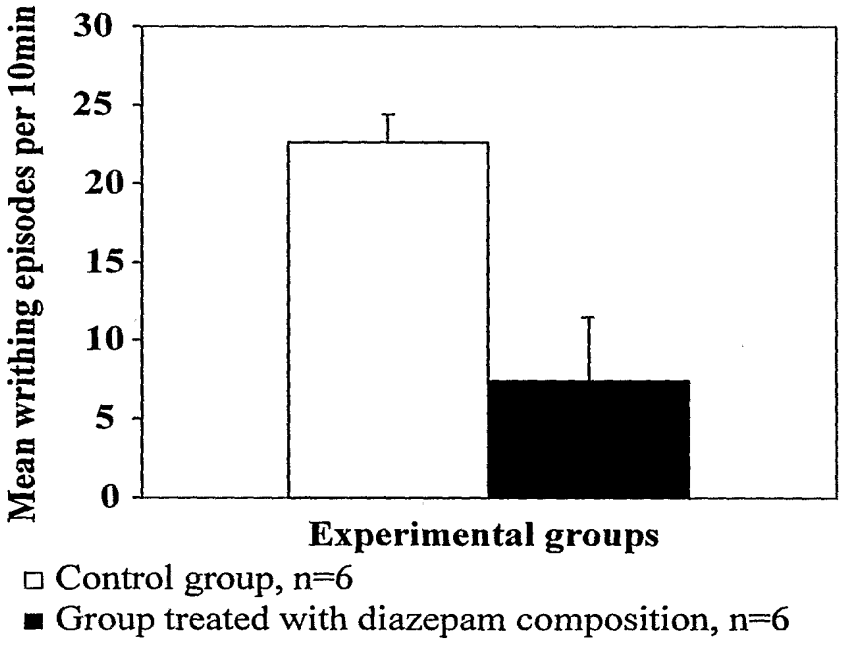
Mean writhing episodes per 10min
30
25
20
15
10
5
0
Experimental groups
□ Control group, n=6
■ Group treated with diazepam composition, n=6

Fig. 6

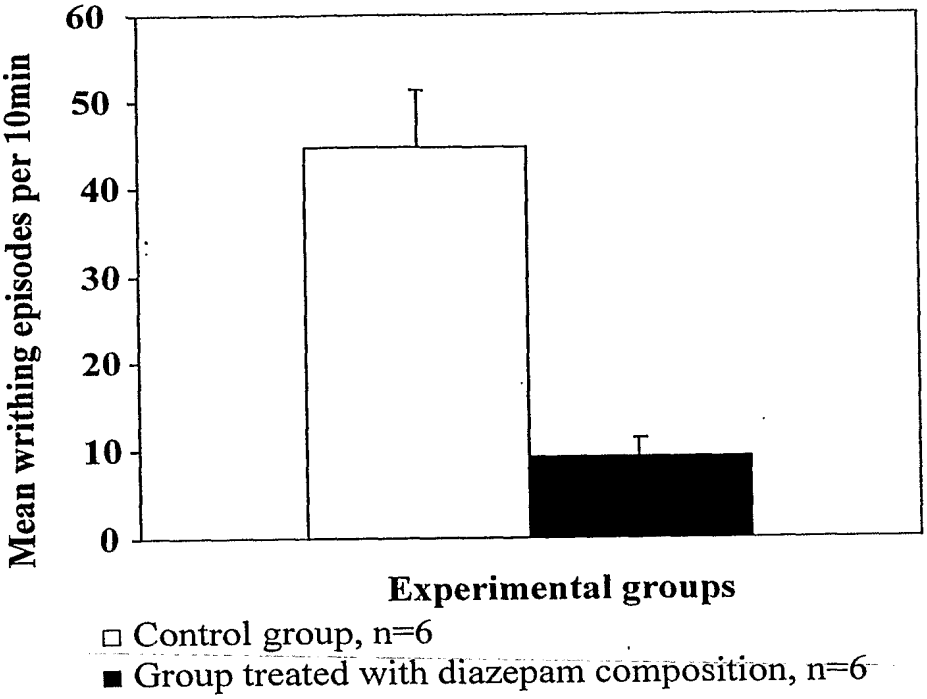
60
50
40
30
20
10
0
Mean writhing episodes per 10min
Experimental groups
□ Control group, n=6
■ Group treated with diazepam composition, n=6

Fig. 7

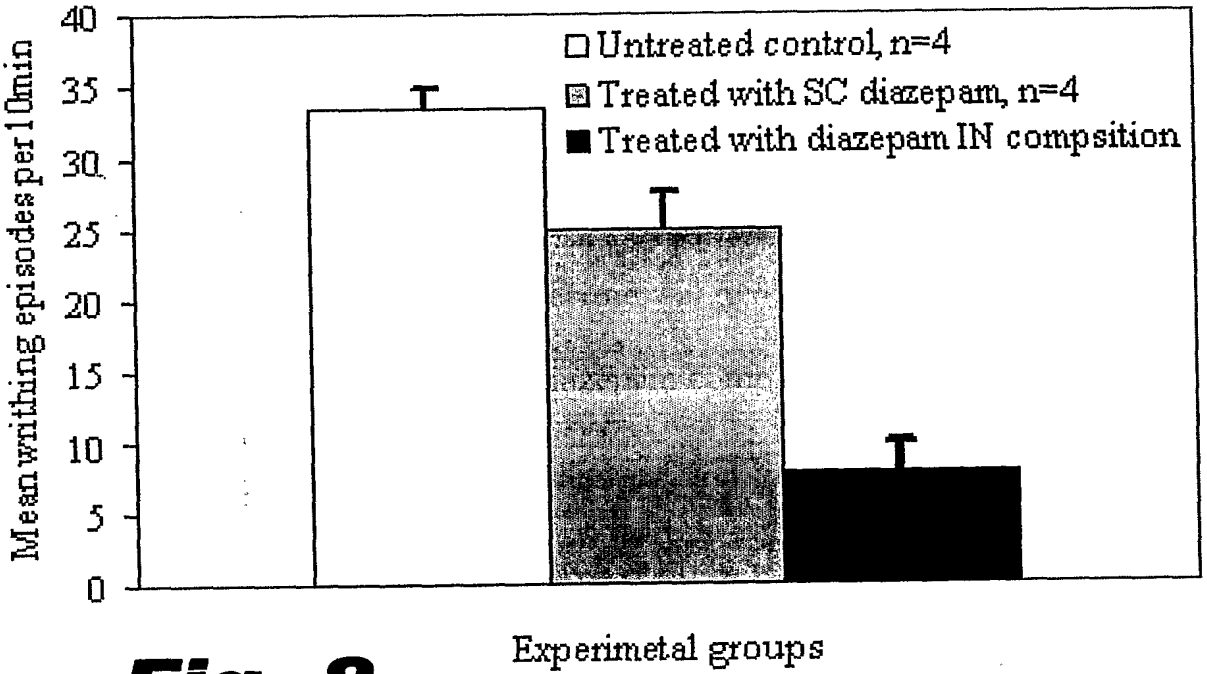
40
35
30
25
20
15
10
5
0
Mean writhing episodes per 10min
□ Untreated control, n=4
▨ Treated with SC diazepam, n=4
■ Treated with diazepam IN compsition
Experimetal groups

Fig. 8

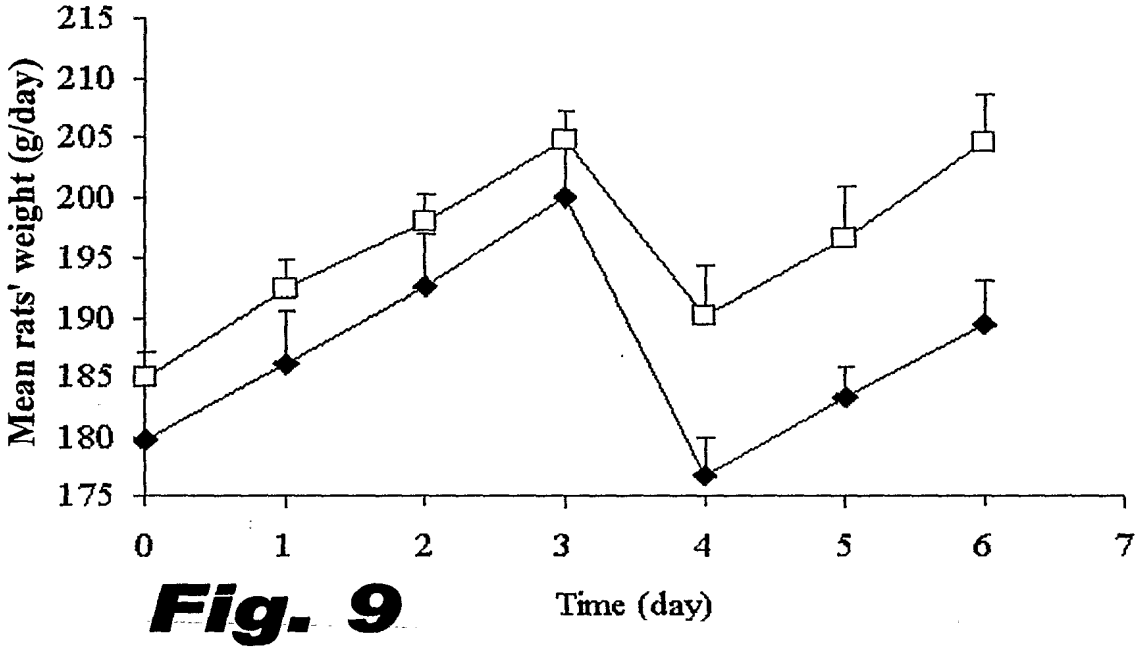
Mean rats' weight (g/day)
215
210
205
200
195
190
185
180
175
0
1
2
3
4
5
6
7
Time (day)

Fig. 9

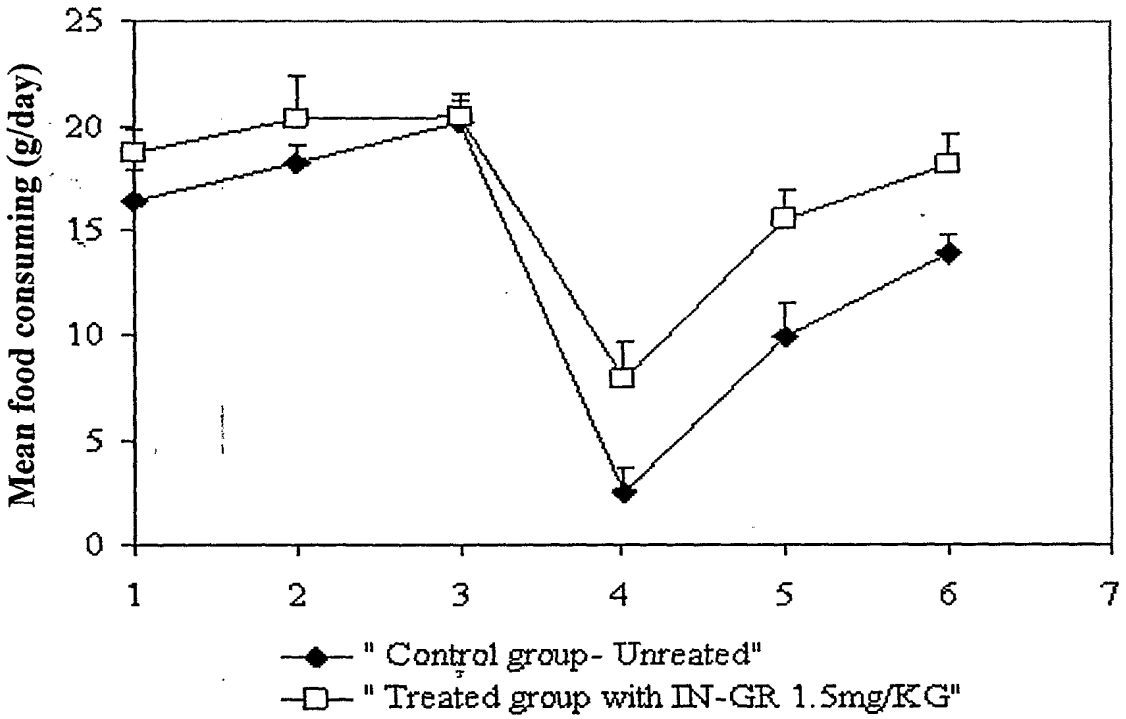
Mean food consuming (g/day)
25
20
15
10
5
0
1
2
3
4
5
6
7
" Control group- Unreated"
" Treated group with IN-GR 1.5mg/KG"

Fig. 10

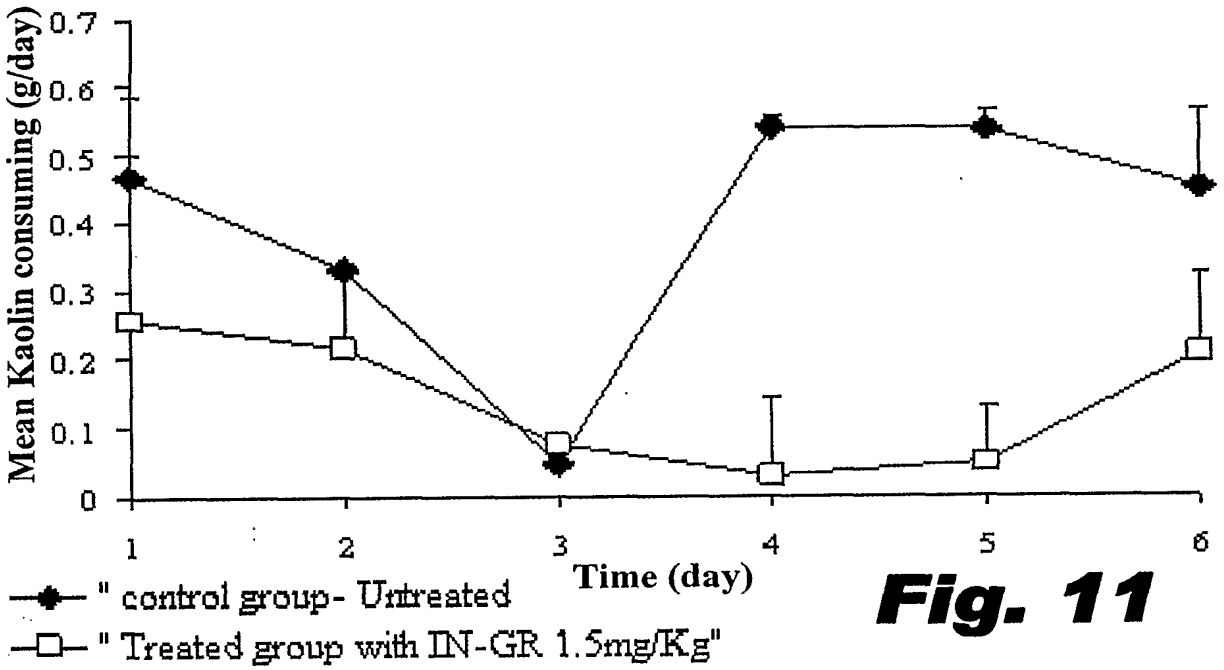
Mean Kaolin consuming (g/day)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
5
6
Time (day)
" control group- Untreated
" Treated group with IN-GR 1.5mg/Kg"

Fig. 11

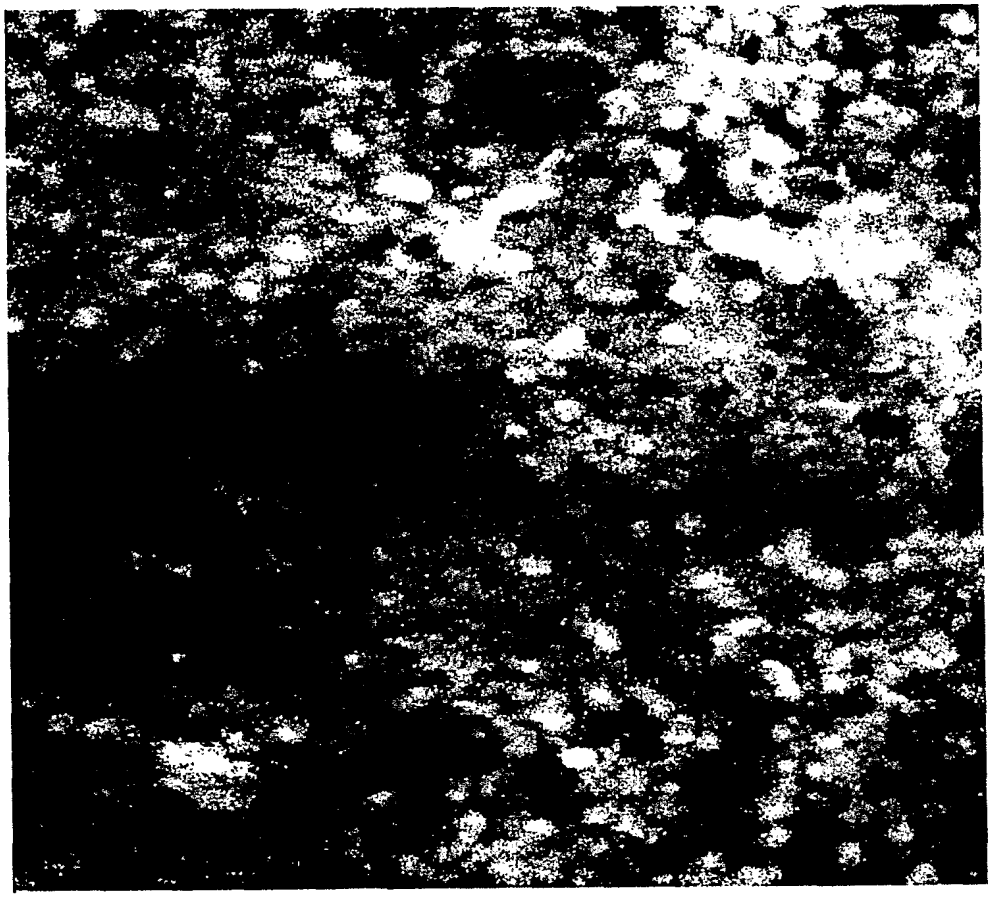

Fig. 12

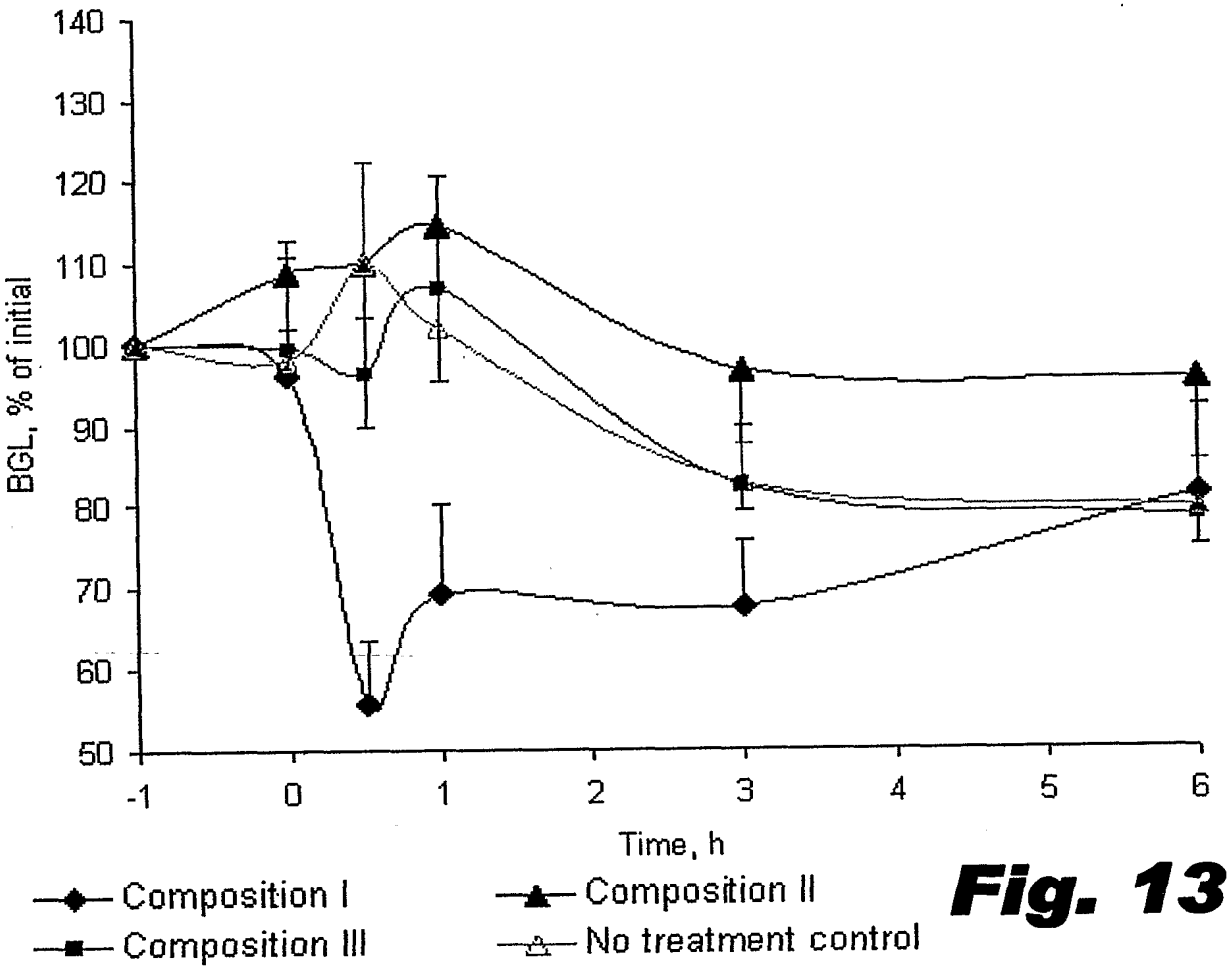
140
130
120
110
100
90
80
70
60
50
BGL, % of initial
-1
0
1
2
3
4
5
6
Time, h
Composition I
Composition II
Composition III
No treatment control

Fig. 13

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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Erklärungen gemäß Regel 4.17:
— *hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii)*
— *Erfindererklärung (Regel 4.17 Ziffer iv)*

Veröffentlicht:
— *ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** SMOKING WITHDRAWAL COMBINATION WAFER

(54) **Bezeichnung:** RAUCHERENTWÖHNUNGS-KOMBINATIONSWAFER

(57) **Abstract:** The present invention relates to a quickly decomposing oral drug preparation, for the application of active ingredient combinations for smoking withdrawal, which contains nicotine, a nicotine salt, a nicotine derivative, or a substance that reacts to nicotine, in combination with another active ingredient, and the use of such a drug preparation for the treatment of smoking withdrawal, and the use of nicotine, and/or nicotine salts or derivatives, for the production of medications for the treatment of smoking withdrawal. The active ingredient that is to be administered, in combination, for this purpose is a centrally active ingredient, preferably an antidepressant for the fighting of psychic dependency in terms of a smoking withdrawal therapy. The administration of the active ingredient combination to the patient should be handled in a simple and reliable way and should exclude side effects to a large extent.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft schnell zerfallende orale Darreichungsformen zur Applikation von Wirkstoffkombinationen zur Raucherentwöhnung mit einem Gehalt an Nikotin, einem Nikotinsalz, einem Nikotinderivat oder einem Stoff mit nikotinerger Wirkung, in Kombination mit einem weiteren Wirkstoff sowie die Verwendung solcher Darreichungsformen zur Behandlung der Nikotinabhängigkeit, zur Nikotinsubstitution oder zur Raucherentwöhnung und die Verwendung von Nikotin bzw. seiner Salze oder Derivate zur Herstellung von Arzneiformen zur Behandlung der Nikotinabhängigkeit. Der in Kombination zu verabreichende Wirkstoff ist dabei ein zentral wirkender Stoff , vorzugsweise ein Antidepressivums zur Bekämpfung der psychischen Abhängigkeit im Rahmen einer Raucherentwöhnungs-Therapie. Die Verabreichung der Wirkstoffkombination soll für den Patienten auf einfache und zuverlässige Weise erfolgen und Nebenwirkungen weitgehend ausschließen.

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Raucherentwöhnungs-Kombinationswafer

Die vorliegende Erfindung betrifft schnell zerfallende orale Darreichungsformen zur Applikation von Wirkstoffkombinationen zur Raucherentwöhnung mit einem Gehalt an Nikotin, einem Nikotinsalz, einem Nikotinderivat oder einem Stoff mit nikotinerger Wirkung, in Kombination mit einem weiteren Wirkstoff.
Die Erfindung betrifft ferner die Verwendung solcher Darreichungsformen zur Behandlung der Nikotinabhängigkeit, zur Nikotinsubstitution oder zur Raucherentwöhnung, sowie die Verwendung von Nikotin bzw. seiner Salze oder Derivate zur Herstellung von Arzneiformen zur Behandlung der Nikotinabhängigkeit.

Ca. 30 % der Weltbevölkerung rauchen und konsumieren dabei jährlich etwa 6 Billionen Zigaretten. Rauchen gehört wie der Alkoholgenuss zu den gesellschaftlich akzeptierten und weit verbreiteten Arten des Drogenkonsums, wobei das im Tabak hauptsächlich vorkommende Alkaloid Nikotin eine anderen Rauschmitteln vergleichbare suchterzeugende Wirkung besitzt, die zu einer physischen Abhängigkeit führt. Die toxischen Effekte des Nikotins, das ein starkes Nervengift ist, werden dabei bei Rauchern durch Gewöhnung zurückgedrängt.

Nikotin erreicht bereits kurz nach der Inhalation das Gehirn und wirkt dort an Acetylcholinrezeptoren, wobei es eine Reihe physiologischer Reaktionen auslöst. Dadurch kommt es zur Zunahme der Herzfrequenz, Verengung der Blut-

gefäße mit einhergehendem Blutdruckanstieg und einer deutlichen Abnahme der Hauttemperatur. Darüber hinaus werden über zentrale Effekte die psychomotorische Leistungsfähigkeit sowie Aufmerksamkeits- und Gedächtnisleistungen gesteigert.

Das hohe Suchtpotential wird neben der direkten Wirkung auf die nikotinergen Acetylcholinrezeptoren vor allem der Beeinflussung des Dopaminsystems zugeschrieben, von dem angenommen wird, das es maßgeblich für den Belohnungseffekt des Rauchens verantwortlich ist.

Da durch regelmäßigen Nikotinkonsum eine Vermehrung der zentralen nikotinergen Acetylcholinrezeptoren eintritt, führt ein Ausbleiben der Nikotinzufuhr zu Entzugserscheinungen.

Neben Nikotin konnten im Tabakrauch bisher mehr als 4000 Verbindungen identifiziert werden, von denen viele eine cancerogene Wirkung aufweisen oder zumindest im Verdacht stehen, krebserzeugend zu sein.

Nikotinkonsum ist eine wesentliche Ursache für Gefäßerkrankungen, Bluthochdruck, Krebs und Asthma sowie die damit einhergehenden Spätfolgen wie Schlaganfall, Herzinfarkt, chronische Bronchitis, COPD (chronisch obstruktive Lungenerkrankungen), Raucherbein, Arteriosklerose und Sehstörungen.

Statistiken zeigen, daß bestimmte schwerwiegende Erkrankungen unmittelbar ursächlich auf das Rauchen zurückzuführen

sind. So betreffen z.B. 90 % bis 95 % der Lungenkrebserkrankungen, 90 % der Amputationen sowie nahezu alle Herzinfarkte vor dem 40. Lebensjahr Raucher. Insgesamt werden sogar 30 % aller Krebserkrankungen dem Zigarettenkonsum zugeschrieben. Es hat sich weiterhin gezeigt, daß das Thromboserisiko bei Einnahme oraler Kontrazeptiva bei Raucherinnen 10-fach höher ist, während neuere Studien zeigen sollen, daß erektile Dysfunktion bei rauchenden Männern deutlich häufiger auftritt.

Insgesamt liegt die Lebenserwartung von Rauchern in Deutschland um ca. 10 % unter der von Nichtrauchern und nahezu ein Viertel aller "vorzeitigen" Todesfälle ist auf Folgeerkrankungen des Rauchens zurückzuführen.
Darüber hinaus wird die Zahl der vorzeitigen Invaliden durch Rauchen auf 70.000 bis 100.000 pro Jahr geschätzt und die Zahl derer, die an den Folgen des "Passivrauchens" sterben, auf ca. 500 bis 3500.

Die gesamten durch das Rauchen verursachten Kosten belaufen sich nach Schätzungen der Deutschen Gesellschaft für Nikotinforschung auf ca. 75 Milliarden Euro jährlich.

Aufgrund der einleitend diskutierten negativen Folgen und der gesundheitlichen Risiken ist das Rauchen vermehrt in den Fokus der gesundheitspolitischen Diskussion geraten. Nicht zuletzt auch deshalb, weil mittlerweile nachgewiesen wurde, daß auch Passivrauchen zu ernsthaften Erkrankungen führen kann.

Der Raum für Raucher wird zunehmend eingeschränkt und Rauchen ist an vielen öffentlichen Plätzen und am Arbeitsplatz weitgehend verboten. In den USA, Italien und Irland ist das Rauchverbot in Restaurants und Gaststätten bereits durch entsprechende Gesetze bestätigt.

Hinzu kommt, daß die Kosten für Tabakwaren in Deutschland in den letzten Jahren stark angestiegen sind und weitere Kosten auf Raucher, z.B. durch einen erhöhten Krankenkassenbeitrag zur Deckung der durch das Rauchen verursachten zusätzlichen Kosten im Gesundheitswesen, zukommen werden. Tabakgenuß wird somit zunehmend ein Luxus mit nicht zu vernachlässigenden finanziellen Aspekten. So verbrennt ein Raucher beispielsweise bei ca. 20 Zigaretten am Tag bei einem Preis von ca. 20 Cent pro Zigarette runde 1.500 Euro pro Jahr.

Angesichts der zuvor genannten Zahlen und der bekannten gesundheitsschädlichen Auswirkungen des Tabakrauchens gibt es demnach viele gute Gründe, außer den ohnehin offenkundigen finanziellen Aspekten, nicht zu rauchen oder aufzuhören.

Dennoch ist für die meisten Nikotinabhängigen eine Beendigung der Abhängigkeit nur schwer möglich. Der Hauptgrund dafür liegt in den Entzugserscheinungen, welche sich nach Beendigung des Tabakkonsums einstellen.

Der Ausstieg aus dieser Suchtabhängigkeit wird deshalb erleichtert, wenn der Nikotinbedarf zumindest während einer Entwöhnungsphase auf andere Weise gedeckt wird, z. B. im

Rahmen einer Nikotin-Substitutionstherapie. Dies kann beispielsweise mittels sogenannter Nikotinpflaster erfolgen, die Nikotin über die Haut an den menschlichen Organismus abgeben und so die Nikotin-Entzugserscheinungen unterdrücken, wodurch die Raucherentwöhnung erleichtert wird. Nachteilig an diesen transdermalen therapeutischen Systemen (TTS) ist aber, daß diese über einen langen Zeitraum auf der Haut verbleiben und als störend empfunden werden. In ungünstigen Fällen können sowohl durch das Nikotin als auch durch den Kleber Reizungen der Haut und allergische Reaktionen hervorgerufen werden. Darüber hinaus wird über die TTS zwar kontinuierlich Nikotin an den Organismus abgegeben, Spitzenkonzentrationen, wie sie beim Rauchen auftreten und die für die Belohnungseffekte verantwortlich sein können, bleiben aber aus.

Es hat sich weiterhin gezeigt, daß bei vielen Rauchern neben der wirkstoffbezogenen, d. h. nikotinbezogenen, physischen Abhängigkeit zusätzlich eine psychische Abhängigkeit vorliegt, die durch Nikotinsubstitution alleine nicht behandelt werden kann.

Dieses wird insbesondere deutlich, wenn man die kurze Halbwertzeit des Nikotins berücksichtigt, die zwischen 30 min und 120 min liegt. Demnach müßten Raucher zumindest morgens starke Entzugssymptome zeigen. Die Erfahrung zeigt aber, daß das Bedürfnis nach einer Zigarette und der Zeitraum bis zur nächsten Zigarette oft stark von äußeren Faktoren wie Streß, Sport, Gesellschaft und dergleichen abhängt und nicht von echten physischen Symptomen bestimmt wird. So können sowohl der Tabakkonsum als auch seine Frequenz in

Abhängigkeit von der psychischen Verfassung stark schwanken.

Vielfach ist auch die psychische Abhängigkeit verantwortlich für das Auftreten von Rückfällen.

In diesem Zusammenhang ist es erwähnenswert, daß sich in klinischen Studien gezeigt hat, daß insbesondere die Kombination von Nikotin mit einem Antidepressivum die Erfolgsraten bei der Raucherentwöhnung verbessern kann.
Allerdings ist die unterstützende Verabreichung von Psychopharmaka wegen des Nebenwirkungsrisikos und der Gefahr von Über- bzw. Unterdosierungen nicht unproblematisch.

Die Kombination von Nikotin oder nikotinerg wirkender Stoffe mit einem Antidepressivum in einer Arzneimittelform ist deshalb wünschenswert, da so die Einnahme für den Patienten erleichtert und auch das Risiko fehlerhafter Anwendungen minimiert wird.

Weil Raucher in vielen Situationen des täglichen Lebens das Bedürfnis nach einer Zigarette haben, sollte für diese Art der Therapie eine Applikationsform gewählt werden, die eine einfache und unauffällige Applikation gewährleistet und möglichst nicht an die klassische Arzneiform Tablette erinnert, da die Raucherentwöhnung keine Krankheit im klassischen Sinn darstellt, so daß sichergestellt ist, daß die Darreichungsform eine gute Compliance aufweist.

Zudem sollte die Verabreichung an den Patienten so einfach wie möglich erfolgen und der Patient keine Vorbehalte gegen

die Einnahme der Medikation, z.B. aufgrund der Größe der Darreichungsform oder dergleichen haben. Die Nachteile bekannter Darreichungsformen sollten dabei vermieden werden.

Es war deshalb die Aufgabe der vorliegenden Erfindung, Nikotinhaltige pharmazeutische Darreichungsformen bereitzustellen, die gleichzeitig die Verabreichung eines zusätzlichen Wirkstoffs, vorzugsweise eines Antidepressivums, zur Bekämpfung der psychischen Abhängigkeit im Rahmen einer Raucherentwöhnungs-Therapie ermöglichen. Bei der Verabreichung dieses zusätzlichen Wirkstoffs sollten Nebenwirkungen weitgehend ausgeschlossen werden, und die Anwendung sollte für den Patienten auf einfache und zuverlässige Weise erfolgen können.

Es hat sich gezeigt, daß diese Aufgabe durch flächenförmige Darreichungsformen aus einem hydrophilen Polymerfilm, der in der Mundhöhle zerfällt, gelöst wird, in den mindestens zwei Wirkstoffe eingearbeitet sind, wobei mindestens einer der Wirkstoffe Nikotin, ein Nikotinsalz, ein Nikotinderivat oder ein Stoff mit nikotinerger Wirkung ist, und mindestens ein weiterer Wirkstoff enthalten ist, wobei dieser weitere Wirkstoff zur Gruppe der psychisch wirksamen Substanzen gehört.

Demgemäß enthalten die erfindungsgemäßen Darreichungsformen eine Kombination des Wirkstoffs Nikotin, oder eines Nikotinsalzes, eines Nikotinderivates oder eines Stoffes mit nikotinerger Wirkung, zusammenfassend auch als nikotinerge Wirkstoffe bezeichnet, mit mindestens einem weiteren auf das zentrale Nervensystem wirkenden Stoff.

Die Kombination der Wirkstoffe in der erfindungsgemäßen Darreichungsform erleichtert dem Patienten die Einnahme beider Wirkstoffe.

Zudem wird das Risiko von Medikationsfehlern verringert, da der Patient nur ein Medikament für beide Wirkstoffe einnehmen muss. Dadurch werden Compliance und Therapieerfolg verbessert.

Infolge der Möglichkeit der direkten Resorption bestimmter Wirkstoffe über die Schleimhaut wird außerdem die Zeit bis zum Wirkungseintritt deutlich verringert, so daß der Patient innerhalb kürzester Zeit eine Linderung der Entzugssymptome spürt.

Durch die Kombination nikotinerg wirkender Substanzen, zu denen selbstverständlich auch Nikotin, Nikotinsalze und Nikotinderivate zählen, mit einem zentral wirkenden Wirkstoff, z.B. einem Antidepressivum, können sowohl die physischen als auch die psychischen Entzugserscheinungen wirksam unterdrückt werden. Darüber hinaus bietet die erfindungsgemäße Darreichungsform gegenüber den TTS den Vorteil, daß die Wirkstoffe so gering dosiert werden können, daß der unter Entzug Leidende immer dann, wenn er zur Zigarette greifen würde, eine Darreichungsform appliziert. Auf diese Weise wird auch der Drang, etwas aktiv gegen den Entzug zu unternehmen, der sich unter normalen Umständen im Anzünden einer Zigarette manifestiert, befriedigt. Die Befriedigung dieses Dranges ist bei der Raucherentwöhnung eine nicht zu unterschätzende Komponente, da das Rauchen nicht nur mit

der Aufrechterhaltung des Nikotinspiegels, sondern auch immer mit einer als entspannend empfundenen Tätigkeit verbunden war.

Darüber hinaus werden bei Applikation des Wafers Konzentrationsspitzen von Nikotin im Blut erzeugt, so daß im Gegensatz zur kontinuierlichen Abgabe von Nikotin aus einem TTS mit einem konstanten Plasmaspiegel ein dem Rauchen analoger Konzentrationsverlauf erhalten wird.

Um die Applikation der Darreichungsform zusätzlich mit einem Belohnungseffekt zu verbinden, können dieser besonders angenehm empfundene Geschmacks- oder Aromastoffe zugesetzt sein.

Da die Applikation der Darreichungsform die Entzugssymptome unterdrückt und die Stimmung verbessert, kann eine gute Compliance und eine optimale Wirksamkeit gewährleistet werden.

Die Verabreichung dieser Wirkstoffkombinationen in flächenförmigen Darreichungsformen (Wafern) ermöglicht nicht nur, wie bereits dargelegt, eine einfache Einnahme, sondern auch eine exakte Abstimmung der Wirkstoffkomponenten untereinander, so daß Fehldosierungen durch vergessenene oder doppelte Einnahme nur eines Wirkstoffs und somit eine unzureichende Therapie einer Suchtkomponente unterbleiben.

Durch die Variation des Verhältnisses der Wirkstoffe zueinander können zudem die Dosierungen an die jeweiligen Bedürfnisse angepaßt werden. So kann z.B. der Nikotingehalt

im Laufe der Entwöhnung langsam gesenkt werden, so daß sich die Zahl nikotinerger Acetylcholinrezeptoren wieder den normalen physiologischen Gegebenheiten anpaßt. Ebenso können die zur Unterdrückung der psychischen Abhängigkeit gegebenen Antidepressiva ausschleichend dosiert werden.

Aufgrund der einfachen und kostengünstigen Herstellung der Wafer ist es möglich, eine große Anzahl von Arzneimitteln mit unterschiedlichen Wirkstoffkonzentrationen bereitzustellen.
Ist der Wafer aus einem Laminat aufgebaut, so kann bei der Herstellung z.B. nur die Schichtdicke einer wirkstoffhaltigen Schicht oder die Konzentration des Wirkstoffes verändert werden.
Andererseits können Arzneimittel mit unterschiedlichem Wirkstoffgehalt aber gleichem Wirkstoffverhältnis einfach über unterschiedliche Flächenzuschnitte der Darreichungsform hergestellt werden.

Darüber hinaus können die erfindungsgemäßen Wafer mit den Wirkstoffkombinationen aufgrund ihrer flachen Form leicht mitgeführt werden, z.B. in der Brieftasche, und sind auch unterwegs sofort verfügbar und einfach einzunehmen.

Als wasserlösliche oder quellfähige Polymere für den hydrophilen wasserlösliche und/oder quellfähige Polymerfilm eignen sich als Grundpolymer Polymere aus der Gruppe, die Dextran, Polysaccharide, einschließlich der Stärke und Stärkederivate, Cellulosederivate, wie Carboxymethylcellulose, Ethyl- oder Propylcellulose, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Natrium-Carboxymethyl-

cellulose (z. B. Walocel), Methylcellulose, Hydroxyethylcellulose und Hydroxypropylethylcellulose, Polyvinylalkohole, Polyethylenglykole, Polyacrylsäuren, Polyacrylate, Polyvinylpyrrolidone, Alginate, Pektine, Gelatine, Alginsäure, Kollagen, Chitosan, Arabinogalactan, Galactomannan, Agar-Agar, Agarose, Carrageen natürliche Gummen, Tragant, hochdisperses Siliziumdioxid, Bentonit, sowie Derivate der vorgenannten hydrophilen Polymere bzw. Kombinationen aus zwei oder mehreren dieser Polymere umfaßt. Alternativ kann der Polymerfilm auch aus einem Polyvinylalkohol-Polyethylenglycol-Pfropfcopolymer hergestellt sein.

Der Polymeranteil an einer erfindungsgemäßen Darreichungsform beträgt vorzugsweise 5 bis 95 Gew.-%, besonders bevorzugt 15 bis 75 Gew.-%, bezogen auf die Trockenmasse der Darreichungsform.

Bei dem in den erfindungsgemäßen Darreichungsformen zusätzlich zu Nikotin enthaltenen, auf das zentrale Nervensystem wirkenden Stoff handelt es sich vorzugsweise um einen Wirkstoff aus der Gruppe der Psychopharmaka, welche die Wirkstoffgruppen der Antidepressiva, Tranquilizer, Nootropika, Neuroleptika, Psychotonika oder Psychomimetika umfaßt.

Besonders bevorzugt sind dabei Wirkstoffe aus der Gruppe der Antidepressiva, da sie sich hinsichtlich der Überwindung der psychischen Abhängigkeit als sehr geeignet erwiesen haben. Die Erfindung umfaßt ferner auch nikotinhaltige Darreichungsformen der genannten Art, welche zwei oder mehrere Psychopharmaka aus den genannten Wirkstoffgruppen als zusätzliche Wirkstoffe enthalten.

Insbesondere kann der zusätzliche, auf das Zentralnervensystem wirkende Stoff ausgewählt sein aus der Gruppe, die Phenothiazine, Azaphenothiazine, Thioxanthene, Butyrophenone, Diphenylbutylpiperidine, Iminodibenzylderivate, Iminostilbenderivate, Dibenzocycloheptadienderivate, Dibenzodiazepinderivate, Dibenzoxepinderivate, Benzodiazepine, Indolderivate, Phenylethylaminderivate und Hypericinderivate sowie pharmazeutisch akzeptable Salze oder Derivate dieser Verbindungen umfaßt, wobei der Wirkstoff aus der Gruppe, die Chlorpromazin, Perphenazin, Sulpirid, Clozapin, Risperidon, Reserpin, Lorazepam, Mirtazapin, Maprotilin, Mianserin, Tranylcypromin, Moclobemid, Oxitriptan, Viloxazin, Reboxetin, Meprobamat, Hydroxyzin, Buspiron, Coffein, Fenetyllin, Methylphenidat, Prolintan, Fenfluramin, Meclofenoxat, Nicergolin, Piracetam, Pyritinol sowie pharmazeutisch akzeptable Salze dieser Wirkstoffe umfaßt, ausgewählt ist.

Bevorzugt werden Brotizolam, Triazolam und Buprion als Antidepressiva eingesetzt.

Als Nikotinsalze bzw. Nikotinderivate können in den erfindungsgemäßen Darreichungsformen vorzugsweise Nikotinhydrochlorid, Nikotindihydrochlorid, Nikotinsulfat, Nikotinbitartrat, Nikotin-Zinkchlorid und Nikotinsalicylat eingesetzt werden, entweder einzeln oder in Kombination, oder auch in Kombination mit Nikotin.

Als Substanzen mit nikotinerger Wirkung, d. h. Substanzen mit Wirkung am Nikotin-Rezeptor, werden neben Nikotin

selbst bevorzugt Lobelin, Succinylcholin und andere periphere Muskelrelaxantien eingesetzt.

Die für eine Behandlung der psychischen Abhängigkeit geeigneten Wirkstoffdosen und Plasmaspiegel sind dem Fachmann bekannt. Vorzugsweise wird die Dosis des auf das Zentralnervensystem wirkenden Stoffes auf die in der Darreichungsform vorhandene Nikotindosis abgestimmt, derartig, daß beide Wirkstoffe möglichst den jeweils therapeutisch günstigen Plasmaspiegel aufbauen.

In einer bevorzugten Darreichungsform enthält die erfindungsgemäße Arzneimittelzubereitung eine Kombination aus zwei Wirkstoffen, nämlich Nikotin, einem Nikotinsalz, einem Nikotinderivat oder einem Stoff mit nikotinerger Wirkung, sowie als weitere Wirkstoffkomponente zusätzlich einen auf das Zentralnervensystem wirkenden Stoff, welcher aus den oben genannten Stoffen oder Stoffgruppen ausgewählt werden kann.

In einer anderen Ausführungsform enthält die Arzneimittelzubereitung zwei nikotinerge Wirkstoffe, wobei diese auch Nikotin, ein Nikotinsalz oder ein Nikotinderivat sein können, und einen der vorhergehend definierten zentral wirkenden Stoffe, wobei die maximale Anzahl der kombinierten Wirkstoffe fünf nicht überschreitet.

In einer anderen Ausführungsform enthält die Arzneimittelzubereitung einen nikotinergen Wirkstoff, wobei dieser auch Nikotin, ein Nikotinsalz oder ein Nikotinderivat sein kann, und mindestens zwei der vorhergehend definierten zentral

wirkenden Stoffe, wobei die maximale Anzahl der kombinierten Wirkstoffe fünf nicht überschreitet.

Die erfindungsgemäßen Darreichungsformen ermöglichen nicht nur eine Nikotinsubstitution, sondern sie gestatten gleichzeitig eine Behandlung der psychischen Abhängigkeitskomponente der Nikotinsucht.

Zur Verbesserung der physiko-chemischen Eigenschaften, z.B. Verringerung der Brüchigkeit oder Versprödung, können dem Film Feuchthaltemittel zugesetzt sein, wie z.B. Glycerin, Propylenglycol, Sorbitol, Mannitol, Polyethylenglycol, Polyglycerinester und dergleichen.

In einer weiteren Ausführungsform können dem Wafer zur Stabilisierung des Films und der Wirkstoffe Antioxidantien zugesetzt sein, z.B. Vitamin C (Ascorbinsäure), Ascorbylpalmitat, Vitamin E (Tocopherolacetat), Hydroxybenzoesäurederivate. Weiterhin können auch saure und basische Ionentauscher als Stabilisatoren verwendet werden.

In weiteren Ausführungsformen können dem Film weitere Inhaltsstoffe wie Farbstoffe, Pigmente, Geschmacksstoffe, natürliche und/oder synthetische Aromastoffe, Süßstoffe, puffernde Systeme zugesetzt sein. Insbesondere Geschmacks- und Aromastoffe können dabei den oft schlechten Eigengeschmack oder Geruch der Wirkstoffe überdecken und/oder der Darreichungsform einen angenehmen Geschmack verleihen, so daß die Bereitschaft zur Einnahme der Medikation durch den Patienten deutlich verbessert wird.

Der Zusatz von puffernden Systemen dient zum einen der Stabilisierung des Films und der Wirkstoffe gegen äußere Einflüsse und bei der Lagerung, zum anderen kann so der pH-Wert der Darreichungsform auf einen physiologisch akzeptablen pH-Wert eingestellt werden, so daß Schleimhautreizungen vermieden werden. Durch ein Puffersystem kann auch die Löslichkeit von aciden oder basischen Wirkstoffen in der Matrix verbessert werden.

Die erfindungsgemäßen Darreichungsformen sind dünn, beispielsweise in Form einer Oblate gestaltet. Die Dicke der Darreichungsform beträgt vorzugsweise 0,1 bis 5 mm, besonders bevorzugt 0,5 bis 1 mm. Die untere Grenze für die Dicke der Darreichungsformen liegt bei etwa 50 µm. Die Fläche der Darreichungsform beträgt dabei zwischen 0,09 cm^2 und 12 cm^2, bevorzugt zwischen 1 cm^2 und 8 cm^2, und besonders bevorzugt zwischen 3 cm^2 und 6 cm^2.

In einer weiteren Ausführungsform enthalten die Wafer der vorliegenden Erfindung ein Sprengmittel oder ein Dochtmittel, z.B. ein Bicarbonat-Säure-Gemisch oder ein Aerosil, daß durch Kontakt mit Flüssigkeit aktiviert wird und den Zerfall des Wafers nach Applikation und somit auch die Wirkstofffreisetzung beschleunigt.

In einer bevorzugten Ausführungsform liegt der Wafer als Schaum vor, so daß die Wirkstoffabgabe aufgrund der vergrößerten Oberfläche noch schneller erfolgt. Hierbei können in den Hohlräumen des Schaums auch einer oder mehrere der Wirkstoffe in flüssiger Form vorliegen.

Zur Verbesserung der Resorption der Wirkstoffe durch die Schleimhaut können in dem Film auch Permeationsförderer, z.B. Stoffe aus den Gruppen der Fettalkohole, Fettsäuren, Polyoxyethylenfettalkoholether, Polyoxyethylenfettsäureester, Fettalkoholester und Fettsäureester, insbesondere Sorbitanmonolaurat oder Ester von langkettigen Fettsäuren mit Methyl-, Ethyl- oder Isopropylalkohol, oder Ester von Fettalkoholen mit Essigsäure oder Milchsäure, oder auch Stoffe wie DMSO (Dimethylsulfoxid) und Ölsäurediethanolamin zugesetzt sein. Der Mengenanteil dieser Stoffe beträgt 0,1 bis 25 Gew.-%, vorzugsweise von 1 bis 10 Gew.-%, jeweils bezogen auf das Gesamtgewicht der Wirkstoffmatrix.

Darüber hinaus können in der Zusammensetzung des Wafers Verbindungen enthalten sein, die die Wirkstofffreisetzung verzögern (z.B. Mikroverkapselung).

In einer weiteren Ausführungsform besitzt der Wafer mukoadhäsive Eigenschaften, so daß dieser an der Schleimhaut bis zur vollständigen Auflösung haftet.

In einer bevorzugten Ausführungsform ist mindestens einer der Wirkstoffe an einen Ionentauscher gebunden, so daß das hydrophile Polymer schnell im Mundraum zerfällt, die Freisetzung des Wirkstoffes aber erst verzögert oder bei verändertem pH-Wert, z.B. im Gastrointestinaltrakt erfolgt. Auf diese Weise können Wirkstoffe mit unterschiedlichem Wirk- und Resorptionsmechanismus in einer Darreichungsform verabreicht werden, d.h. mindestens einer der freigesetzten Wirkstoffe wird entweder am Applikationsort resorbiert,

z.B. über die Mundschleimhaut oder er wird weitertransportiert und an einem anderen Ort resorbiert.

Der Wafer kann auch als Laminat mit unterschiedlichen Schichten aufgebaut sein, wobei die Wirkstoffe in diskreten Schichten enthalten sind, die räumlich voneinander getrennt sind und sich in ihrem Aufbau voneinander unterscheiden. Die Wirkstoffe können so an unterschiedlichen Wirkorten oder aber auch verzögert freigesetzt werden, wenn sich die Zerfallszeit der unterschiedlichen Schichten das Wafers unterscheidet.

Ebenso können die Wirkstoffe in Schichten angeordnet sein, die unterschiedlich schnell zerfallen, so daß die gesamte Zubereitung einen Retardeffekt aufweist.

In einer weiteren Ausführungsform kann eine der äußeren Schichten mukoadhäsiv sein, um das Anhaften der Darreichungsform auf der Schleimhaut zu begünstigen und die Wirkstoffresorption über die Schleimhaut durch den direkten Kontakt zu vereinfachen.

Der Zerfall in wäßrigem Medium der erfindungsgemäßen Darreichungsform erfolgt vorzugsweise im Bereich von 1 s bis 5 min, stärker bevorzugt im Bereich von 5 s bis 1 min, und am meisten bevorzugt im Bereich von 10 s bis 30 s.

Die erfindungsgemäßen Darreichungsformen eignen sich in vorteilhafter Weise für die Verabreichung von Medikamenten in der Mundhöhle oder zur rektalen, vaginalen oder intra-

nasalen Verabreichung. Sie können in der Humanmedizin wie auch in der Veterinärmedizin eingesetzt werden.

Die vorliegende Erfindung ist weiterhin auf die Verwendung einer der erfindungsgemäßen Wirkstoffkombination zur Herstellung einer oralen Darreichungsform zur Raucherentwöhnung gerichtet, wobei die Darreichungsform bevorzugt als Wafer formuliert wird.

Weiterhin ist die vorliegende Erfindung auf ein Verfahren zur therapeutischen Raucherentwöhnung gerichtet, wobei die Verabreichung einer zuvor beschriebenen Wirkstoffkombination von Nikotin und zentral wirkendem Stoff mittels einer oral applizierbaren Darreichungsform mit transmukosaler Resorption erfolgt.

Schließlich ist die vorliegende Erfindung auch auf ein Verfahren zur Herstellung einer flächenförmigen Darreichungsform gerichtet, das die folgenden Schritte umfaßt:

- Herstellen einer Lösung, die zumindest ein Polymer und mindestens zwei Wirkstoffe, von denen einer Nikotin, ein Nikotinsalz, ein Nikotinderivat oder eine nikotinerg wirkende Substanz und der andere ein Psychopharmakon ist, enthält;
- Ausstreichen der Lösung auf eine Beschichtungsunterlage; und
- Verfestigen der ausgestrichenen Lösung durch Trocknen und Entzug des Lösemittels.

Ansprüche

1. Flächenförmige, bei Kontakt mit Feuchtigkeit schnell zerfallende Arzneimittelzubereitung auf Basis hydrophiler Polymere zur Freisetzung einer Wirkstoffkombination zur Raucherentwöhnung, dadurch gekennzeichnet, daß die Arzneimittelzubereitung eine Wirkstoffkombination aus mindestens zwei Wirkstoffen enthält, von denen mindestens einer aus der Gruppe der nikotinergen Wirkstoffe ausgewählt ist.

2. Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die Gruppe der nikotinergen Wirkstoffe Nikotin, Nikotinderivate, die korrespondierenden pharmazeutisch akzeptablen Salze von Nikotin und Nikotinderivaten sowie Verbindungen mit nikotinerger Wirkung umfaßt.

3. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß ein zweiter Wirkstoff aus der Gruppe ausgewählt ist, die die Psychopharmaka umfaßt.

4. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Psychopharmaka aus der Gruppe ausgewählt sind, die die Antidepressiva, Tranquilizer, Nootropika, Neuroleptika, Psychotonika und Psychomimetika umfaßt.

5. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß mindestens einer der Wirkstoffe neben Nikotin aus der Gruppe ausgewählt ist, die Phenothiazine, Azaphenothiazine, Thioxanthene, Butyropheno-

ne, Diphenylbutylpiperidine, Iminodibenzylderivate, Iminostilbenderivate, Dibenzocycloheptadienderivate, Dibenzodiazepinderivate, Dibenzoxepinderivate, Benzodiazepine, Indolderivate, Phenylethylaminderivate und Hypericinderivate sowie pharmazeutisch akzeptable Salze oder Derivate dieser Verbindungen umfaßt.

6. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß mindestens einer der Wirkstoffe neben Nikotin aus der Gruppe ausgewählt ist, die Chlorpromazin, Perphenazin, Sulpirid, Clozapin, Risperidon, Reserpin, Lorazepam, Mirtazapin, Maprotilin, Mianserin, Tranylcypromin, Moclobemid, Oxitriptan, Viloxazin, Reboxetin, Meprobamat, Hydroxyzin, Buspiron, Coffein, Fenetyllin, Methylphenidat, Prolintan, Fenfluramin, Meclofenoxat, Nicergolin, Piracetam, Pyritinol, Brotizolam, Triazolam und Buprion sowie ihre pharmakologisch akzeptablen Salze umfaßt.

7. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Nikotinsalze und Nikotinderivate aus der Gruppe ausgewählt sind, die Nikotinhydrochlorid, Nikotindihydrochlorid, Nikotinsulfat, Nikotinbitartrat, Nikotin-Zinkchlorid und Nikotinsalicylat sowie Kombinationen dieser Verbindungen umfaßt.

8. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Substanzen mit nikotinerger Wirkung aus der Gruppe ausgewählt sind, die Nikotin, Lobelin, Succinylcholin und andere periphere

Muskelrelaxantien sowie Kombinationen dieser Substanzen umfaßt.

9. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer ausgewählt ist aus der Gruppe, die Dextran, Polysaccharide, einschließlich der Stärke und Stärkederivate, Cellulosederivate, wie Carboxymethylcellulose, Ethyl- oder Propylcellulose, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Natrium-Carboxymethylcellulose (z. B. Walocel), Methylcellulose, Hydroxyethylcellulose und Hydroxypropylethylcellulose, Polyvinylalkohole, Polyethylenglykole, Polyacrylsäuren, Polyacrylate, Polyvinylpyrrolidone, Alginate, Pektine, Gelatine, Alginsäure, Kollagen, Chitosan, Arabinogalactan, Galactomannan, Agar-Agar, Agarose, Carrageen natürliche Gummen, Tragant, hochdisperses Siliziumdioxid, Bentonit, sowie Derivate der vorgenannten hydrophilen Polymere bzw. Kombinationen aus zwei oder mehreren dieser Polymere umfaßt.

10. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Polymerfilm aus einem Polyvinylalkohol-Polyethylenglycol-Pfropfcopolymer hergestellt ist.

11. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung ein Feuchthaltemittel, ausgewählt aus der Gruppe, die Glycerin, Propylenglycol, Sorbitol, Mannitol, Polyethylenglycol und Polyglycerinester umfaßt, enthält.

12. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung ein Antioxidans enthält, ausgewählt aus der Gruppe, die Vitamin C (Ascorbinsäure), Ascorbylpalmitat, Vitamin E (Tocopherolacetat) und Hydroxybenzoesäurederivate umfaßt.

13. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der Wirkstoff der Zubereitung zur Geschmacksmaskierung an einen sauren oder basischen Ionentauscher gebunden ist.

14. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung Farbstoffe und/oder Pigmente enthält.

15. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung natürliche und/oder synthetische Aromastoffe enthält.

16. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung ein Sprengmittel oder Dochtmittel enthält.

17. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß der pH-Wert der Zubereitung über ein Puffersystem eingestellt ist.

18. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer in weniger als 5 min, bevorzugt in weniger als 3 min, weiter bevorzugt in weniger als 1 min, und besonders bevor-

zugt in weniger als 30 s nach Applikation im Mundraum zerfällt.

19. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das hydrophile Polymer schnell im Mundraum zerfällt, der Wirkstoff aber an einen Ionentauscher gebunden bleibt, der den Wirkstoff erst im Gastrointestinaltrakt freisetzt.

20. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Wirkstoffe in diskreten Schichten enthalten sind, die räumlich voneinander getrennt sind und sich in ihrem Aufbau voneinander unterscheiden.

21. Arzneimittelzubereitung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Zubereitung als Schaum vorliegt und mindestens einer der Wirkstoffe in flüssiger Form in den Hohlräumen des Schaums vorliegt.

22. Arzneimittelzubereitung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß sie eine Kombination aus einem nikotinergen Wirkstoff und einem Antidepressivum enthält.

23. Verwendung einer Darreichungsform nach einem oder mehreren der Ansprüche 1 bis 22 zur rektalen, vaginalen oder intranasalen Verabreichung von pharmazeutischen Wirkstoffen an Menschen oder Tiere.

24. Verwendung einer Wirkstoffkombination aus nikotinergem Wirkstoff und Psychopharmakon zur Herstellung einer oralen

Darreichungsform nach einem der vorhergehenden Ansprüche zur Raucherentwöhnung.

25. Verwendung einer Wirkstoffkombination aus nikotinergem Wirkstoff und Antidepressivum zur Herstellung einer oralen Darreichungsform nach einem der vorhergehenden Ansprüche zur Raucherentwöhnung.

26. Verwendung nach einem oder mehreren der Ansprüche 23 - 26, dadurch gekennzeichnet, daß das Arzneimittel als Wafer formuliert wird.

27. Verfahren zur therapeutischen Behandlung einer unter Entzugserscheinungen der Raucherentwöhnung leidenden Person, dadurch gekennzeichnet, daß die Verabreichung der Wirkstoffkombination aus nikotinergem Wirkstoff und Psychopharmakon mittels einer oral applizierbaren Darreichungsform mit transmukosaler Resorption erfolgt.

28. Verfahren zur Herstellung einer flächenförmigen Darreichungsform nach einem der Ansprüche 1 bis 22, gekennzeichnet durch das

- Herstellen einer Lösung, die zumindest ein Polymer und mindestens zwei Wirkstoffe enthält, von denen einer Nikotin, ein Nikotinsalz, ein Nikotinderivat oder eine nikotinerg wirkende Substanz und der andere ein Psychopharmakon ist;
- Ausstreichen der Lösung auf eine Beschichtungsunterlage und
- Verfestigen der ausgestrichenen Lösung durch Trocknen und Entzug des Lösemittels.

Electronic Acknowledgement Receipt

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Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Peter R. Munson./Ann Lygas/Matthew V. Grumbling
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	35401-716-201SIDSTransmittal.pdf	307206 4c797a1bb7d9403231052fe0a5230fc3aaba0f29	no	4

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2	Information Disclosure Statement (IDS) Filed (SB/08)	35401-716-201SIDSFiled.pdf	97786 fe553926c453e341db151d2d3b85c8cd2ee85481	no	1
Warnings:					
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3	Foreign Reference	WO05117830A1.pdf	3458643 f9e4c7c7570a2d177faf00589f9616a35e6ec517	no	69
Warnings:					
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4	Foreign Reference	WO06075123A1.pdf	3163073 4795b155f06de8ac30fed88fbb405003623ce55c	no	62
Warnings:					
Information:					
5	Foreign Reference	WO07043057A2.pdf	2735478 432e7fb73cb599cc467605f02fd3aeefe67b4192	no	63
Warnings:					
Information:					
6	Foreign Reference	WO07144081A2.pdf	972848 f7c57d3a69add57e551773d52d3fe419c9172c16	no	25
Warnings:					
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7	NPL Documents	PCTUS0938696SrchRpt.pdf	461286 ca56e311b0d56dff5d897cd074f16c21a03856e7	no	5
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		Total Files Size (in bytes):	11196320		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt et al.	Group Art Unit: 1614
Serial Number: 12/413,439	Examiner: Ardin H. Marschel
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: Administration of Benzodiazepine Compositions	

Certificate of Electronic Filing

I hereby certify that the attached Information Disclosure Statement and all marked attachments are being deposited by Electronic Filing on November 17 2009 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Ann Lygas
Ann Lygas

Date: November 17, 2009

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Sir:

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.

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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:

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D. ☐ *37 CFR §1.97(e).* Statement.

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

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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.

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

-- AND/OR --

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-- AND/OR --

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

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I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.35401-716.201).

Respectfully submitted,

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
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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]
	1.	WO-2005-044234 A2	05-19-2005	Elan Pharma		

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[6]
	2.	WERMELING et al., "Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers," Anesthesia & Analgesia 103(2):344-349 (2006)	
	3.	EP08747813 Supplementary Search Report dated June 2, 2010	

Examiner Signature		Date Considered	

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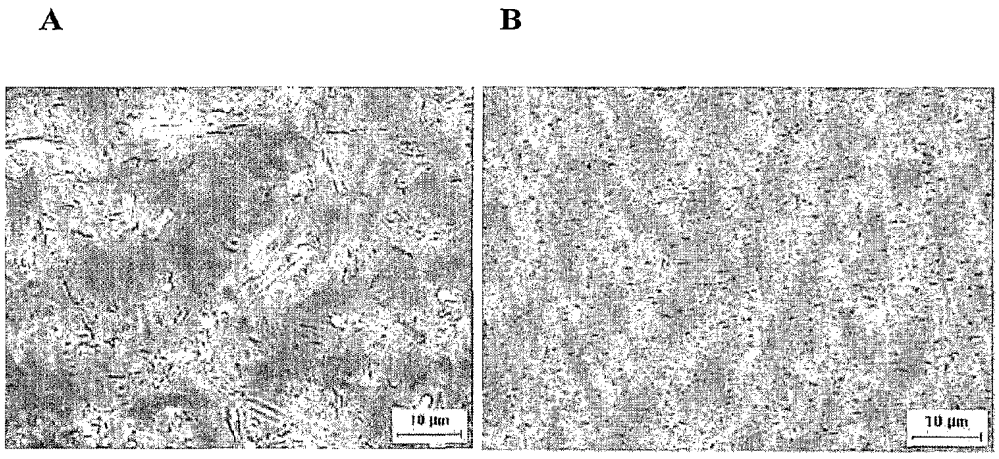
(54) Title: NANOPARTICULATE COMPOSITIONS HAVING A PEPTIDE AS A SURFACE STABILIZER



(57) Abstract: The present invention is directed to nanoparticulate active agent compositions comprising at least one peptide as a surface stabilizer. Also encompassed by the invention are pharmaceutical compositions comprising a nanoparticulate active agent composition of the invention and methods of making and using such nanoparticulate and pharmaceutical compositions.

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CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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NANOPARTICULATE COMPOSITIONS HAVING A PEPTIDE AS A SURFACE STABILIZER

FIELD OF THE INVENTION

The present invention is directed to nanoparticulate active agent compositions having a peptide adsorbed onto or associated with the surface of the active agent as a surface stabilizer, and methods of making and using such compositions.

BACKGROUND OF THE INVENTION

Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto, or associated with, the surface thereof a non-crosslinked surface stabilizer. The '684 patent describes the use of a variety of surface stabilizers for nanoparticulate compositions. The use of a peptide as a surface stabilizer for nanoparticulate active agent compositions is not described by the '684 patent.

The '684 patent describes a method of screening active agents to identify useful surface stabilizers that enable the production of a nanoparticulate composition. Not all surface stabilizers will function to produce a stable, non-agglomerated nanoparticulate composition for all active agents. Moreover, known surface stabilizers may be unable to produce a stable, non-agglomerated nanoparticulate composition for certain active agents. Thus, there is a need in the art to identify new surface stabilizers useful in making nanoparticulate active agent compositions. Additionally, such new surface stabilizers may have superior properties over prior known surface stabilizers.

Methods of making nanoparticulate active agent compositions are described, for example, in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool

and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making

Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," Patent No. 6,582,285 for "Apparatus for Sanitary Wet Milling;" 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,742,734 for "System and Method for Milling Materials," and 6,745,962 for "Small Scale Mill and Method Thereof," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate active agent compositions, and are specifically incorporated by reference. None of these references describe nanoparticulate active agent compositions comprising a peptide surface stabilizer.

Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated

Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

There is a need in the art for new surface stabilizers useful in preparing nanoparticulate active agent compositions. The present invention satisfies this need.

SUMMARY OF THE INVENTION

The present invention is directed to nanoparticulate compositions comprising at least one active agent and at least one peptide as a surface stabilizer adsorbed on to, or associated with, the surface of the active agent.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate active agent composition of the invention. The pharmaceutical compositions preferably comprise at least one active agent, at least one peptide, and a pharmaceutically acceptable carrier, as well as any desired excipients.

In yet another embodiment, the invention is directed to bioadhesive nanoparticulate active agent compositions comprising at least one cationic peptide as a surface stabilizer, or at least one non-cationic peptide surface stabilizer in combination with at least one secondary cationic surface stabilizer. Such compositions can coat the gut, or the desired site of application, and be retained for a period of time, thereby increasing the efficacy of the active agent as well as eliminating or decreasing the frequency of dosing.

This invention further discloses a method of making a nanoparticulate active agent composition having a peptide surface stabilizer adsorbed on or associated with the surface of the active agent. Such a method comprises contacting an active agent with at least one peptide for a time and under conditions sufficient to provide a Nanoparticle active agent/peptide composition. The peptide surface stabilizer can be contacted with the active agent either before, preferably during, or after size reduction of the active agent.

The present invention is further directed to a method of treatment comprising administering to a mammal a therapeutically effective amount of a nanoparticulate active agent/peptide composition according to the invention.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: Shows representative photomicrographs of nystatin crystals before (Fig. 1A) and after (Fig. 1B) milling;

FIGURE 2: Shows the results of monitoring the particle size stability over time at 5°C (solid line), 25°C (dashed line), and 40°C (dotted line) for a nanoparticulate nystatin composition comprising the peptide poly(Lysine, Tryptophan) 4:1 hydrobromide as a surface stabilizer; and

FIGURE 3: Shows representative micrographs of cells with anionic particles (Fig. 3A) and cationic particles (Fig. 3B).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compositions comprising nanoparticulate active agents having at least one peptide as a surface stabilizer adsorbed on or associated with the surface thereof, and methods of making and using such nanoparticulate compositions.

As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. The discovery of the present invention is surprising in that peptides are biological compounds having secondary and tertiary structures which are critical to the activity of the peptide. It was surprising that such a compound could be successfully used to stabilize a

nanoparticulate active agent. Moreover, it was even more surprising that milling of a peptide surface stabilizer did not change the activity or function of the peptide.

A "peptide" is defined as any compound consisting of two or more amino acids where the alpha carboxyl group of one is bound to the alpha amino group of another. A polypeptide is a long peptide chain. A protein is a large macromolecule composed of one or more polypeptide chains. In the context of the present invention, "peptide" refers to a peptide or a polypeptide, but not a protein.

A striking characteristic of peptides is that they have well-defined three dimensional structures. Peptides fold into compact structures with nominal bond lengths. The strong tendency of hydrophobic amino acid residues to flee from water drives the folding of soluble peptides.

A stretched-out or randomly arranged polypeptide chain is devoid of biological activity. This is because the function of a peptide arises from conformation, which is the three dimensional arrangement of atoms in a structure. *See e.g.*, L. Stryer, *Biochemistry,* 3rd Edition, p. 1-41 (W.H. Freeman & Co., NY, 1988). Amino acid sequences are important because they specify the conformation of peptides. *Id.*

Peptides have several different defined structures, including a primary, secondary, and tertiary structure. The primary structure of a peptide is generally the amino acid sequence of the peptide and the location of disulfides. *See e.g.*, L. Stryer, *Biochemistry,* 3rd Edition, p. 31 (W.H. Freeman & Co., NY, 1988). Secondary structure refers to the spatial arrangement of amino acid residues that are near one another in the linear sequence. Examples of these steric relationships are structures known as an alpha helix, a beta pleated sheet, and a collagen helix. *Id.* Tertiary structure refers to the spatial arrangement of amino acid residues in a peptide or polypeptide that are far apart in the linear sequence.

Proteins, comprising multiple polypeptide chains, also have a quaternary structure, which refers to the spatial arrangement of the polypeptide subunits and the nature of their contacts. *Id.*

It was very surprising that such complex compounds as peptides and polypeptides could be successfully utilized as a surface stabilizer for a nanoparticulate active agent. In addition to enabling the use of a new class of surface stabilizers for nanoparticulate active agents, this discovery is significant as the peptide surface stabilizer in the compositions of the invention may also have therapeutic or diagnostic properties. This is in contrast to prior art nanoparticulate active agent compositions, in which the surface stabilizer is generally a surfactant, which lacks such therapeutic or diagnostic properties.

The nanoparticulate active agent compositions of the invention may also offer the following advantages as compared to prior conventional or non-nanoparticulate active agent compositions: (1) faster onset of action; (2) a potential decrease in the frequency of dosing; (3) smaller doses of active agent required to obtain the same pharmacological effect; (4) increased bioavailability; (5) an increased rate of dissolution; (6) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher active agent dose loading and smaller tablet or liquid dose volumes; (7) improved pharmacokinetic profiles, such as improved T_{max}, C_{max}, and AUC profiles; (8) substantially similar or bioequivalent pharmacokinetic profiles of the nanoparticulate active agent compositions when administered in the fed versus the fasted state; (9) bioadhesive active agent compositions, which can coat the gut or the desired site of application and be retained for a period of time, thereby increasing the efficacy of the active agent as well as eliminating or decreasing the frequency of dosing; (10) high redispersibility of the nanoparticulate active agent particles present in the compositions of the invention following administration; (11) the nanoparticulate active agent compositions can be formulated in a dried form which readily redisperses; (12) low viscosity liquid nanoparticulate active agent dosage forms can be made; (13) for liquid nanoparticulate active agent compositions having a low viscosity - better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (14) for liquid nanoparticulate active agent compositions having a low viscosity - ease of dispensing because one can use a cup or a syringe; (15) the nanoparticulate active

agent compositions can be used in conjunction with other active agents; (16) the nanoparticulate active agent compositions can be sterile filtered; (17) the nanoparticulate active agent compositions are suitable for parenteral administration; and (18) the nanoparticulate active agent compositions do not require organic solvents or pH extremes.

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, granules, liquid dispersions, oral suspensions, gels, aerosols (including nasal and pulmonary), ointments, and creams.

The dosage form of the invention can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof.

In addition, the compositions of the invention can be formulated for any suitable administration route, such as oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, or topical administration.

The present invention is described herein using several definitions, as set forth below and throughout the application.

As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

"Conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2 microns. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2 microns.

"Pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salts" as used herein refers to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

"Poorly water soluble drugs" as used herein means those having a solubility of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml. Such drugs tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation.

As used herein with reference to stable drug particles, "stable" includes, but is not limited to, one or more of the following parameters: (1) that the active agent particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the active agent particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the active agent

particles are chemically stable; and/or (4) where the active agent has not been subject to a heating step at or above the melting point of the active agent in the preparation of the nanoparticles of the invention.

"Therapeutically effective amount" as used herein with respect to an active agent dosage, shall mean that dosage that provides the specific pharmacological response for which the active agent is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that active agent dosages are, in particular instances, measured as oral dosages, or with reference to active agent levels as measured in blood.

I. Preferred Characteristics of the Nanoparticulate Active Agent Compositions of the Invention

A. Increased Bioavailability, Frequency of Dosing, and Dosage Quantity

The nanoparticulate active agent compositions of the invention, having at least one peptide as a surface stabilizer, may preferably exhibit increased bioavailability and require smaller doses as compared to prior non-nanoparticulate compositions of the same active agent administered at the same dose.

Any active agent can have adverse side effects. Thus, lower doses of an active agent that can achieve the same or better therapeutic effects as those observed with larger doses of a non-nanoparticulate composition of the same active agent are desired. Such lower doses may be realized with the nanoparticulate active agent compositions of the invention because the nanoparticulate active agent compositions may exhibit greater bioavailability as compared to non-nanoparticulate compositions of the same active agent, which means that smaller doses of the active agent are likely required to obtain the desired therapeutic effect.

The nanoparticulate active agent compositions of the invention may be administered less frequently and at lower doses, as compared to conventional non-nanoparticulate compositions of the same active agent, in dosage forms such as liquid dispersions, powders, sprays, aerosols (pulmonary and nasal), solid re-dispersable dosage forms, gels, ointments, creams, *etc.* of the nanoparticulate active agent. Lower dosages can be used because the small particle size of the active agent particles ensure greater absorption, and in the case of bioadhesive nanoparticulate active agent compositions, the active agent is retained at the desired site of application for a longer period of time as compared to conventional, non-nanoparticulate active agent dosage forms.

In one embodiment of the invention, the therapeutically effective amount of the nanoparticulate active agent compositions is 1/6, 1/5, ¼, 1/3rd, or ½ of the therapeutically effective amount of a non-nanoparticulate composition of the same active agent.

Such lower doses are preferred as they may decrease or eliminate adverse effects of the active agent. In addition, such lower doses decrease the cost of the dosage form and may increase patient compliance.

B. Pharmacokinetic Profiles of the Nanoparticulate Active Agent Compositions of the Invention

The invention also preferably provides nanoparticulate active agent compositions, having at least one peptide as a surface stabilizer, and having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the active agent compositions preferably includes, but is not limited to: (1) a T_{max} for an active agent, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate composition of the same active agent, administered at the same dosage; (2) a C_{max} for an active agent, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate composition of the same active agent, administered at the same dosage; and/or (3) an AUC for an active agent, when assayed in the plasma of a

mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate composition of the same active agent, administered at the same dosage.

The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of the active agent. The compositions can be formulated in any way as described herein and as known to those of skill in the art.

A preferred active agent composition of the invention, comprising at least one peptide as a surface stabilizer, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same active agent, administered at the same dosage, a T_{max} not greater than about 100%, not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 40%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} exhibited by the non-nanoparticulate active agent composition. This shorter T_{max} translates into a faster onset of therapeutic activity.

A preferred active agent composition of the invention, comprising at least one peptide as a surface stabilizer, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same active agent, administered at the same dosage, a C_{max} which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 110%, at least about 120%, at least about 130%, at least about 140%, at least about 150%, at least about 160%, at least about 170%, at least about 180%, at least about 190%, or at least about 200% greater than the C_{max} exhibited by the non-nanoparticulate active agent composition.

A preferred active agent composition of the invention, comprising at least one peptide as a surface stabilizer, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate composition of the same active agent, administered at the same

dosage, an AUC which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 110%, at least about 120%, at least about 130%, at least about 140%, at least about 150%, at least about 160%, at least about 170%, at least about 180%, at least about 190%, or at least about 200% greater than the AUC exhibited by the non-nanoparticulate active agent formulation.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods.

C. The Pharmacokinetic Profiles of the Nanoparticulate Active Agent Compositions of the Invention are Preferably not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses nanoparticulate active agent compositions, comprising at least one peptide as a surface stabilizer, wherein preferably the pharmacokinetic profile of the active agent is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of active agent absorbed or the rate of active agent absorption when the nanoparticulate active agent compositions are administered in the fed versus the fasted state. Thus, the nanoparticulate active agent compositions of the invention can preferably substantially eliminate the effect of food on the pharmacokinetics of the active agent.

In another embodiment of the invention, the pharmacokinetic profile of the active agent compositions of the invention, comprising at least one peptide as a surface stabilizer, when administered to a mammal in a fasted state, is bioequivalent to the pharmacokinetic profile of the same nanoparticulate active agent composition administered at the same dosage, when administered to a mammal in a fed state.

"Bioequivalency" is preferably established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both C_{max} and AUC under U.S. Food and Drug Administration (USFDA) regulatory guidelines, or a 90% CI for AUC of between

0.80 to 1.25 and a 90% CI for C_{max} of between 0.70 to 1.43 under the European Medicines Evaluation Agency (EMEA) regulatory guidelines (T_{max} is not relevant for bioequivalency determinations under USFDA and EMEA regulatory guidelines).

Preferably the difference in AUC (*e.g.*, absorption) of the nanoparticulate active agent composition of the invention, comprising at least one peptide as a surface stabilizer, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

In addition, preferably the difference in C_{max} of the nanoparticulate active agent composition of the invention, comprising at least one peptide as a surface stabilizer, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

Finally, preferably the difference in the T_{max} of the nanoparticulate active agent compositions of the invention, comprising at least one peptide as a surface stabilizer, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference.

Benefits of a dosage form that substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

D. Redispersibility Profiles of the Nanoparticulate Active Agent Compositions of the Invention

An additional feature of the nanoparticulate active agent compositions of the invention, comprising at least one peptide as a surface stabilizer, comprising at least one peptide as a surface stabilizer, is that the compositions redisperse such that the effective average particle size of the redispersed active agent particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate active agent particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating the active agent into a nanoparticulate particle size.

This is because the nanoparticulate active agent compositions of the invention benefit from the small particle size of the active agent; if the nanoparticulate active agent particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

Moreover, the nanoparticulate active agent compositions of the invention exhibit dramatic redispersion of the active agent particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength

of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

In other embodiments of the invention, the redispersed active agent particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

Redispersibility can be tested using any suitable means known in the art. *See e.g.,* the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

E. Bioadhesive Nanoparticulate Active Agent Compositions

Bioadhesive nanoparticulate active agent compositions of the invention comprise at least one cationic peptide surface stabilizer, or in addition to at least one non-cationic peptide as a surface stabilizer, at least one secondary non-peptide cationic surface stabilizer. Exemplary non-peptide cationic surface stabilizers are described in more detail below. Bioadhesive formulations of active agents exhibit exceptional bioadhesion to biological surfaces, such as mucous and skin.

Cationic surface stabilizers generally confer relatively large, positive zeta potentials to particles on which they adsorb or associate. To increase the bioadhesive properties of a nanoparticulate composition, two or more cationic surface stabilizers can be utilized.

In the case of bioadhesive nanoparticulate active agent compositions, the term "bioadhesion" is used to describe the adhesion between the nanoparticulate active agent compositions and a biological substrate (*i.e.*, gastrointestinal mucin, lung tissue,

nasal mucosa, *etc.*). *See e.g.,* U.S. Patent No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers," which is specifically incorporated by reference.

There are basically two mechanisms which may be responsible for this bioadhesion phenomena: mechanical or physical interactions and chemical interactions. The first of these, mechanical or physical mechanisms, involves the physical interlocking or interpenetration between a bioadhesive entity and the receptor tissue, resulting from a good wetting of the bioadhesive surface, swelling of the bioadhesive polymer, penetration of the bioadhesive entity into a crevice of the tissue surface, or interpenetration of bioadhesive composition chains with those of the mucous or other such related tissues. The second possible mechanism of bioadhesion incorporates forces such as ionic attraction, dipolar forces, van der Waals interactions, and hydrogen bonds. It is this form of bioadhesion which is primarily responsible for the bioadhesive properties of the nanoparticulate active agent compositions of the invention. However, physical and mechanical interactions may also play a secondary role in the bioadhesion of such nanoparticulate active agent compositions.

The bioadhesive active agent compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive active agent compositions preferably coat the targeted surface in a continuous and uniform film that is invisible to the naked human eye.

A bioadhesive nanoparticulate active agent composition slows the transit of the composition, and some active agent particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to the active agent, thereby increasing absorption and the bioavailability of the administered dosage.

The adhesion exhibited by the inventive compositions means that nanoparticulate active agent particles are not easily washed off, rubbed off, or otherwise removed from the biological surface for an extended period of time. The period of time in which a biological cell surface is replaced is the factor that limits

retention of the bioadhesive nanoparticulate active agent particles to that biological surface.

F. Low Viscosity Active Agent Dosage Forms

A liquid dosage form of a conventional microcrystalline or non-nanoparticulate active agent composition would be expected to be a relatively large volume, highly viscous substance which would not be well accepted by patient populations. Moreover, viscous solutions can be problematic in parenteral administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

Liquid dosage forms of the nanoparticulate active agent compositions of the invention, comprising at least one peptide as a surface stabilizer, provide significant advantages over a liquid dosage form of a conventional microcrystalline or solubilized active agent composition. The low viscosity and silky texture of liquid dosage forms of the nanoparticulate active agent compositions of the invention result in advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of active agent resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

Liquid active agent dosage forms that are easier to consume are especially important when considering juvenile patients, terminally ill patients, and elderly patients. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by these patient populations. Liquid oral dosage forms can be particularly preferably for patient populations who have difficulty consuming tablets, such as infants and the elderly.

The viscosities of liquid dosage forms of a nanoparticulate active agent according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of a liquid oral dosage form of a non-nanoparticulate composition of the same active agent, at about the same concentration per ml of active agent.

Typically liquid nanoparticulate active agent dosage forms of the invention, comprising at least one peptide as a surface stabilizer, have a viscosity at a shear rate of 0.1 (1/s) measured at 20°C, is from about 2000 mPa s to about 1 mPa s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, or from about 5 mPa·s to about 1 mPa·s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

Viscosity is concentration and temperature dependent. Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20°C. (The viscosity of water at 20°C is 1 mPa s.) The invention encompasses equivalent viscosities measured at different temperatures.

Another important aspect of the invention is that the nanoparticulate active agent compositions of the invention, formulated into a liquid dosage form, are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate active agent compositions of the invention, formulated into a liquid dosage form, can be poured out of or extracted from a container as easily as water, whereas a liquid dosage form of a non-nanoparticulate or solubilized composition of the same active agent is expected to exhibit notably more "sluggish" characteristics.

The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than a liquid dosage form of a non-nanoparticulate composition of the same active agent.

G. Sterile Filtered Nanoparticulate Active Agent Compositions

The nanoparticulate active agent compositions of the invention can be sterile filtered. This obviates the need for heat sterilization, which can harm or degrade an active agent, as well as result in crystal growth and particle aggregation of the active agent.

Sterile filtration can be difficult because of the required small particle size of the composition. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize suspensions of micron-sized active agents because the active agent particles are too large to pass through the membrane pores.

A sterile nanoparticulate active agent dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile liquid dosage form.

Because the nanoparticulate active agent compositions of the invention, comprising at least one peptide as a surface stabilizer and formulated into a liquid dosage form, can be sterile filtered, and because the compositions can have a very small active agent effective average particle size, the compositions are suitable for parenteral administration.

H. Combination Pharmacokinetic Profile Compositions

In yet another embodiment of the invention, a first nanoparticulate active agent composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other active agent composition that generates a desired different pharmacokinetic profile. More than two active agent compositions can be co-administered, sequentially administered, or combined. While the first active agent composition has a nanoparticulate particle size, the additional one or more active agent compositions can be nanoparticulate, solubilized, or have a microparticulate particle size.

The second, third, fourth, *etc.*, active agent compositions can differ from the first, and from each other, for example: (1) in the identity of the active agent; (2) in the effective average particle sizes of the active agent; or (3) in the dosage of the active agent. Such a combination composition can reduce the dose frequency required.

For example, a first active agent composition can have a nanoparticulate particle size, conferring a short T_{max} and typically a higher C_{max}. This first active agent composition can be combined, co-administered, or sequentially administered with a second composition comprising: (1) the same active agent having a larger (but still nanoparticulate as defined herein) particle size, and therefore exhibiting slower absorption, a longer T_{max}, and typically a lower C_{max}; or (2) a microparticulate or solubilized composition of the same active agent, exhibiting a longer T_{max}, and typically a lower C_{max}.

If the second active agent composition has a nanoparticulate particle size, then preferably the active agent particles of the second composition have at least one

surface stabilizer associated with the surface of the active agent particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first active agent composition.

Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

I. Miscellaneous Benefits of the Nanoparticulate Active Agent Compositions of the Invention

The nanoparticulate active agent compositions of the invention, comprising at least one peptide as a surface stabilizer, preferably exhibit an increased rate of dissolution as compared to microcrystalline or non-nanoparticulate forms of the same active agent. In addition, the nanoparticulate active agent compositions preferably exhibit improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes. Moreover, the nanoparticulate active agent compositions of the invention do not require organic solvents or pH extremes.

II. Compositions

The compositions of the invention comprise a nanoparticulate active agent and at least one peptide as a surface stabilizer adsorbed to or associated with the surface of the active agent. In addition, the compositions can comprise one or more secondary surface stabilizers. Surface stabilizers useful herein physically adhere to or associate with the surface of the nanoparticulate active agent but do not chemically react with the active agent or itself. Individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The present invention also includes nanoparticulate active agent compositions, having at least one peptide as a surface stabilizer, formulated into compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers.

A. Peptide Surface Stabilizer

The choice of a surface stabilizer is non-trivial and usually requires extensive experimentation to realize a desirable formulation. Accordingly, the present invention is directed to the surprising discovery that a peptide, used as a nanoparticulate surface stabilizer, yields stable nanoparticulate active agent compositions that exhibit low degrees of aggregation.

A "peptide" is defined as any compound consisting of two or more amino acids, which are the basic structural units or "building blocks" of peptides. All peptides in all species, from bacteria to humans, are constructed from the same set of twenty commonly occurring, genetically encoded amino acids, as shown in the table below.

Each amino acid contains an "amine" group (NH_3), a "carboxy" group (COOH), a hydrogen atom, and a distinctive R group, or sidechain, bonded to a carbon atom. The amino acids vary in their sidechains, with variations in size, shape, charge, hydrogen-bonding capacity, and chemical reactivity. *See e.g.*, L. Stryer, *Biochemistry,* 3rd Edition, 1-40 (W.H. Freeman & Co., NY, 1988).

Amino Acid	3 Letter Abbreviation	1 Letter Abbreviation
alanine	ALA	A
asparagine	ASN	N
aspartic acid	ASP	D
arginine	ARG	R
cysteine	CYS	C
glutamic acid	GLU	E
glutamine	GLN	Q
glycine	GLY	G
histidine	HIS	H
isoleucine	ILE	I
leucine	LEU	L

Amino Acid	3 Letter Abbreviation	1 Letter Abbreviation
lysine	LYS	K
methionine	MET	M
phenylalanine	PHE	F
proline	PRO	P
serine	SER	S
threonine	THR	T
tryptophan	TRP	W
tyrosine	TYR	Y
valine	VAL	V
aspartic acid or asparagines	ASX	
glutamic acid or glutamine	GLX	
Unknown or other	Xaa	X

Peptides useful in the present invention can also comprise substituents other than amino acids. There are also naturally occurring chemical modifications of these twenty genetically encoded amino acids, such as hydroxylation of proline, addition of carbohydrates and lipids, and phosphorylation of serine and tyrosine. In addition, D-isomers of the amino acids, as opposed to the L-isomers found in naturally-occuring peptides and proteins, have been synthesized.

The amino acids of a peptide are connected by a amide, covalent linkage between the alpha carboxyl group of one amino acid and the alpha amino group of another amino acid. Many amino acids are joined by peptide bonds to form a polypeptide chain, which is unbranched. A polypeptide chain is a long peptide chain, consisting of a regularly repeating part, called the main chain, and a variable part, comprising the distinctive sidechains. Disulfide cross-links can be formed by cysteine residues in polypeptides. Most natural polypeptide chains contain between 50 and