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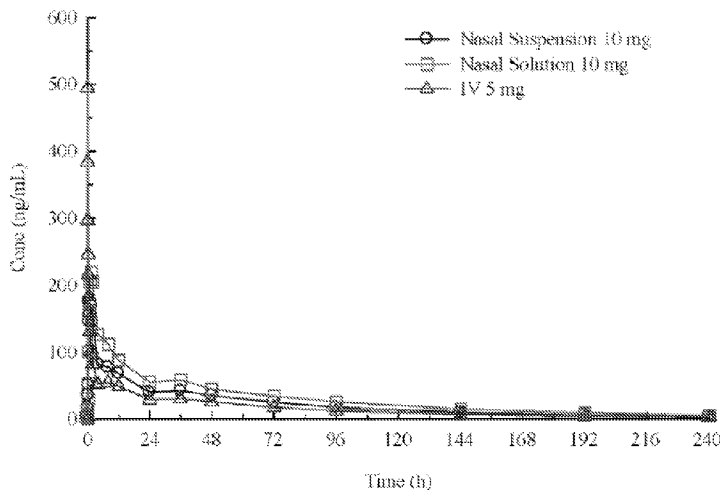
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(54) Title: ADMINISTRATION OF BENZODIAZEPINE

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

FIG. 1

Linear Scale



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ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to United States provisional application 61/497,017, filed June 14, 2011 and United States provisional application 61/570,110, filed December 13, 2011, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

[008] Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful

and is likely impractical for patients suffering from a phobia of needles. In addition, intravenous administration of benzodiazepines is associated with respiratory depression. Thus, use of intravenous benzodiazepines is limited to professional health care environments.

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

SUMMARY OF THE INVENTION

[010] In some embodiments, there are provided (non-aqueous) pharmaceutical solutions for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically-acceptable solution for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to

about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, e.g. about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)).

[011] Some embodiments described herein provide a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 % (w/v) of benzodiazepine, e.g. about 1 to about 20 % (w/v) of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)), or ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some

embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, e.g. about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 % (w/v)), dodecyl maltoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)); more particularly the solution may consist of diazepam (9-11 % (w/v)), dodecyl maltoside (0.1-0.5 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (15-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)); and even more particularly, the solution may consist of diazepam (10 % (w/v)), dodecyl maltoside (0.15-0.3 % (w/v)), vitamin E (50-60 % (w/v)), ethanol (17-20 % (w/v)) and benzyl alcohol (10-12 % (w/v)). In some embodiments, the patient is human. In some embodiments, the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg. In some embodiments, the benzodiazepine is administered as in a dosage volume from about 10 μ L to about 200 μ L. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril. In some embodiments, administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril. In some embodiments, the method further comprises, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril. In some embodiments, nasal administration of the pharmaceutical composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition. In some embodiments, the treatment achieves bioavailability that is from about 80-125% (e.g. about 90-110%, or more particularly about 92.5-107.5%) of that achieved with the same benzodiazepine administered intravenously, e.g. In this context, it is intended that bioavailability be determined by a suitable pharmacodynamic method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (e.g. 10 mg of nasal diazepam) with another dose of the same benzodiazepine administered intravenously (e.g. 5 mg of i.v. diazepam), taking into consideration the difference in dose. Thus, for the sake of illustration, a 10 mg nasal diazepam dose that achieves an AUC that is precisely half of the AUC obtained with 5 mg of i.v. diazepam would have a bioavailability of 100%. In some embodiments, the disorder to be treated is a seizure, such as an epileptic seizure, a breakthrough seizure, or other seizure. In some embodiments, the solution and treatment with the solution are substantially non-irritating and well-tolerated.

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

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

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

[015] In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the glycols

exclude glycol polymers having an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INCORPORATION BY REFERENCE

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

[043] In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil,

flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the benzodiazepine drug comprises benzodiazepine microparticles, nanoparticles, or combinations thereof. In some embodiments, the benzodiazepine nanoparticles have an effective average particle size of less than about 5000 nm. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

[044] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the carrier system includes one or more synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985, which is incorporated herein by reference in its entirety. In particular, it has been found that in some particulate suspensions of benzodiazepines, wherein the benzodiazepine is not dissolved in a tocopherol phase, Vitamin E TPGS can be a desirable excipient for stabilizing the particulate (microparticle, nanoparticle or combination) suspension. In some embodiments, on the other hand, the carrier system specifically excludes synthetic tocopherols having a polymer glycol covalently bonded or linked to a tocopherol core, such as Vitamin E TPGS, which is described in United States Patent No. 6,193,985, which is incorporated herein by reference in its entirety.

[045] In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the alcohol is ethanol (dehydrated, USP). In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the glycol is propylene glycol USP. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

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

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

thereof, in an amount of about 70% (w/w). In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

[048] In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 55%, about 10% to about 40%, about 10% to about 35%, about 12% to about 55%, about 12% to about 40%, about 12% to about 35%, about 15% to about 55%, about 15% to about 40%, about 15% to about 35%, about 10%, about 12.5%, about 15%, about 17.5%, about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5% or about 55% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w). In some embodiments, the carrier system comprises one or more alcohols or glycols, or any combinations thereof, in an amount of about 30% (w/w). In some embodiments, the alcohol is ethanol or contains ethanol. In some preferred embodiments, the glycols exclude glycol polymers. In some preferred embodiments, the glycols exclude glycol polymers having an average molecular weight of greater than 200. In some embodiments, the glycols exclude polyethylene glycol having an average molecular weight of greater than about 200.

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

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

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

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

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

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

[054] In some embodiments, the composition contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol and one or more alcohols or glycols. In some embodiments, substantially all the benzodiazepine drug is in a

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

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

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

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

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

[058] In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocopherols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. A synthetic tocopherol may include a tocopherol that has been modified to include a hydrophilic group, such as a polyethylene glycol group, which may be directly covalently bonded to the tocopherol or may be linked to the tocopherol through a covalent linking group, such as a diacid. An exemplary synthetic tocopherol of this type is Vitamin E Polyethylene Glycol Succinate (Vitamin E TPGS), although the person skilled in the art will be able to envision other synthetic tocopherols that have similar diacid and/or hydrophilic groups.

[059] In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof. In

some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, one or more glycols specifically excludes polymeric glycols, such as polyethylene glycol. In some embodiments, one or more glycols specifically excludes a polymeric glycol having a molecular weight of greater than about 200 g/mol.

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

[061] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w). In some embodiments, especially where particulate suspensions of a benzodiazepine drug are contemplated, the compositions may include a tocopherol, especially a synthetic tocopherol having a hydrophilic group covalently linked to a tocopherol. In other embodiments, especially where a solution of benzodiazepine drug is contemplated, the tocopherol is substantially or completely free of Vitamin E TPGS.

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

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

[064] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is an alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130, which is

incorporated herein by reference in its entirety. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetraose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α - or β -D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

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

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

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

Definitions

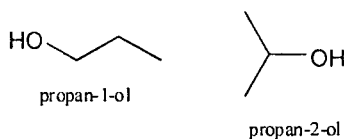
[068] As used herein the phrase "therapeutically effective amount" (or more simply "effective amount") includes an amount sufficient to provide a specific therapeutic response for which the drug is administered to

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

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

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

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



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

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

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

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

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

[077] As used herein, the phrase “consisting essentially of” is a transitional phrase used in a claim to indicate that the a following list of ingredients, parts or process steps must be present in the claimed

composition, machine or process, but that the claim is open to unlisted ingredients, parts or process steps that do not materially affect the basic and novel properties of the invention.

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

Benzodiazepine Drugs

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

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

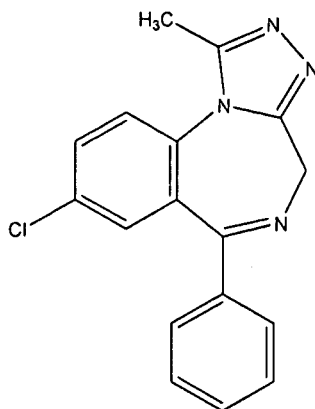
[081] For example, most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. By use of the present carrier system, which in some embodiments, provides an improved ability to dissolve benzodiazepine drugs, the present invention allows benzodiazepine drugs to be administered to one or more mucosal membranes, including to nasal mucosal membranes. This can allow one to administer the drug without hospitalization or unnecessary discomfort. Additionally, in some embodiments of the present invention, such as nasal administration, the digestive system largely may be bypassed. This latter improvement can yield improved bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

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

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

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

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



[086] Alprazolam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic. Alprazolam has also been shown to be useful in the treatment of panic disorder. The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

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

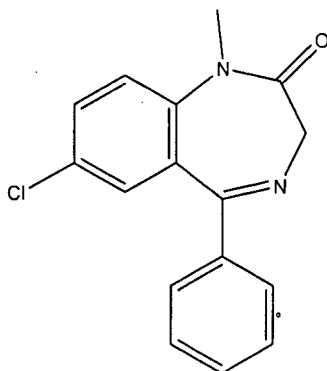
[088] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam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

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

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

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

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



[092] Diazepam is a benzodiazepine drug having sedative, tranquilizing and muscle-relaxing properties. It is classified as an anxiolytic and skeletal muscle relaxant. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties. The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents

3,371,085; 3,109,843; 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

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

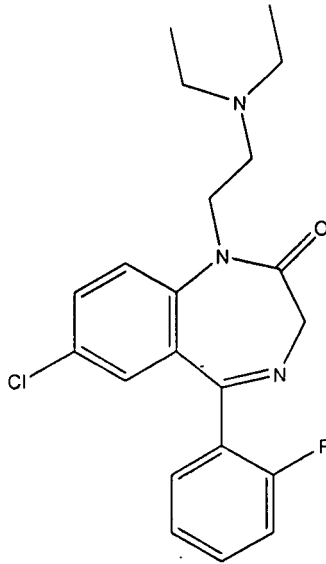
[094] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam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

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

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

seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

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



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

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

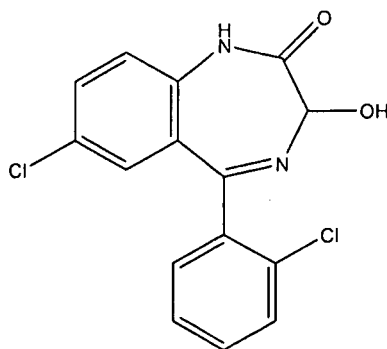
[0100] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of flurazepam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of flurazepam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of flurazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In

addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with flurazepam to provide a synergistic anticonvulsant effect.

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

[0102] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

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



[0104] Lorazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Lorazepam has also been shown to be useful in the treatment of nausea. The dosage of lorazepam varies by indication, however it is expected that a therapeutic

dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249, which is incorporated herein by reference in its entirety.

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

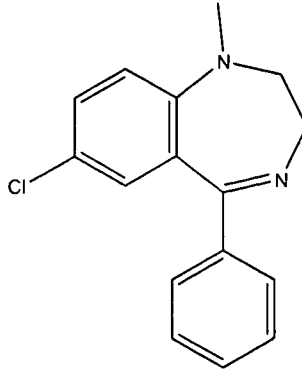
[0106] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam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

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

[0108] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during

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

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



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

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

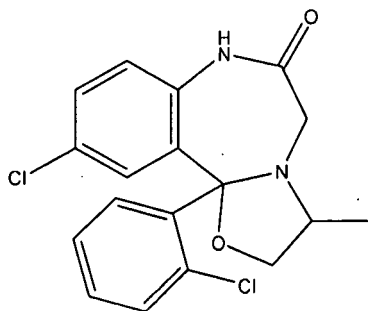
[0112] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam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

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

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

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

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



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

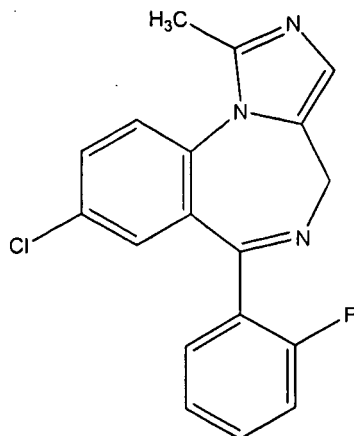
[0117] In some embodiments, mexazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

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

[0119] Mexazolam may also be administered by another person (e.g. an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (e.g. general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the mexazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The mexazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

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

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



[0122] Midazolam is a tricyclic benzodiazepine having anxiolytic, amnesic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. Midazolam is considered soluble in water at a pH lower than about 4, but is relatively insoluble in most aqueous solutions at neutral pH (e.g. about 6 to 8). Thus it is desirable in some embodiments for aqueous nasal preparations of midazolam to have a pH above about 5.5, preferably above about 6.0, or above about 6.5. In some preferred embodiments, the pH is between about 6 and 9, between about 6 and 8. It is considered that preparations of midazolam are particularly suitable for nasal administration as the lipid-soluble (at approximately neutral pH) midazolam is rapidly absorbed across nasal mucosa, leading to efficient uptake of midazolam. It is further considered that midazolam may be formulated in a non-aqueous delivery vehicle, such as is known in the aerosol administration art, such as hydrofluorocarbon propellants, hydrocarbon propellants, etc.

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

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

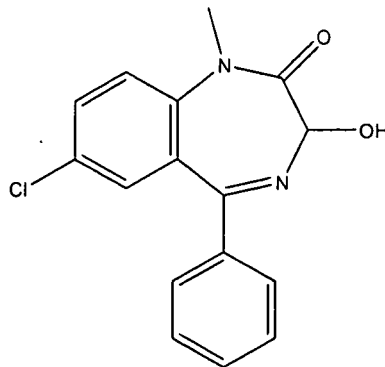
[0125] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam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

midazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with midazolam to provide a synergistic anticonvulsant effect.

[0126] Midazolam may also be administered by another person (e.g. an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (e.g. general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the midazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The midazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

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

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



[0129] Temazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Temazepam has also been shown to be useful in the treatment of nausea. The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

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

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

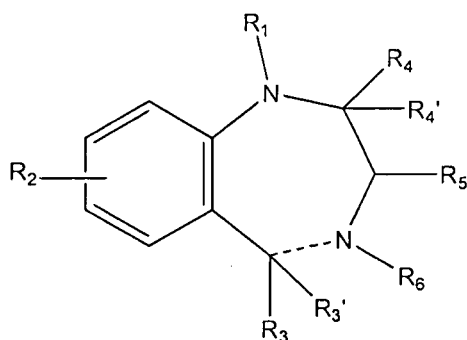
[0132] Temazepam may also be administered by another person (e.g. an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to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

[0133] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui*

generis for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

Pharmaceutically Acceptable Salts

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



Formula I

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

[0135] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4 , H_2SO_3 , H_3PO_4 , H_3PO_3 , and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. Thus, in some embodiments, the pharmaceutically acceptable acid may be selected from the group consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic 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 acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid,

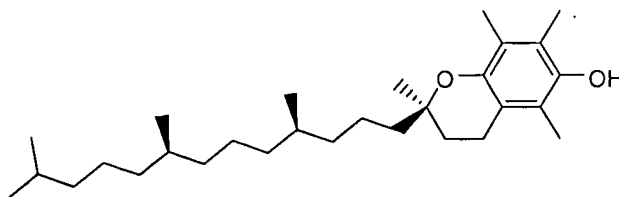
glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (- L), malonic acid, mandelic acid (DL), methanesulfonic acid, benzenesulfonic acid (besylic acid), naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid (- L), salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (p) and undecylenic acid. Other pharmaceutically acceptable acids may be pharmaceutically acceptable acidic (anionic) polymers or pharmaceutically acceptable amphoteric polymers. One skilled in the art will recognize that other basic active pharmaceutical ingredients may be combined with the foregoing acids to produce acid addition salts. Likewise the person skilled in the art will recognize that in some embodiments it may be advantageous that some or all of the added acid be an active pharmaceutical ingredient in its own right.

[0136] In some embodiments, the invention provides nasal compositions comprising one or more acidic pharmaceutically active ingredients. It is considered well within the ordinary skill in the art to determine which of the compounds set for the above are acidic. Such compounds may be prepared as base addition salts, e.g. by the addition of one or more mineral bases (e.g. NaOH, KOH, NaHCO₃, Na₂CO₃, NH₃) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

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

Carrier System

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



α -tocopherol

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

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

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

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

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

Additional Excipients

[0144] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is at least one alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130, which is incorporated herein by reference in its entirety. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetraose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α - or β -D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Specific excipients that may be employed in a nasal composition according to the invention include alkylsaccharide is

dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof. Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail[®] by Aegis Therapeutics, LLC, San Diego, CA. Other alkyl glycosides may be selected from those having a hydrophile-lipophile balance (HLB) number of from about 10-20, especially about 11-15. The HLB number may be determined as set forth in the publication US2009/0047347, published on 19 February 2009, the entirety of which, and especially paragraphs [0075]-[0079], is incorporated herein by reference. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01% (w/v) to about 1% (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05% (w/v) to about 0.5% (w/v), or about 0.125% (w/v) to about 0.5% (w/v).

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

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

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

[0148] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about

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

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

Mucosal Membrane Preparations

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

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

Alprazolam

[0152] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured

using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

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

Diazepam

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

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

Flurazepam

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

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

Lorazepam

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

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

Medazepam

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

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

Mexazolam

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

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

Midazolam

[0164] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

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

Temazepam

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

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

Formulation

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

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

embodiments disclose a carrier system that is about 70% (w/w) Vitamin E and about 30% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof.

[0170] Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of the desired result. Other dosage levels disclose a dosage level of about 2.0 mg to about 15.0 mg until the desired result is achieved. Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.

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

Formulation Process

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

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

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

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

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

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

[0177] Figure 5 depicts one embodiment of a process of manufacturing a suspension of benzodiazepine according to the instant invention. First, the benzodiazepine (*e.g.*, diazepam) is sieved to produce a micronized benzodiazepine (*e.g.*, diazepam). The micronized benzodiazepine (*e.g.*, diazepam) is then split into two intermediates products - Diazepam A (high pressure) is a small particle size (mean particle size < 2000 nm) and Diazepam B (low pressure) is a large particle size (mean particle diameter > 2000 nm). After in-process testing, the two intermediate products are combined with one or more excipients in correct proportions to produce a bimodal particle suspension having a pre-selected mean particle diameter, which in some embodiments is greater than 2000 nm. In some embodiments, the excipients are prepared according to the second column in Figure 5, *e.g.* by first combining propylene glycol, water and vitamin E polyethylene glycol succinate to form a mixture and heating the mixture until the ingredients are dissolved, then adding methylparaben, propyl paraben and Intravail[™] (alkyl glycoside) to the mixture and mixing until the newly added ingredients are dissolved, and finally cooling the mixture, *e.g.* to 25°C ± 2°C. The excipients can then be combined with Micronized Diazepam A and Micronized Diazepam B and mixed vigorously to disperse the micronized Diazepam to form the suspension. Next, povidone is added to the mixture, which is mixed until the povidone is fully dissolved. Finally, the suspension is brought to its final target weight with purified water and mixed well to achieve homogeneity. The final product can then be filled into suitable containers. In some embodiments, 3 mL may be filled into 4 mL amber glass vials with PTFE lined phenolic closures, though other containers are of course possible and contemplated within the scope of the invention. As diazepam is depicted in Figure 5 as an exemplary benzodiazepine, any benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam,

triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof may also be employed.

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

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

Additional Active and Inactive Ingredients

[0180] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from active ingredients. By way of non-limiting example, such active ingredients include insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof, enkephalins, LHRH and analogues (Nafarelin, Buserelin, Zolidex), GHRH (growth hormone releasing hormone), nifedipin, THF (thymic humoral factor), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, antibiotics, metoclopramide, ergotamine, Pizotizin, nasal vaccines (particularly HIV vaccines, measles, rhinovirus Type 13 and respiratory syncytial virus), pentamidine, CCK (Cholecystikinine), DDAVP, Interferons, growth hormone (solatotropir polypeptides or their derivatives (preferably with a molecular weight from 1000 to 300000), secretin, bradykinin antagonists, GRF (Growth releasing factor), TRH (Thyrotropin releasing hormone), ACTH analogues, IGF (Insulin like growth factors), CGRP (Calcitonin gene related peptide) Atrial Natriuretic peptide, Vasopressin and analogues (DDAVP, Lypressin), Metoclopramide, Migraine treatment (Dihydroergotamine, Ergometrine, Ergotamine, Pizotizin), Nasal Vaccines (Particularly AIDS vaccines) FACTOR VIII, Colony Stimulating factors, G-CSF (granulocyte-colony stimulating factor), EPO (Erythropoitin) PTH (Parathyroid hormone) or pharmaceutically acceptable salts or combinations thereof.

[0181] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: paraldehyde; aromatic allylic alcohols (such as stiripentol); barbiturates (e.g. phenobarbitol, primidone, methylphenobarbital, metharbital and barbexalone); 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); hydantoin (e.g. ethotoin, phenytoin, mephenytoin and fosphenytoin); oxazolidinediones (such as paramethadione, trimethadione, ethadione); propionates (e.g. beclamide), pyrimidinediones (e.g. primidone); pyrrolidines (e.g. brivaracetam, levetiracetam and seletracetam); succinimides (e.g. ethosuximide, phensuximide and mesuximide); sulfonamides (e.g. acetazolamide, sulthiame, methazolamide and zonisamide); triazines (such

as lamotrigine); ureas (such as pheneturide, phenacemide); valproylamides (such as valpromide and valnoctamide); as well as other anticonvulsants or pharmaceutically acceptable salts or combinations thereof.

[0182] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: antibiotics and antimicrobial agents such as tetracycline 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, chlorpheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

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

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

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

[0186] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% (w/v).

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

Administration

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

Alprazolam

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

[0190] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL , especially about 100 μL , metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Diazepam

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

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

Flurazepam

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

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

Lorazepam

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

[0196] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL , especially about 100 μL , metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Medazepam

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

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

Mexazolam

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

[0200] As a nasal formulation, mexazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μL , especially about 100 μL , metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Midazolam

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

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

Temazepam

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

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

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

Examples

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

Example 1

[0207] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in adults. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 5.0 mg/puff (5.0 mg/0.1 mL and 0.1 mL/puff)) every 5 minutes until cessation of the seizure. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 2.5 mg/puff (5.0 mg/0.1 mL and 0.05 mL/puff)) every 5 minutes until cessation of the seizure. The composition according to this example is set forth in the following table.

Table 1-1

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

Example 2

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

Table 2-1

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

Example 3 – Formulation of Diazepam Solutions

[0209] In general, benzodiazepine solutions may be formulated by combining one or more natural or synthetic tocopherols or tocotrienols and one or more lower alcohols or glycols and mixing until a

homogeneous mixture is formed, adding the benzodiazepine drug to the homogeneous mixture, heating and mixing the ingredients until the benzodiazepine is fully dissolved in the homogeneous mixture, cooling the mixture, and bringing the mixture to its final mass or volume with lower alcohol or glycol.

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

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

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

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

Example 4 -- Formulation of Diazepam Suspensions

[0212] In general, benzodiazepine suspensions are formulated by micronizing benzodiazepine and combining the benzodiazepine with a carrier. The carrier is prepared by combining one or more lower alcohols or glycols with water, adding a natural or synthetic tocopherol or tocotrienol, heating the mixture until the tocopherol or tocotrienol is dissolved, adding one or more parabens and mixing until the parabens are dissolved and cooling the carrier. Once the benzodiazepine is added to the carrier, additional excipients, such as surfactants, can optionally be added and dissolved in the carrier. The suspension is then brought up to its final mass or volume with water.

[0213] Two different diazepam suspensions were formulated by the foregoing general process. Two different diazepam particle sizes were prepared – A: a small particle size by prepared by high pressure micronization, and B: a large particle size prepared by low pressure micronization. The carrier was prepared by combining propylene glycol USP and purified water USP, then adding Vitamin E Polyethylene Glycols Succinate NF, then mixing and heating the combined ingredients to about 45°C. Mixing was continued until the Vitamin E Polyethylene Glycol Succinate was fully dissolved. The carrier was then cooled to 20-25°C. The micronized

diazepam (A and B) was then added to the carrier with vigorous mixing until the diazepam was fully dispersed in the carrier. Polyvinylpyrrolidone Povidone USP/NF was then added to the mixture and mixed until fully dissolved. The suspension was then brought up to weight with purified water USP. The suspension was then mixed until homogeneous, sampled for in-process testing, and packaged in 3 mL amber glass bottles.

Table 4-1: Diazepam Suspension Formulations

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

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

Example 5 -- Stability of Diazepam Solutions and Suspensions

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

Table 5-1: Summary of PSI sample control numbers

Formulation #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00 – 70 mg/ml solution, 65% Vitamin E	083101.01	083101.02	083101.02
Solution 02 – 70 mg/ml solution, 80%	083102.01	083102.02	083102.03

vitamin E			
Suspension 01 - 100 mg/ml suspension	083103.01	083103.02	083103.03
Suspension 03 - 200 mg/ml suspension	083104.01	083104.02	083104.03

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

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

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

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

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

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

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

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

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

Table 5-4: Summary of Solution 00 results

Solution 00, 70mg/ml, 65% Vitamin E	Specifications	Initial	1	1	1	3	3	3	6	6	6	
			mont	mont	mont	mont	mont	mont	mont	mont	mont	mont
			h	h	h	h	h	h	h	h	h	h
			25°C/	30°C/	40°C/	25°C/	30°C/	40°C/	25°C/	30°C/	40°C/	
			60	65	75	60	65	75	60	65	75	
			%R	%R	%R	%R	%R	%R	%R	%R	%R	
			H	H	H	H	H	H	H	H	H	

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

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

Table 5-5: Summary of Solution 02 results

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

Identification – UV	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	1 month	1 month	3 month	3 month	3 month	6 month	6 month	6 month
			25°C/60%RH	30°C/65%RH	40°C/75%RH	25°C/60%RH	30°C/65%RH	40°C/75%RH	25°C/60%RH	30°C/65%RH	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 w disper

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%-115.0%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
Propylparaben (%)	80.0%-115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235
Fill volume (ml)	report results	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
Spray delivered (µl)	report results	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	not tested	137.6
Average Spray Content (%)	report results	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	not tested	95.94
Viscosity (Pa*s)	report results	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

(1) LOQ is approximately 0.006%; LOD is approximately 0.002%. 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
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	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%-115.0%	93.4	101.1	93.8	99.7	101.5	101.6	101.2	103.5	97.2	102.1
Propylparaben (%)	80.0%-115.0%	95.6	100.2	94	98.4	100.1	101.3	99.2	97.1	91.9	95.9
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.276	1.28	1.259	1.272	1.279	1.279	1.276	1.280	1.262	1.260
Fill volume (ml)	report results	1.186	1.19	1.171	1.183	1.19	1.19	1.187	1.190	1.173	1.172

Spray delivered (µl)	report results	112.4	137.4	134.3	119.9	138.9	139.3	134.3	149.4	not tested	138.0
Average Spray Content (%)	report results	82.8	99.3	97.3	86.7	98.6	102.3	96.2	98.2	not tested	98.7
Viscosity (Pa*s)	report results	0.021	0.017	0.017	0.019	0.016	0.016	0.018	0.014	0.013	0.015

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

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.13061	0.13259	9.59355	97.89
2	0.13217	0.13451	9.78206	99.82
3	0.12365	0.13332	8.85797	90.39
4	0.12761	0.13072	9.39720	95.89
5	0.14702	0.15216	8.91438	90.96
6	0.13414	0.13702	9.22442	94.13
7	0.12959	0.13384	9.84590	100.47
8	0.12367	0.14603	8.88093	90.62
9	0.13367	0.13425	9.92610	101.29
Average	0.13135	0.13716	9.380	95.72
St. Dev.	0.0070	0.0071	0.4309	4.3970
% RSD	5.35	5.20	4.59	4.59

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.14139	0.15111	10.57237	107.88
2	0.14731	0.15146	11.62831	118.66
3	0.14489	0.14684	10.94206	111.65
4	0.14237	0.14873	11.94883	121.93
5	0.12188	0.13415	9.78103	99.81
6	0.12756	0.13047	9.78347	99.83

7	0.13549	0.13841	10.45221	106.66
8	0.12323	0.12543	9.41177	96.04
9	0.14299	0.14517	11.35701	115.89
Average	0.13635	0.14131	10.653	108.70
St. Dev.	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.12280	0.12611	8.88043	90.62
2	0.13318	0.13549	9.55581	97.51
3	0.13260	0.13452	9.71837	99.17
4	0.12064	0.12305	9.48123	96.75
5	0.13215	0.13582	9.34463	95.35
6	0.13559	0.13790	9.48722	96.81
7	0.13158	0.13371	9.43613	96.29
8	0.13357	0.13495	9.79164	99.91
9	0.12165	0.12443	8.84732	90.28
Average	0.12931	0.13178	9.394	95.85
St. Dev.	0.0058	0.0056	0.3303	3.3701
% RSD	4.52	4.25	3.52	3.52

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.12336	0.12563	9.02005	92.04
2	0.05723	0.05792	9.43076	96.23
3	0.13554	0.13908	9.93829	101.41
4	0.13619	0.13679	9.87755	100.79
5	0.13227	0.13414	9.64403	98.41
6	0.13331	0.13515	9.80808	100.08

7	0.13455	0.13844	9.31952	95.10
8	0.13314	0.13736	9.28106	94.70
9	0.13249	0.13387	9.32935	95.20
Average	0.12423	0.12649	9.517	97.11
St. Dev.	0.0254	0.0260	0.3148	3.2119
% RSD	20.45	20.57	3.31	3.31

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.12873	0.12999	12.85366	91.81
2	0.14011	0.14247	13.68122	97.72
3	0.14515	0.14757	14.09449	100.67
4	0.13205	0.13347	14.18775	101.34
5	0.14554	0.14743	14.48202	103.44
6	0.14473	0.14682	14.39897	102.85
7	0.13229	0.13411	14.87853	106.28
8	0.14357	0.14581	14.82712	105.91
9	0.14741	0.14940	14.86732	106.20
Average	0.13995	0.14190	14.252	101.80
St. Dev.	0.0070	0.0074	0.6602	4.7154
% RSD	5.03	5.18	4.63	4.63

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.14411	0.14869	13.04770	93.20
2	0.14066	0.14151	13.23277	94.52
3	0.13012	0.13485	13.78126	98.44
4	0.14667	0.14879	13.36970	95.50
5	0.14294	0.14338	12.54309	89.59
6	0.13797	0.14253	13.25396	94.67

7	0.13374	0.13594	13.41984	95.86
8	0.12388	0.12559	14.34944	102.50
9	0.13790	0.14011	13.88564	99.18
Average	0.13755	0.14015	13.431	95.94
St. Dev.	0.0073	0.0073	0.5223	3.7310
% RSD	5.28	5.19	3.89	3.89

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
1	0.13604	0.13897	25.93418	92.62
2	0.14608	0.14792	26.21721	93.63
3	0.15294	0.15425	30.05570	107.34
4	0.14728	0.14910	25.78804	92.10
5	0.15352	0.15493	26.60721	95.03
6	0.15242	0.15401	29.51030	105.39
7	0.15118	0.15254	28.43104	101.54
8	0.15322	0.15556	28.03664	100.13
9	0.15197	0.15393	26.82906	95.82
Average	0.14941	0.15125	27.490	98.18
St. Dev.	0.0057	0.0053	1.5812	5.6472
% RSD	3.79	3.50	5.75	5.75

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
1	0.13574	0.13797	28.14588	100.52
2	0.13639	0.13803	27.04437	96.59
3	0.14082	0.14195	26.78985	95.68
4	0.12962	0.13249	29.07192	103.83
5	0.12518	0.12683	27.39785	97.85
6	0.14423	0.14541	28.50133	101.79

7	0.13922	0.14096	27.34617	97.66
8	0.14146	0.14313	27.17415	97.05
9	0.14902	0.15344	27.20939	97.18
Average	0.13796	0.14002	27.631	98.68
St. Dev.	0.0073	0.0076	0.7642	2.7294
% RSD	5.28	5.43	2.77	2.77

Example 6

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

Example 7

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

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

Example 8

[0224] The solutions and suspensions of Examples 3, 4 and 6 are evaluated for their ability to deliver drug across the blood brain barrier in a suitable animal model, such as in mice, rats, rabbits or dogs. Each animal is administered, intranasally, an amount of a solution or suspension as described in Examples 3, 4 and 6, with the solution or suspension optionally containing an imaging agent, such as a dye, that may be used as a proxy for determining the ability of the drug to cross the blood brain barrier. The drug or imaging agent is detected

at selected time points after administration of the suspension or solution to determine how well the drug or imaging agent crosses the blood brain barrier. These results may be compared with analogous result obtained with an intravenous solution containing the drug or imaging agent.

Example 9

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

Example 10

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

Example 11

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

Table 11-1

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

*Vitamin E, **Dodecyl maltoside

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

serious adverse events were noted. PK data were compared with those obtained with 5 mg of diazepam administered intravenously. The PK data are summarized in Table 11-3 and Figures 1-3.

[0236] The solution of Table 11-1 and the suspension of Table 11-2 were found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% of i.v.) The intranasal formulation of Table 11-1 exhibited a T_{max} of 1.5 hours, a C_{max} of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diastat®).

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

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

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

Table 11-3

Parameter ^a	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
	n	Mean (SD) ^b	n	Mean (SD) ^b	n	Mean (SD) ^b
C _{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T _{max} (h) ^b	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC ₀₋₁ (h×ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
AUC _{0-∞} (h×ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λ _z (h ⁻¹)	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
t _{1/2} (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

a: Mean values are presented as arithmetic means.

b: Median (min, max) reported for T_{max}

[0240] The data collected in the study are further illustrated in Figures 1-3. Figure 1 is a linear scale plot of the arithmetic mean of the plasma concentration of diazepam after intranasal (IN) administration of 10 mg of

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

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

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical solution for nasal administration consisting of:
 - (a) a benzodiazepine drug;
 - (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);
 - (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and
 - (d) an alkyl glycoside,in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient.
2. The pharmaceutical solution of claim 1, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).
3. The pharmaceutical solution of claim 2, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.
4. The pharmaceutical solution of claim 3, wherein the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof.
5. The pharmaceutical solution of claim 1, containing about 1 to about 20 % (w/v) of benzodiazepine.
6. The pharmaceutical solution of claim 5, containing about 1 to about 20 % (w/v) of diazepam.
7. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.
8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof.

9. The pharmaceutical solution of claim 1, containing two or more alcohols.
10. The pharmaceutical solution of claim 1, containing ethanol (1-25 % (w/v)) and benzyl alcohol (1-25 % (w/v)).
11. The pharmaceutical solution of claim 1, containing ethanol (10-22.5 % (w/v)) and benzyl alcohol (7.5-12.5 % (w/v)).
12. The pharmaceutical solution of claim 11, wherein the benzodiazepine is present in the pharmaceutical solution in a concentration from about 20 mg/mL to about 200 mg/mL.
13. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w).
14. The pharmaceutical solution of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w).
15. The pharmaceutical solution of claim 1, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w).
16. The pharmaceutical solution of claim 15, wherein the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 25% to about 40% (w/w).
17. The solution of claim 1, consisting of diazepam (5-15 % (w/v)), alkyl glycoside (0.01-1 % (w/v)), vitamin E (45-65 % (w/v)), ethanol (10-25 % (w/v)) and benzyl alcohol (5-15 % (w/v)).
18. The solution of claim 1, wherein the pharmaceutically-acceptable formulation comprises at least about 0.01% (w/w) of an alkyl glycoside.
19. The solution of claim 18, wherein the pharmaceutically-acceptable formulation about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside.
20. The solution of claim 1, consisting essentially of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.
21. The solution of claim 20, consisting of diazepam, vitamin E, ethanol, benzyl alcohol and dodecyl maltoside.
22. The solution of claim 21, consisting of about 56.47% (w/v) vitamin E, about 10.5 % (w/v) benzyl alcohol, about 10 % (w/v) diazepam, about 0.25 % (w/v) dodecyl maltoside, q.s. dehydrated ethanol.

23. A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside.

24. The method of claim 23, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

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

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

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

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

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

30. The method of claim 23, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocopherols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

31. The method of claim 23, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

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

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

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

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

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

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

38. The method of claim 23, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).

39. The method of claim 38, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).

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

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

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

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

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

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

46. The method of claim 45, wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.

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

48. The method of claim 46, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical solution.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

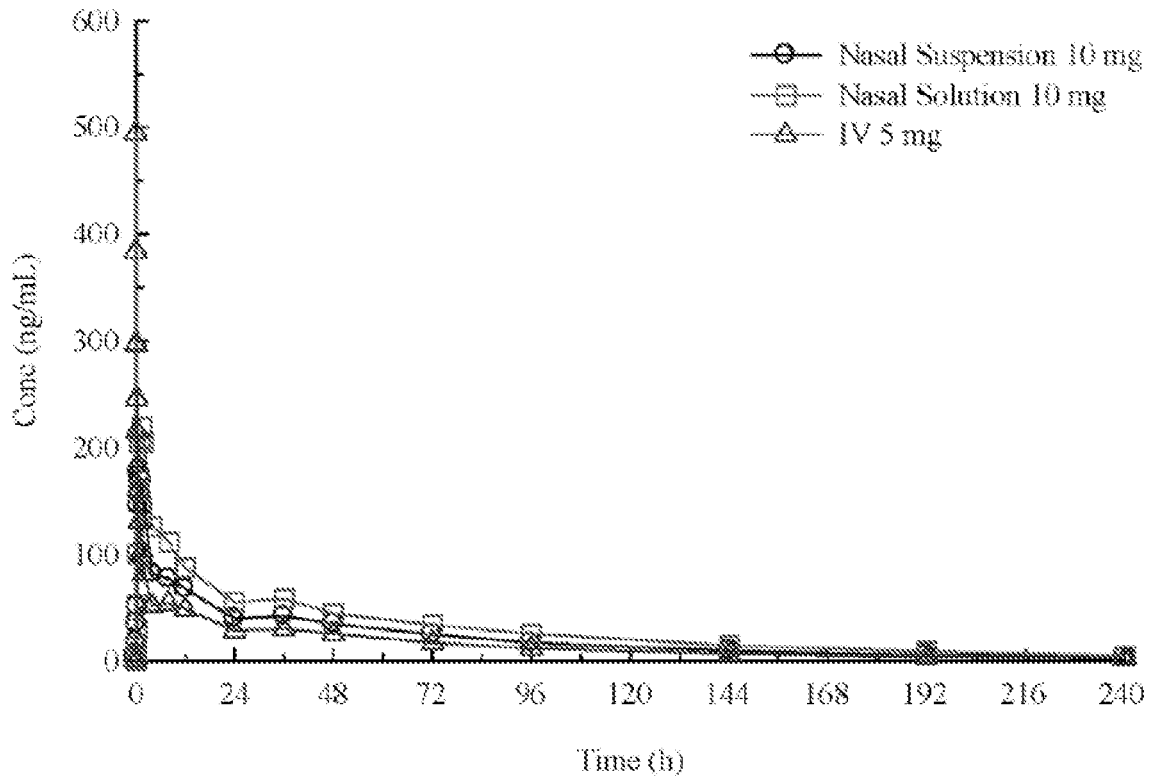
64. The method of claim 63, wherein said treatment achieves bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously.

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

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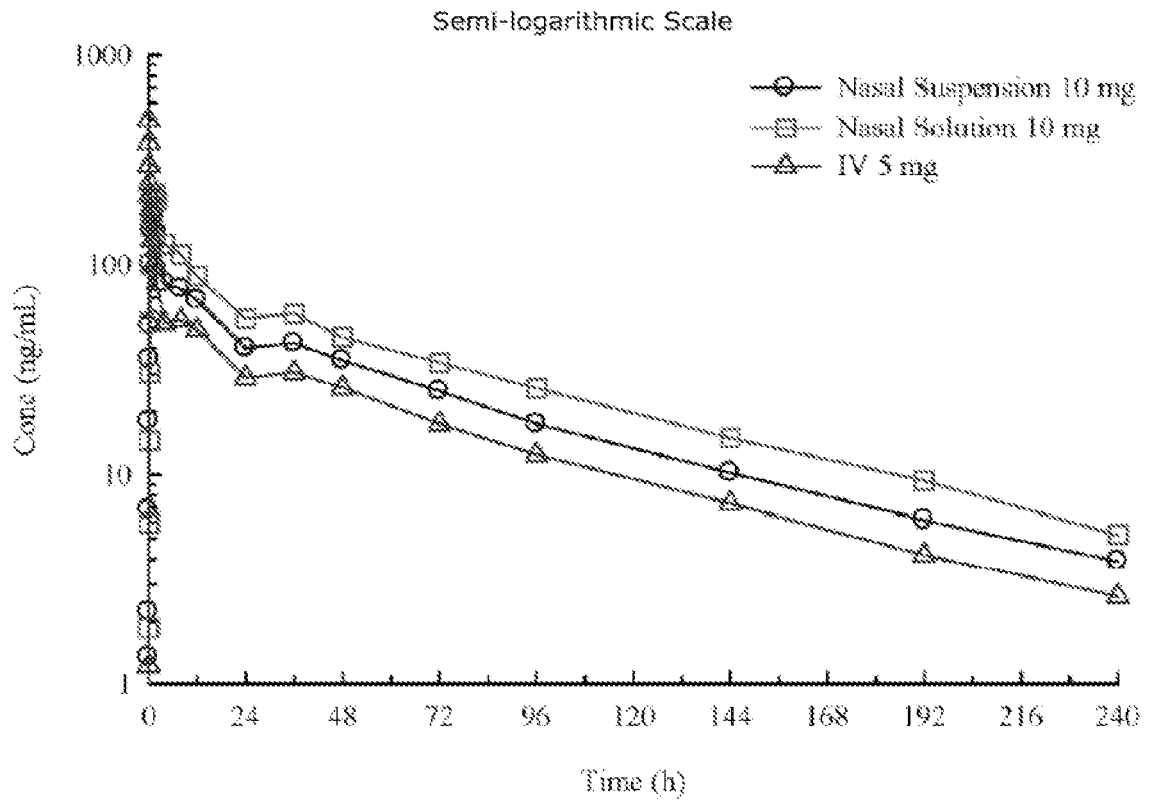
FIG. 1

Linear Scale



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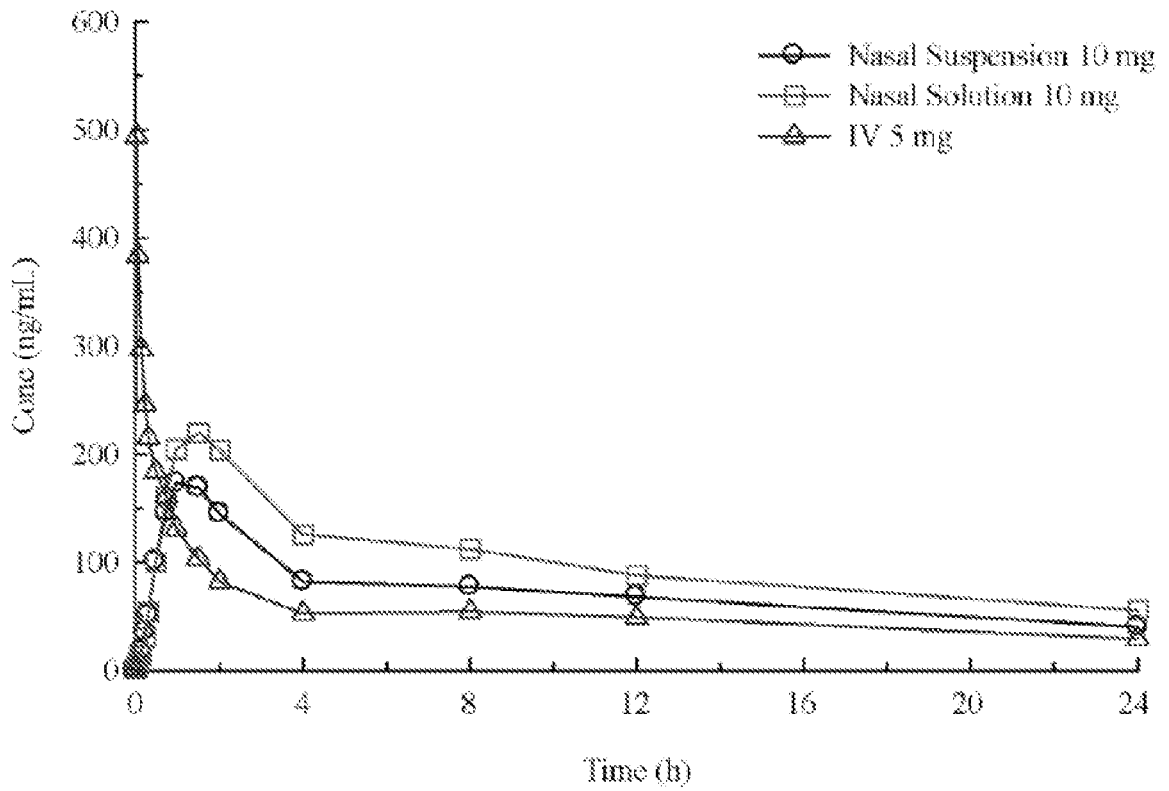
FIG. 2



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FIG. 3

Linear Scale



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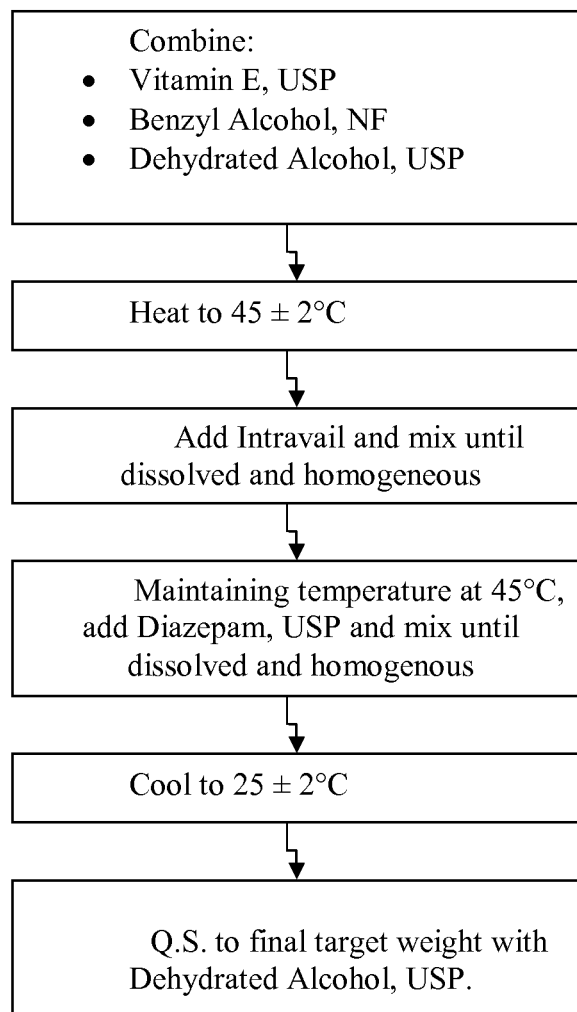
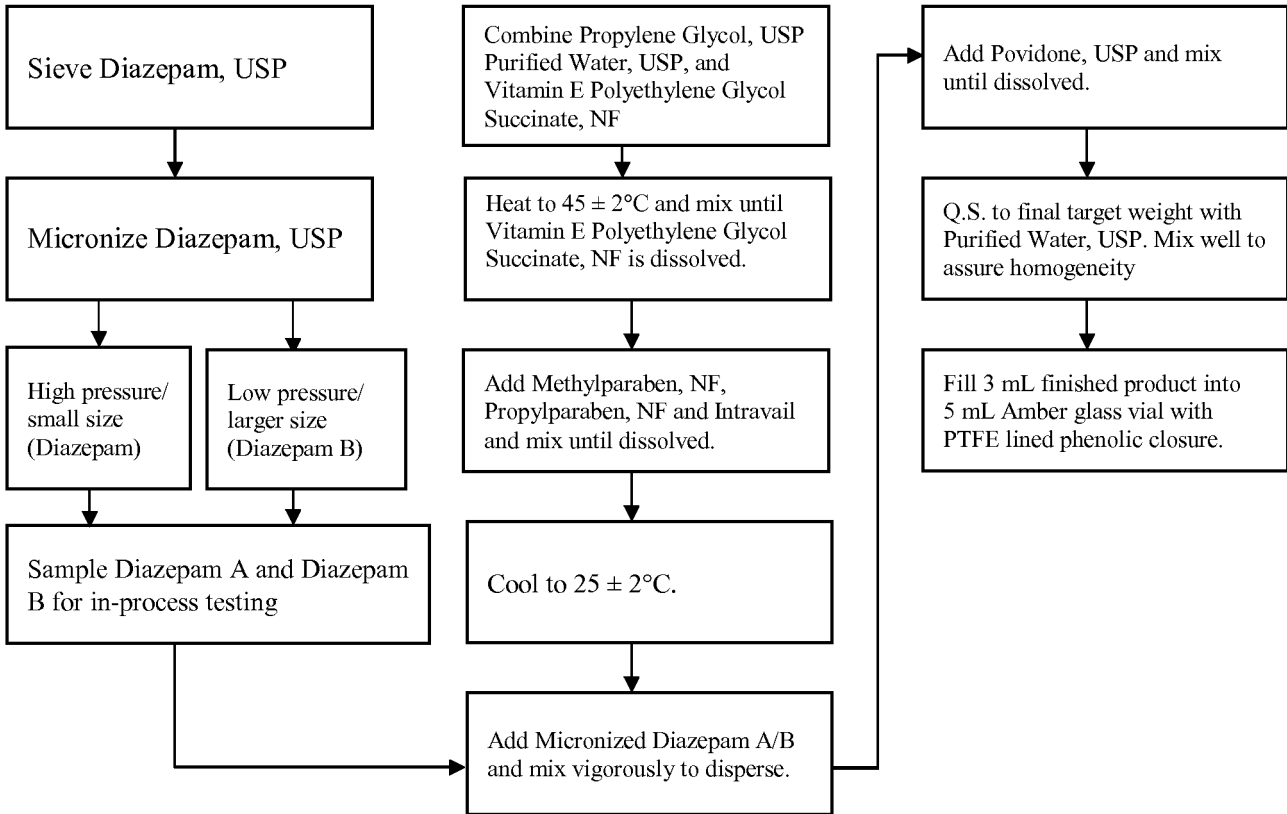
FIG. 4: Flow Diagram for the Manufacture of Diazepam Solution

FIG. 5: Flow Diagram for Preparation of Diazepam Suspension

Flow Diagram for the Manufacture of NRL-1A



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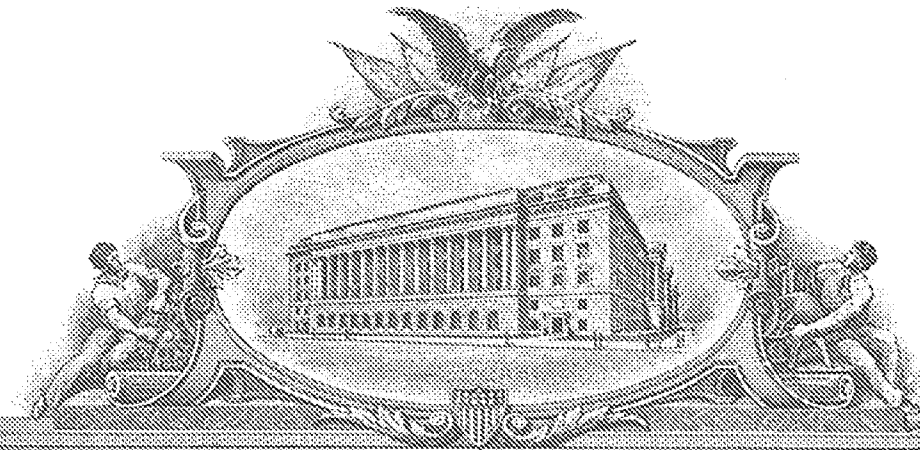
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

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Title of Invention

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Attorney Docket Number (if applicable)

35401-716.103

Correspondence Address

Direct all correspondence to (select one):

The address corresponding to Customer Number

Firm or Individual Name

Doc Code: **TR.PROV**

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Applicant claims small entity status under 37 CFR 1.27

- Yes, applicant qualifies for small entity status under 37 CFR 1.27
 No

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Signature	/Matthew Grumbling/			Date (YYYY-MM-DD)	2011-12-13
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PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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By: /Linda Anders/

Date: December 13, 2011

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

[002] 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.

[003] 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 gamma-aminobutyric acid (GABA).

[004] 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.

[005] 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.

[006] 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.

[007] 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.

[008] 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

[009] In some embodiments, there are provided (non-aqueous) pharmaceutical solutions for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically-acceptable solution for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, 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 solution contains about 1 to about 20 %w/v of benzodiazepine, e.g. about 1 to about 20 %w/v of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 %w/v) and benzyl alcohol (1-25 % w/v), or ethanol (10-22.5 %w/v) and benzyl alcohol (7.5-12.5 % w/v). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 %w/v), alkyl glycoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl

glycoside, e.g. about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v); more particularly the solution may consist of diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v); and even more particularly, the solution may consist of diazepam (10 %w/v), dodecyl maltoside (0.15-0.3 %w/v), vitamin E (50-60 w%/v), ethanol (17-20 w%/v) and benzyl alcohol (10-12 %w/v).

[010] Some embodiments described herein provide a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, lopraxolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 %w/v of benzodiazepine, e.g. about 1 to about 20 %w/v of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocopherols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 %w/v) and benzyl alcohol (1-25 % w/v), or ethanol (10-22.5 %w/v) and benzyl alcohol (7.5-12.5 % w/v). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 %w/v), alkyl glycoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and

benzyl alcohol (5-15 %w/v). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v); more particularly the solution may consist of diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v); and even more particularly, the solution may consist of diazepam (10 %w/v), dodecyl maltoside (0.15-0.3 %w/v), vitamin E (50-60 w%/v), ethanol (17-20 w%/v) and benzyl alcohol (10-12 %w/v). In some embodiments, the patient is human. In some embodiments, the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg. In some embodiments, the benzodiazepine is administered as in a dosage volume from about 10 μ L to about 200 μ L. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril. In some embodiments, administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril. In some embodiments, the method further comprises, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril. In some embodiments, nasal administration of the pharmaceutical composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition. In some embodiments, the treatment achieves bioavailability that is from about 80-125% (*e.g.* about 90-110%, or more particularly about 92.5-107.5%) of that achieved with the same benzodiazepine administered intravenously, *e.g.* In this context, it is intended that bioavailability be determined by a suitable pharmacodynamic method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (*e.g.* 10 mg of nasal diazepam) with another dose of the same benzodiazepine administered intravenously (*e.g.* 5 mg of *i.v.* diazepam), taking into consideration the difference in dose. Thus, for the sake of illustration, a 10 mg nasal diazepam dose that achieves an AUC that is precisely half of the AUC obtained with 5 mg of *i.v.* diazepam would have a bioavailability of 100%. In some embodiments, the disorder to be treated is a seizure, such as an epileptic seizure, a breakthrough seizure, or other seizure. In some embodiments, the solution and treatment with the solution are substantially non-irritating and well-tolerated.

[011] 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.

[012] 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.

[013] 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.

[014] 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.

[015] 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.

[016] 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).

[017] 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).

[018] 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.

[019] 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.

[020] 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.

[021] 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, lorazepam, 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.

[022] 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.

[023] 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).

[024] 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.

[025] 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).

[026] 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).

[027] 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.

[028] 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 μ L to 200 μ L.

[029] 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.

[030] 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.

[031] 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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

[038] 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.

[039] 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.

[040] 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, lopraxolam, 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.

[041] 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.

[042] 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.

[043] 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.

[044] 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.

[045] 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.

[046] 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).

[047] 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.

[048] 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.

[049] 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.)

[050] 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.)

[051] 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 pyrrolidone). 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.

[052] 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 alkylglycoside 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.

[053] 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.

[054] 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.

[055] 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.

[056] 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.

[057] 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.

[058] 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.

[059] 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).

[060] 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.

[061] 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, maltotetraose, 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).

[062] 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 μ L to 200 μ L.

[063] 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.

[064] 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.

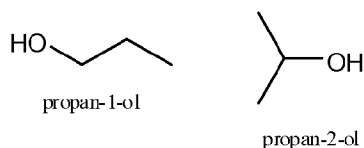
Definitions

[065] 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.

[066] 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 $\pm 20\%$, $\pm 10\%$, $\pm 5\%$, $\pm 2\%$, or $\pm 1\%$ or less.

[067] 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.

[068] 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.



[069] 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 auras are not uncommon amongst those who suffer the worst type of seizures, especially tonic-clonic seizures.)

[070] 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.

[071] 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.”

[072] As used herein, unless otherwise qualified, “a” and “an” can mean one or more.

[073] 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.

[074] 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.

[075] 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

[076] 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.

[077] 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.

[078] 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

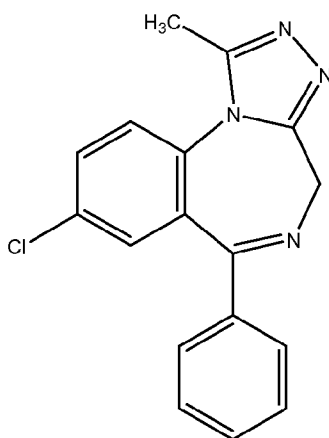
bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

[079] 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.

[080] 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.

[081] 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.

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



[083] 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.

[084] 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.

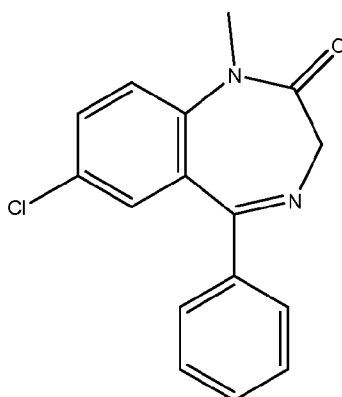
[085] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the

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.

[086] 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.

[087] 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.

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



[089] 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.

[090] 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.

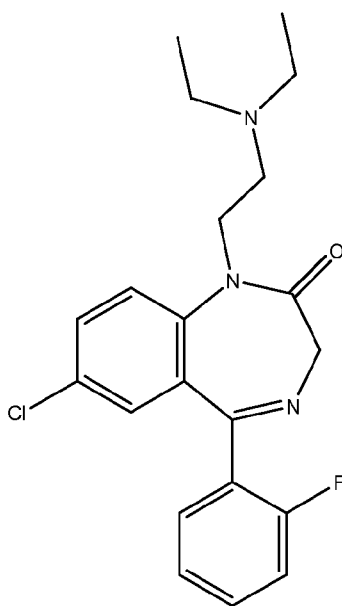
[091] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam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

[092] 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.

[093] 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.

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



[095] 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.

[096] 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.

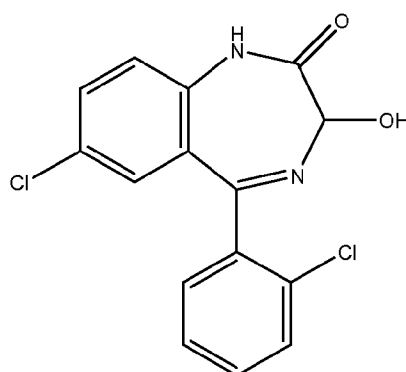
[097] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam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

[098] 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.

[099] 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.

[0100] Lorazepam (7-chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0101] 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.

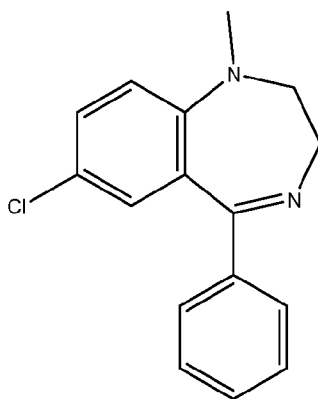
[0102] In some embodiments, lorazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] **Medazepam** ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



[0107] 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.

[0108] 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.

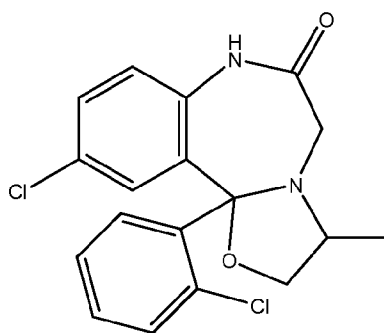
[0109] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam 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.

[0110] 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.

[0111] 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.

[0112] Mexazolam (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methyloxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



[0113] 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.

[0114] 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.

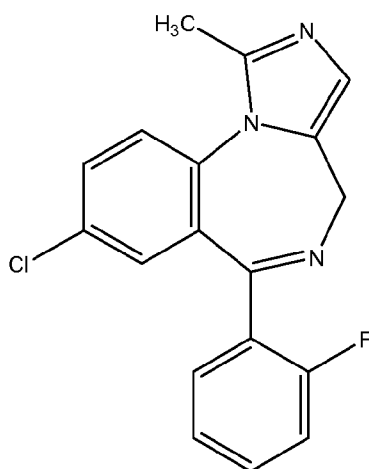
[0115] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam 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.

[0116] 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.

[0117] 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.

[0118] **Midazolam** (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



[0119] 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.

[0120] 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.

[0121] 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.

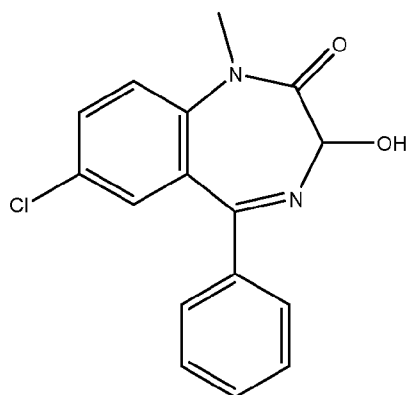
[0122] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam 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.

[0123] 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.

[0124] 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.

[0125] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0126] 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.

[0127] 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.

[0128] 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.

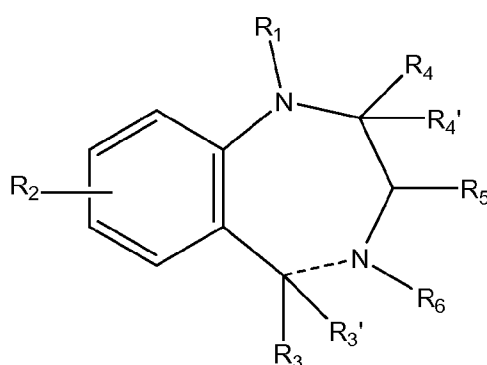
[0129] Temazepam may also be administered by another person (e.g. an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to 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.

[0130] 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

[0131] 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.

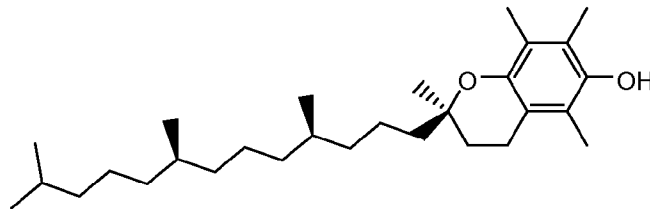
[0132] Pharmaceutically acceptable mineral acids include HCl, H₂SO₄, H₂SO₃, H₃PO₄, H₃PO₃, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. 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 acid, ascorbic 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 acid, fumaric 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, pantoic acid, phosphoric acid, propionic 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.

[0133] 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, NaHCO₃, Na₂CO₃, NH₃) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

[0134] 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

[0135] 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

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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

[0141] 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, maltotetraose, 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).

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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

[0147] 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.

[0148] 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

[0149] 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.

[0150] 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

[0151] 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.

[0152] 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

[0153] 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.

[0154] As a nasal formulation, flurazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Lorazepam

[0155] 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.

[0156] As a nasal formulation, lorazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Medazepam

[0157] 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.

[0158] As a nasal formulation, medazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Mexazolam

[0159] 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.

[0160] As a nasal formulation, mexazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Midazolam

[0161] 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.

[0162] As a nasal formulation, midazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Temazepam

[0163] 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.

[0164] 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

[0165] 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.

[0166] 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.

[0167] 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.

[0168] In some embodiments of the method, the dosage volume ranges from about 10 μL to about 200 μL . In some embodiments, the dosage volume ranges from about 20 μL to about 180 μL . Further, some embodiments disclose a dosage volume of about 50 μL to about 140 μL . In some embodiments, the dosage volume is 50 μL , 75 μL or 100 μL per nostril.

Formulation Process

[0169] 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.

[0170] 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.

[0171] 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.

[0172] 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

[0173] 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 syncytial 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 (Calcitonin 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.

[0174] 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); hydantoin (e.g. ethotoin, phenytoin, mephentoin 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.

[0175] 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 tetracycline 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, chlorpheniramine 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.

[0176] 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.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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

[0181] 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

[0182] 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.

[0183] As a nasal formulation, alprazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0184] 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.

[0185] As a nasal formulation, diazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0186] 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.

[0187] As a nasal formulation, flurazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0188] 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.

[0189] As a nasal formulation, lorazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0190] 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.

[0191] As a nasal formulation, medazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0192] 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.

[0193] As a nasal formulation, mexazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0194] 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.

[0195] As a nasal formulation, midazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0196] 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.

[0197] As a nasal formulation, temazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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.

[0198] 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

[0199] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

[0200] 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/0.1 mL	Diazepam
70.0 mg	α -tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 2

[0201] 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/0.1 mL	Diazepam
70.0 mg	α -tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 3 – Formulation of Diazepam Solutions

[0202] 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.

[0203] 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)	Solution 02 (80% Vitamin E)
	Concentration (mg/mL)	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

[0204] 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

[0205] 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.

[0206] 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

[0207] 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

[0208] 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/ml suspension	083103.01	083103.02	083103.03
Suspension 03 - 200 mg/ml suspension	083104.01	083104.02	083104.03

[0209] 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>.

[0210] 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.

[0211] 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.

[0212] 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%

[0213] 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	1	1	3	3	3	6	6	6
			month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %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/mL, 65% Vitamin E	Specifications	Initial	1	1	1	3	3	3	6	6	6
			month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %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	1 month	1 month	3 month	3 month	3 month	6 month	6 month	6 month
			25°C/60 %RH	30°C/65 %RH	40°C/75 %RH	25°C/60 %RH	30°C/65 %RH	40°C/75 %RH	25°C/60 %RH	30°C/65 %RH	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%-115.0%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
Propylparaben (%)	80.0%-115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235

Fill volume (ml)	report results	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
Spray delivered (µl)	report results	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	not tested	137.6
Average Spray Content (%)	report results	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	not tested	95.94
Viscosity (Pa*s)	report results	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

(1) LOQ is approximately 0006%, LOD is approximately 0.002%. 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	1	1	3	3	3	6	6	6
			month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %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%-115.0%	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

[0214] 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

[0215] 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.

[0216] Toxicity is assessed by known means. In particular, histological samples are collected from the nasal mucosal tissues of the test animals. Other toxicological methods are optionally employed as well.

Example 8

[0217] 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

[0218] 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

[0219] The above-described solutions and/or suspensions can be evaluated for efficacy in a suitable animal model. Briefly, for each dose of suspension or solution to be tested, a test animal is stimulated with a seizure inducing stimulus. The stimulus may be light, sound, chemical or other stimulus effective to induce seizure in the model animal. Once the animal has begun to seize, a solution or suspension as described herein is administered intranasally to the animal. The efficacy of the dose of the solution and/or suspension is evaluated based upon the animal's response to the test dose. This procedure is repeated through sufficient iterations, and at sufficient numbers of doses, to identify a dose that is considered effective to treat seizure by intranasal administration of the drug.

Example 11

[0220] A pharmaceutical composition comprising diazepam was prepared as a composition formulated as a solution to be delivered via a nasal delivery device. The ingredients used in the solution formulation are set forth in Table 11-1, below:

Table 11-1

<u>Ingredient</u>	<u>Concentration (%w/vol)</u>
Diazepam	10.00 w/v
α -tocopherol*	56.47 % w/v
Ethanol (dehydrated)	q.s. (~18.07 % w/v)

Intravail A3**	0.25 % w/v
Benzyl alcohol	10.50 % w/v

*Vitamin E, **Dodecyl maltoside

[0221] The suspension formulation is set forth in Table 11-2, below:

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

[0222]

[0223] A three-period, three-treatment, six-sequence, randomized cross-over study was conducted in healthy volunteers. For each dose, each volunteer was domiciled for at least 12 hours prior to each dose and until after a 24 hour pharmacokinetic sample was collected. Single doses of 100 µL of the pharmaceutical compositions described in Tables 11-1 and 11-2 were administered to each volunteer as one spray to the left nostril of 100 µL per spray. Pharmacokinetic samples were collected at 22 time points over 10 days. (PK time points: 2.5, 5, 10, 15, 20, 30 and 45 minutes, 1, 1.5, 2, 4, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours after each dose.) No serious adverse events were noted. PK data were compared with those obtained with 5 mg of diazepam administered intravenously. The PK data are summarized in Table 11-3 and Figures 1-3.

[0224] The solution of Table 11-1 and the suspension of Table 11-2 were found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% of i.v.) The intranasal formulation of Table 11-1 exhibited a Tmax of 1.5 hours, a Cmax of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diasstat®).

[0225] Solutions similar to those set forth in Table 11-1 can be prepared consisting of: diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v); diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v); or diazepam (10 %w/v), dodecyl maltoside (0.15-0.3 %w/v), vitamin E (50-60 w%/v), ethanol (17-20 w%/v) and benzyl alcohol (10-12 %w/v).

[0226] Solutions similar to those set forth in Table 11-1 achieve bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously, *e.g.* bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously or about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously. Such solutions may be used in methods of treating a patient with a disorder which may be treatable with a benzodiazepine drug, such as seizure, epileptic seizure and/or breakthrough seizure. In some embodiments, solutions described herein may be used to treat a disorder such as is treated with Diastat[®] diazepam gel.

[0227] A summary of pharmacokinetic data obtained for the solution and a suspension form of diazepam is shown below in Table 11-3:

[0228] Table 11-3

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

Parameter ^a	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
	n	Mean (SD) ^b	n	Mean (SD) ^b	n	Mean (SD) ^b
C _{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T _{max} (h) ^b	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC ₀₋₁ (h×ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
AUC _{0-∞} (h×ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λ _z (h ⁻¹)	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
t _{1/2} (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

a: Mean values are presented as arithmetic means.

b: Median (min, max) reported for T_{max}

[0229] The data collected in the study are further illustrated in Figures 1-3. Figure 1 is a linear scale plot of the arithmetic mean of the plasma concentration of diazepam after intranasal (IN) administration of 10 mg of diazepam as the suspension of Table 11-2 and after IN administration of 10 mg of diazepam as a solution of Table 11-1 compared to intravenous (IV) administration of 5 mg of diazepam. Figure 2 is a semi-logarithmic scale plot of the same data shown in Figure 1. Figure 3 shows the first 24 hours of data from Figure 1 on a linear scale.

[0230] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the

invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical solution for nasal administration consisting of:

- (a) a benzodiazepine drug;
- (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);
- (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and
- (d) an alkyl glycoside,

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

2. The pharmaceutical solution of claim 1, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

3. The pharmaceutical solution of claim 2, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, lorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loperazolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

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

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

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

7. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocopherols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23. A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside.

24. The method of claim 23, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

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

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

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

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

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

30. The method of claim 23, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

31. The method of claim 23, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.
32. The method of claim 23, wherein the solution contains two or more alcohols.
33. The method of claim 23, wherein the solution contains ethanol (1-25 %w/v) and benzyl alcohol (1-25 % w/v).
34. The method of claim 33, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 10 mg/mL to about 250 mg/mL.
35. The method of claim 34, wherein the benzodiazepine drug is present in the pharmaceutical solution in a concentration of from about 20 mg/mL to about 50 mg/mL.
36. The method of claim 23, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w).
37. The method claim 36, wherein the pharmaceutical solution comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w).
38. The method of claim 23, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 15% to about 55% (w/w).
39. The method of claim 38, wherein the pharmaceutical solution comprises one or more alcohols or glycols, or any combinations thereof, in an amount from about 25% to about 40% (w/w).
40. The method of claim 23, wherein the solution contains ethanol (10-22.5 %w/v) and benzyl alcohol (7.5-12.5 % w/v).
41. The method of claim 23, wherein the solution is in a pharmaceutically-acceptable spray formulation.
42. The method of claim 41, wherein the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg.
43. The method of claim 42, wherein said pharmaceutical solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μ L to about 200 μ L.

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

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

46. The method of claim 45, wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.

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

48. The method of claim 46, wherein nasal administration of the pharmaceutical solution begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical solution.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

ABSTRACT

[0231] The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

35401-716.103

Figure 1

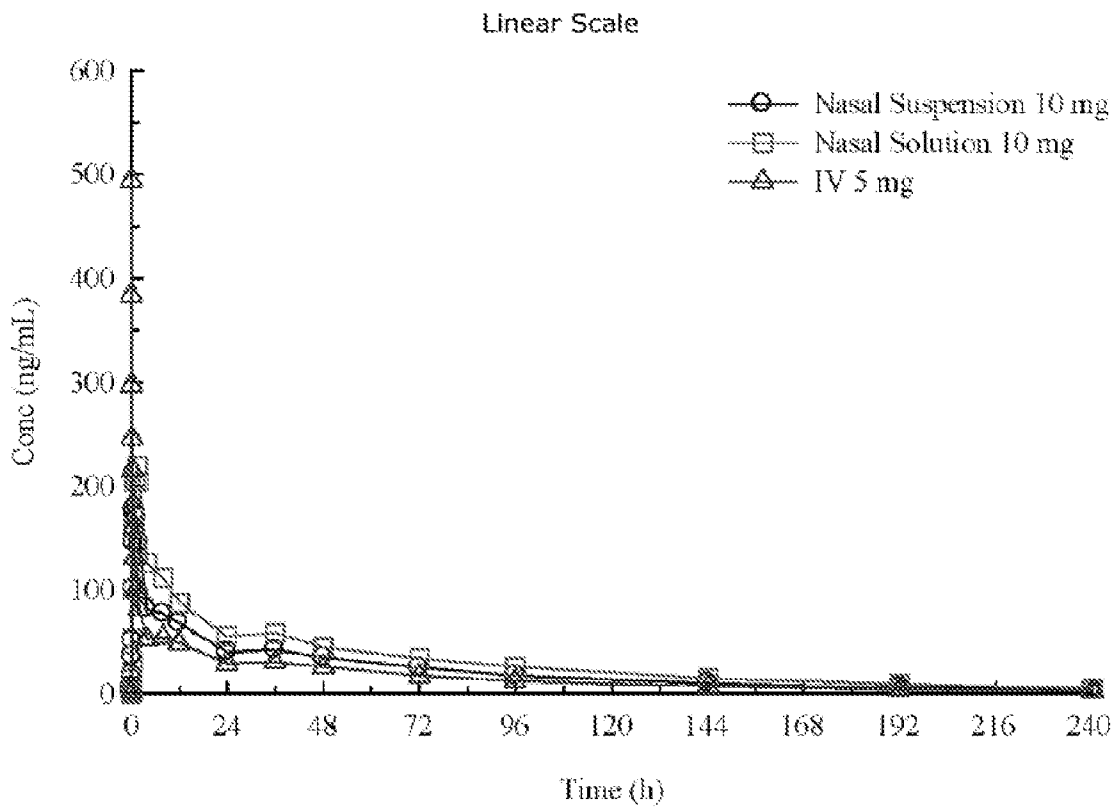
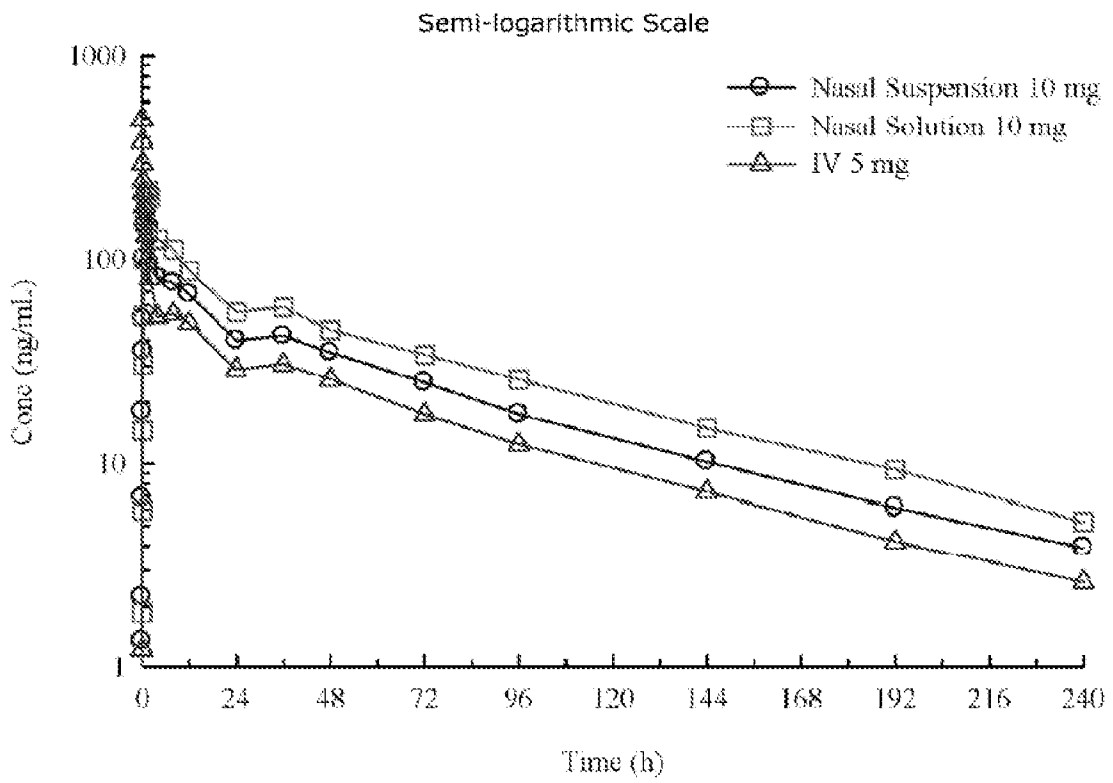


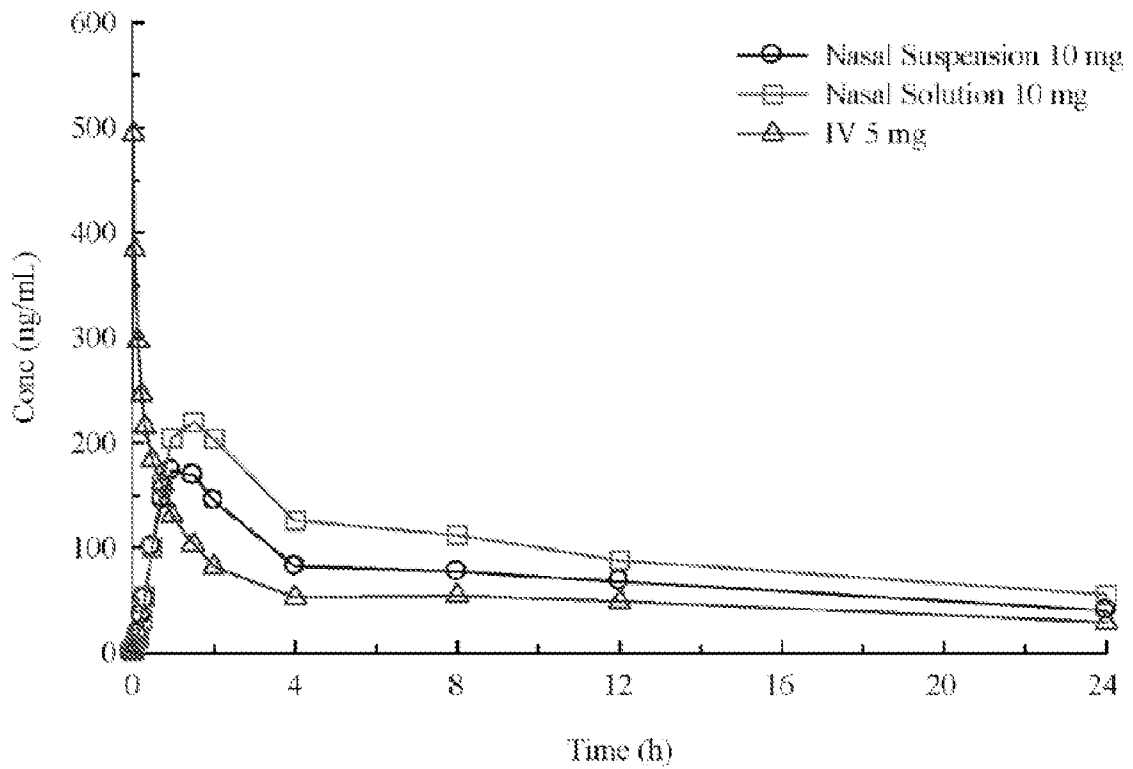
Figure 2



35401-716.103

Figure 3

Linear Scale



Electronic Acknowledgement Receipt

EFS ID:	11609281
Application Number:	61570110
International Application Number:	
Confirmation Number:	7298
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Linda Anders
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Attorney Docket Number:	35401-716.103
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Submitted with Payment	yes
Payment Type	Deposit Account
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1	Provisional Cover Sheet (SB16)	35401-716-103-provisionalcoversheetTBF.pdf	205104 <small>db0dcd1b38aadbd6124c722a31f9e4a4699ecc37</small>	no	4
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Warnings:					
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3	Drawings-only black and white line drawings	35401-716-103-figures.pdf	131210 <small>01842b4102b0150444972dfced58bfc83d3757b</small>	no	3
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Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29917 <small>161e1c4b4c56295f7d71aebf065953c110e1ea3a</small>	no	2
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PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

[002] 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.

[003] 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 gamma-aminobutyric acid (GABA).

[004] 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.

[005] 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.

[006] 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.

[007] 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.

[008] 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

[009] In some embodiments, there are provided (non-aqueous) pharmaceutical solutions for nasal administration consisting of: (a) a benzodiazepine drug; (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and (d) an alkyl glycoside, in a pharmaceutically-acceptable solution for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, 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 solution contains about 1 to about 20 %w/v of benzodiazepine, e.g. about 1 to about 20 %w/v of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocophersolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 %w/v) and benzyl alcohol (1-25 % w/v), or ethanol (10-22.5 %w/v) and benzyl alcohol (7.5-12.5 % w/v). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 %w/v), alkyl glycoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl

glycoside, e.g. about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v); more particularly the solution may consist of diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v); and even more particularly, the solution may consist of diazepam (10 %w/v), dodecyl maltoside (0.15-0.3 %w/v), vitamin E (50-60 w%/v), ethanol (17-20 w%/v) and benzyl alcohol (10-12 %w/v).

[010] Some embodiments described herein provide a method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside. In some embodiments, the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w). In some embodiments, the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, lopraxolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof. In some embodiments, the benzodiazepine drug is diazepam, or a pharmaceutically-acceptable salt thereof. In some embodiments, the solution contains about 1 to about 20 %w/v of benzodiazepine, e.g. about 1 to about 20 %w/v of diazepam. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocopherolan, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof. In some embodiments, the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the solution contains two or more alcohols, such as ethanol (1-25 %w/v) and benzyl alcohol (1-25 % w/v), or ethanol (10-22.5 %w/v) and benzyl alcohol (7.5-12.5 % w/v). In some embodiments, the benzodiazepine is present in the pharmaceutical composition in a concentration from about 20 mg/mL to about 200 mg/mL. In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 45% to about 85% (w/w). In some embodiments, the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 50% to about 75% (w/w). In some embodiments, the one or more alcohols or glycols, or any combinations thereof, is in an amount from about 15% to about 55% (w/w), e.g. about 25% to about 40% (w/w). In some embodiments, the solution consists of diazepam (5-15 %w/v), alkyl glycoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and

benzyl alcohol (5-15 %w/v). In some embodiments, the solution comprises at least about 0.01% (w/w) of an alkyl glycoside, *e.g.* about 0.01% to 1% (w/w) of an alkyl glycoside, such as dodecyl maltoside. In some embodiments, the solution consists of diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v); more particularly the solution may consist of diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v); and even more particularly, the solution may consist of diazepam (10 %w/v), dodecyl maltoside (0.15-0.3 %w/v), vitamin E (50-60 w%/v), ethanol (17-20 w%/v) and benzyl alcohol (10-12 %w/v). In some embodiments, the patient is human. In some embodiments, the benzodiazepine is administered in a therapeutically effective amount from about 1 mg to about 20 mg. In some embodiments, the benzodiazepine is administered as in a dosage volume from about 10 μ L to about 200 μ L. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into at least one nostril. In some embodiments, the administration of the pharmaceutical composition comprises spraying at least a portion of the therapeutically effective amount of the benzodiazepine into each nostril. In some embodiments, administration of the pharmaceutical composition comprises spraying a first quantity of the pharmaceutical composition into the first nostril, spraying a second quantity of the pharmaceutical composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical composition into the first nostril. In some embodiments, the method further comprises, optionally after a pre-selected time delay, administering at least a fourth quantity of the pharmaceutical composition to the second nostril. In some embodiments, nasal administration of the pharmaceutical composition begins at any time before or after onset of symptoms of a disorder which may be treatable with the pharmaceutical composition. In some embodiments, the treatment achieves bioavailability that is from about 80-125% (*e.g.* about 90-110%, or more particularly about 92.5-107.5%) of that achieved with the same benzodiazepine administered intravenously, *e.g.* In this context, it is intended that bioavailability be determined by a suitable pharmacodynamic method, such as comparison of area under the blood plasma concentration curve (AUC) for the nasally and intravenously administered drug. It is further understood that the percent bioavailability of the nasally administered benzodiazepine may be determined by comparing the area under the blood plasma concentration curve obtained with one dose of the benzodiazepine (*e.g.* 10 mg of nasal diazepam) with another dose of the same benzodiazepine administered intravenously (*e.g.* 5 mg of *i.v.* diazepam), taking into consideration the difference in dose. Thus, for the sake of illustration, a 10 mg nasal diazepam dose that achieves an AUC that is precisely half of the AUC obtained with 5 mg of *i.v.* diazepam would have a bioavailability of 100%. In some embodiments, the disorder to be treated is a seizure, such as an epileptic seizure, a breakthrough seizure, or other seizure. In some embodiments, the solution and treatment with the solution are substantially non-irritating and well-tolerated.

[011] 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.

[012] 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.

[013] 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.

[014] 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.

[015] 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.

[016] 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).

[017] 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).

[018] 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.

[019] 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.

[020] 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.

[021] 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, lorazepam, 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.

[022] 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.

[023] 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).

[024] 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.

[025] 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).

[026] 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).

[027] 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.

[028] 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 μ L to 200 μ L.

[029] 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.

[030] 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.

[031] 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

[032] 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

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

[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 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.

[035] 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.

[036] 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.

[037] 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, tocopherols, 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.

[038] 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.

[039] 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.

[040] 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.

[041] 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.

[042] 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).

[043] 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.

[044] 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.

[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. 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.)

[046] 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.)

[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 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.

[048] 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 pyrrolidone). 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 alkylglycoside 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.

[049] 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.

[050] 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.

[051] 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, tocopherolan, 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.

[052] 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.

[053] 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.

[054] 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.

[055] 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).

[056] 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.

[057] 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, maltotetraose, 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).

[058] 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 μ L to 200 μ L.

[059] 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.

[060] 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.

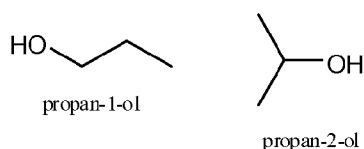
Definitions

[061] 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.

[062] 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 \pm 20%, \pm 10%, \pm 5%, \pm 2%, or \pm 1% or less.

[063] As used herein, the phrase “analog 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.

[064] 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.



[065] 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 auras are not uncommon amongst those who suffer the worst type of seizures, especially tonic-clonic seizures.)

[066] 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.

[067] 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.”

[068] As used herein, unless otherwise qualified, “a” and “an” can mean one or more.

[069] 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.

[070] 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.

[071] 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

[072] 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.

[073] 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.

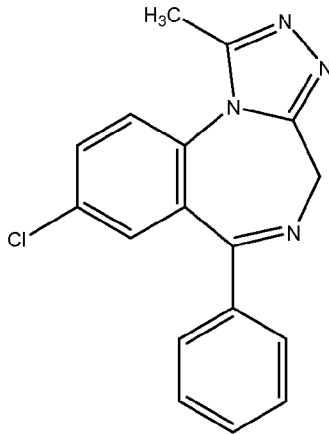
[074] For example, most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. By use of the present carrier system, which in some embodiments, provides an improved 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.

[075] 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.

[076] 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.

[077] 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.

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



[079] 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.

[080] 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.

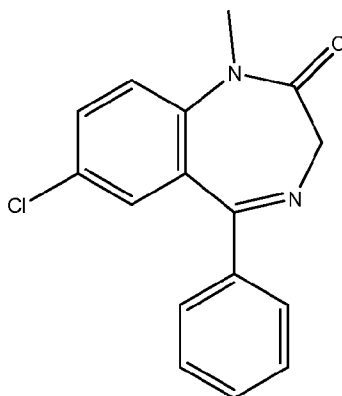
[081] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam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

[082] 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.

[083] 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.

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



[085] 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.

[086] 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.

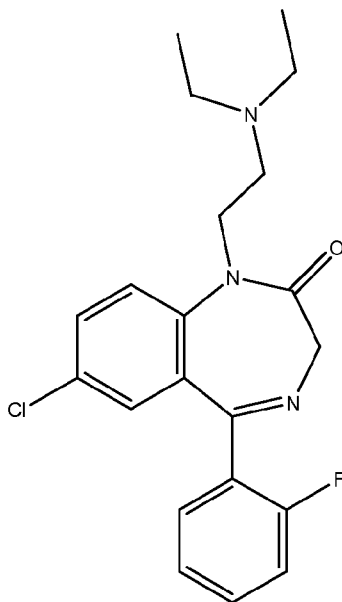
[087] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam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

[088] 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.

[089] 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.

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



[091] 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.

[092] 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.

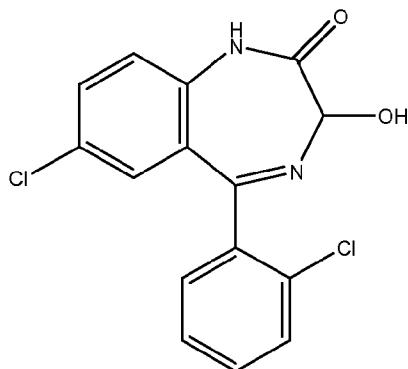
[093] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam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

[094] 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.

[095] 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.

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



[097] 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.

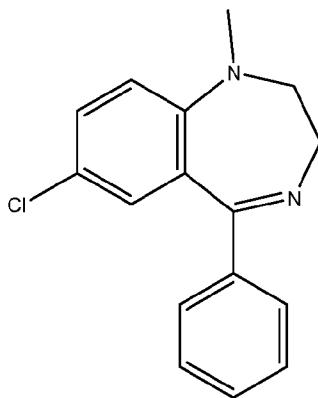
[098] In some embodiments, lorazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[099] 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.

[0100] 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.

[0101] 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.

[0102] **Medazepam** ((7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine)



[0103] 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.

[0104] 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.

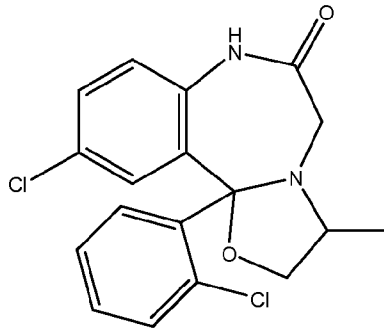
[0105] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam 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.

[0106] 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.

[0107] 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.

[0108] **Mexazolam** (10-Chloro-11b-(2-chlorophenyl)-1,3,7,11b-tetrahydro-3-methylxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one)



[0109] 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.

[0110] 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.

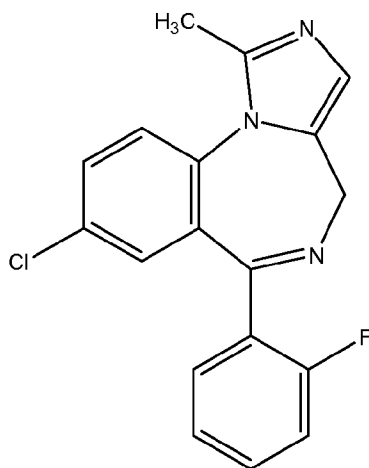
[0111] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam 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.

[0112] 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.

[0113] 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.

[0114] **Midazolam** (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo(1,5-a)benzodiazepine).



[0115] 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.

[0116] 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.

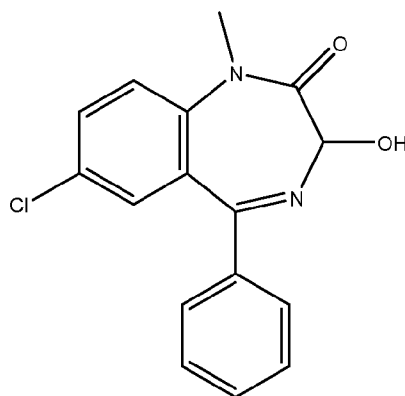
[0117] In some embodiments, midazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[0118] 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.

[0119] 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.

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

[0121] **Temazepam** (7-chloro-1-methyl-5-phenyl-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one)



[0122] 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.

[0123] 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.

[0124] 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

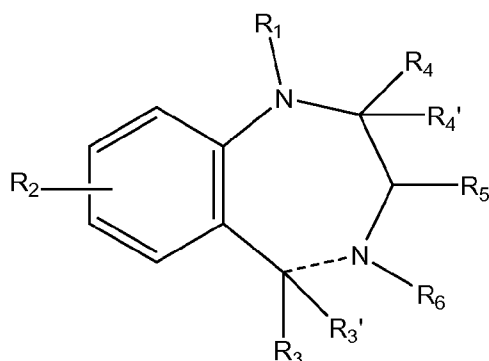
patient is prone to experiencing serial seizures or status epilepticus, administration of temazepam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with temazepam to provide a synergistic anticonvulsant effect.

[0125] 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.

[0126] 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

[0127] 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.

[0128] 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 acid, ascorbic 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 acid, fumaric 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, propionic 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

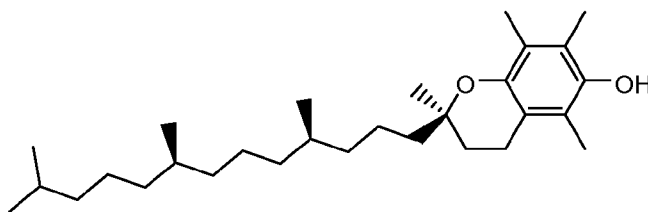
salts. Likewise the person skilled in the art will recognize that in some embodiments it may be advantageous that some or all of the added acid be an active pharmaceutical ingredient in its own right.

[0129] 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, NaHCO₃, Na₂CO₃, NH₃) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

[0130] 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

[0131] 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

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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

[0137] 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, maltotetraose, 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).

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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

[0143] 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.

[0144] 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

[0145] 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.

[0146] 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

[0147] 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.

[0148] As a nasal formulation, diazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Flurazepam

[0149] 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.

[0150] As a nasal formulation, flurazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Lorazepam

[0151] 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.

[0152] As a nasal formulation, lorazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Medazepam

[0153] 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.

[0154] As a nasal formulation, medazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Mexazolam

[0155] 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.

[0156] As a nasal formulation, mexazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Midazolam

[0157] 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.

[0158] As a nasal formulation, midazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Temazepam

[0159] 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.

[0160] As a nasal formulation, temazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 μ L, especially about 100 μ L, metered sprays.

Formulation

[0161] 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.

[0162] 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.

[0163] 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.

[0164] In some embodiments of the method, the dosage volume ranges from about 10 μ L to about 200 μ L. In some embodiments, the dosage volume ranges from about 20 μ L to about 180 μ L. Further, some embodiments disclose a dosage volume of about 50 μ L to about 140 μ L. In some embodiments, the dosage volume is 50 μ L, 75 μ L or 100 μ L per nostril.

Formulation Process

[0165] 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.

[0166] 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.

[0167] 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.

[0168] 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

[0169] 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 syncytial 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 (Calcitonin 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.

[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: paraldehyde; aromatic allylic alcohols (such as stiripentol); barbiturates (e.g. phenobarbital, primidone, methylphenobarbital, metharbital and barbexalone); 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); hydantoin (e.g. ethosoin, phenytoin, mephentyoin 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.

[0171] 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 tetracycline 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 acetone, 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, chlorpheniramine 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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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

[0177] 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

[0178] 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.

[0179] As a nasal formulation, alprazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0180] 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.

[0181] As a nasal formulation, diazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0182] 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.

[0183] As a nasal formulation, flurazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0184] 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.

[0185] 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

[0186] 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.

[0187] 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

[0188] 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.

[0189] As a nasal formulation, mexazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0190] 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.

[0191] As a nasal formulation, midazolam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μ L, especially about 100 μ L, 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

[0192] 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.

[0193] As a nasal formulation, temazepam may be administered in 25 to 250 μ L metered sprays. In some preferred embodiments, temazepam is administered in 50 to 150 μ L, especially about 100 μ L, 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.

[0194] 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

[0195] The invention will now be illustrated with reference to the following illustrative, non-limiting examples.

Example 1

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

Example 2

[0197] 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/0.1 mL	Diazepam
70.0 mg	α -tocopherol
0.1 mL	ethanol (qs ad to 0.1 mL)

Example 3 – Formulation of Diazepam Solutions

[0198] 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.

[0199] 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

[0200] 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

[0201] 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.

[0202] 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

[0203] 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

[0204] 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/ml suspension	083103.01	083103.02	083103.03
Suspension 03 - 200 mg/ml suspension	083104.01	083104.02	083104.03

[0205] 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>.

[0206] 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.

[0207] 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.

[0208] 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%

[0209] 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	1	1	3	3	3	6	6	6
			month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %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/mL, 65% Vitamin E	Specifications	Initial	1	1	1	3	3	3	6	6	6
			month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %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	1	1	3	3	3	6	6	6
			month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH	month 25°C/6 0 %RH	month 30°C/6 5 %RH	month 40°C/7 5 %RH

			%RH	%RH	%RH	%RH	%RH	%RH	%RH	%RH	%RH
Description	Cloudy to white solution	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White 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%-115.0%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2
Propylparaben (%)	80.0%-115.0%	100.2	100.5	92.2	99.2	100.6	99	100	98.5	97.6	96.7
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested
Fill weight (g)	report results	1.254	1.252	1.252	1.244	1.246	1.248	1.247	1.245	1.242	1.235
Fill volume (ml)	report results	1.198	1.196	1.196	1.188	1.191	1.193	1.191	1.190	1.187	1.180
Spray delivered (µl)	report results	132.5	131.2	126	123.9	137.6	137.8	136.3	140.0	not tested	137.6
Average Spray Content (%)	report results	92.2	94.2	91.1	89.9	101.5	100.4	95.3	101.8	not tested	95.94
Viscosity (Pa*s)	report results	0.0098	0.0098	0.0092	0.0090	0.0092	0.0093	0.0089	0.0082	0.0080	0.0092

(1) LOQ is approximately 0.006%, LOD is approximately 0.002%. 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	1	1	3	3	3	6	6	6
			month 25°C/60 %RH	month 30°C/65 %RH	month 40°C/75 %RH	month 25°C/60 %RH	month 30°C/65 %RH	month 40°C/75 %RH	month 25°C/60 %RH	month 30°C/65 %RH	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%-115.0%	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
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(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
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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

[0210] 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

[0211] 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.

[0212] Toxicity is assessed by known means. In particular, histological samples are collected from the nasal mucosal tissues of the test animals. Other toxicological methods are optionally employed as well.

Example 8

[0213] 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

[0214] 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

[0215] The above-described solutions and/or suspensions can be evaluated for efficacy in a suitable animal model. Briefly, for each dose of suspension or solution to be tested, a test animal is stimulated with a seizure inducing stimulus. The stimulus may be light, sound, chemical or other stimulus effective to induce seizure in the model animal. Once the animal has begun to seize, a solution or suspension as described herein is administered intranasally to the animal. The efficacy of the dose of the solution and/or suspension is evaluated based upon the animal's response to the test dose. This procedure is repeated through sufficient iterations, and at sufficient numbers of doses, to identify a dose that is considered effective to treat seizure by intranasal administration of the drug.

Example 11

[0216] A pharmaceutical composition comprising diazepam was prepared as a composition formulated as a solution to be delivered via a nasal delivery device. The ingredients used in the solution formulation are set forth in Table 11-1, below

Table 11-1

<u>Ingredient</u>	<u>Concentration (%w/vol)</u>
Diazepam	10.0
α -tocopherol*	0.25
Ethanol	18.07
Intravail A3**	0.25
Benzyl alcohol	10.5

*Vitamin E, **Dodecyl maltoside

[0217] A three-period, three-treatment, six-sequence, randomized cross-over study was conducted in healthy volunteers. For each dose, each volunteer was domiciled for at least 12 hours prior to each dose and until after a 24 hour pharmacokinetic sample was collected. A single dose of 100 μ L of the pharmaceutical composition described in Table 11-1 was administered to each volunteer as one spray to the left nostril of 100 μ L p. Pharmacokinetic samples were collected at 22 time points over 10 days. (PK time points: 2.5, 5, 10, 15, 20, 30 and 45 minutes, 1, 1.5, 2, 4, 12, 24, 36, 48, 72, 96, 144, 192 and 240 hours after each dose.) No serious adverse events were noted. PK data were compared with those obtained with 5 mg of diazepam administered intravenously.

[0218] The solution of Table 11-1 was found to be well-tolerated with only mild adverse events reported. The solution of Table 11-1 was further found to have similar bioavailability to intravenous administration of diazepam (96% of i.v.) The intranasal formulation of Table 11-1 exhibited a T_{max} of 1.5 hours, a C_{max} of approximately 272 ng/mL. These results are comparable to those reported in the literature for commercially available diazepam gel (Diastat®).

[0219] Solutions similar to those set forth in Table 11-1 can be prepared consisting of: diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v); diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v); or diazepam (10 %w/v), dodecyl maltoside (0.15-0.3 %w/v), vitamin E (50-60 w%/v), ethanol (17-20 w%/v) and benzyl alcohol (10-12 %w/v).

[0220] Solutions similar to those set forth in Table 11-1 achieve bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously, *e.g.* bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously or about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously. Such solutions may be used in methods of treating a patient with a disorder which may be treatable with a benzodiazepine drug, such as seizure, epileptic seizure and/or breakthrough seizure. In some embodiments, solutions described herein may be used to treat a disorder such as is treated with Diastat® diazepam gel.

[0221] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical solution for nasal administration consisting of:

- (a) a benzodiazepine drug;
- (b) one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w);
- (c) one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and
- (d) an alkyl glycoside,

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

2. The pharmaceutical solution of claim 1, wherein the benzodiazepine drug is dissolved in the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

3. The pharmaceutical solution of claim 2, wherein the benzodiazepine drug is selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, diazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, lopraxolam, any pharmaceutically-acceptable salts thereof, and any combinations thereof.

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

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

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

7. The pharmaceutical solution of claim 1, wherein the one or more natural or synthetic tocopherols or tocotrienols are selected from the group consisting of: α -tocopherol, β -tocopherol, γ -tocopherol, δ -tocopherol, α -tocotrienol, β -tocotrienol, γ -tocotrienol, δ -tocotrienol, tocopherols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, and any combinations thereof.

8. The pharmaceutical solution of claim 1, wherein the one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof.

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

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

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

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

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

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

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

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

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

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

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

20. A method of treating a patient with a disorder which may be treatable with a benzodiazepine drug, comprising: administering to one or more nasal mucosal membranes of a patient a pharmaceutical solution for nasal administration consisting of a benzodiazepine drug, one or more natural or synthetic tocopherols or

tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w); and an alkyl glycoside.

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 the natural or synthetic tocopherols or tocotrienols is Vitamin E.

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 solution contains about 1 to about 20 %w/v of benzodiazepine.

26. The method of claim 25, wherein the solution contains about 1 to about 20 %w/v of diazepam.

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 solution contains two or more alcohols.

30. The method of claim 20, wherein the solution contains ethanol (1-25 %w/v) and benzyl alcohol (1-25 % w/v).

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

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

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

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

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

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

37. The method of claim 20, wherein the solution contains ethanol (10-22.5 %w/v) and benzyl alcohol (7.5-12.5 % w/v).

38. The method of claim 20, wherein the solution 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 solution is in a pharmaceutically-acceptable spray formulation having volume from about 10 μ L to about 200 μ L.

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

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

43. The method of claim 42, wherein the administration of the pharmaceutical solution comprises spraying a first quantity of the pharmaceutical solution into the first nostril, spraying a second quantity of the

pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the pharmaceutical solution into the first nostril.

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

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

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

47. The method of claim 21, wherein the solution contains about 0.01% to 1% (w/w) of an alkyl glycoside.

48. The method of claim 47, wherein the solution contains about 0.01% to 1% (w/w) of dodecyl maltoside.

49. The method of one of claims 20-48, wherein the solution consists of diazepam, alkyl glycoside, vitamin E, ethanol, and benzyl alcohol.

50. The method of one of claims 20-48, wherein the solution consists of diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v).

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

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

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

54. The method of claim 20, wherein the solution consists of diazepam (5-15 %w/v), dodecyl maltoside (0.01-1 %w/v), vitamin E (45-65 w%/v), ethanol (10-25 w%/v) and benzyl alcohol (5-15 %w/v).

55. The method of claim 20, wherein the solution consists of diazepam (9-11 %w/v), dodecyl maltoside (0.1-0.5 %w/v), vitamin E (50-60 w%/v), ethanol (15-22.5 w%/v) and benzyl alcohol (7.5-12.5 %w/v).

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

57. The method of one of claims 20-50 or 54-56, wherein said treatment achieves bioavailability that is from about 80-125% of that achieved with the same benzodiazepine administered intravenously.

58. The method of claim 57, wherein said treatment achieves bioavailability that is from about 90-110% of that achieved with the same benzodiazepine administered intravenously.

59. The method of claim 58, wherein said treatment achieves bioavailability that is from about 92.5 to 107.5% that obtained with the same benzodiazepine administered intravenously.

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

ABSTRACT

[0222] The invention relates to pharmaceutical compositions comprising one or more benzodiazepine drugs for nasal administration, methods for producing and for using such compositions.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	35401-716.102
		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					<input type="button" value="Remove"/>
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118	
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Steve		Cartt		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	San Carlos	State/Province	CA	Country of Residence i	US
Citizenship under 37 CFR 1.41(b) i		US			
Mailing Address of Applicant:					
Address 1					
Address 2					
City		State/Province			
Postal Code		Countryi			
Applicant 2					<input type="button" value="Remove"/>
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118	
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City	South San Francisco	State/Province	CA	Country of Residence i	US
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Mailing Address of Applicant:					
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Address 2					
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Applicant 3					<input type="button" value="Remove"/>
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118	
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Garry	Thomas	Gwozdz		
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	35401-716.102	
		Application Number		
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS			
Citizenship under 37 CFR 1.41(b) i	US			
Mailing Address of Applicant:				
Address 1				
Address 2				
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Applicant 4				Remove
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118
Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
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Mailing Address of Applicant:				
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Applicant 5				Remove
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118
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	Mark		Mitchnick	
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> 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:				
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City			State/Province	
Postal Code			Country ⁱ	
Applicant 6				Remove
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118
Prefix	Given Name	Middle Name	Family Name	Suffix
	David		Hale	
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
City	San Diego	State/Province	CA	Country of Residence ⁱ
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.102
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Mailing Address of Applicant:			
Address 1			
Address 2			
City		State/Province	
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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.			<input type="button" value="Add"/>

Correspondence Information:

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<input type="checkbox"/> An Address is being provided for the correspondence information of this application.			
Customer Number	21971		
Email Address	patentdocket@wsgr.com	<input type="button" value="Add Email"/>	<input type="button" value="Remove Email"/>

Application Information:

Title of the Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		
Attorney Docket Number	35401-716.102	Small Entity Status Claimed	<input checked="" type="checkbox"/>
Application Type	Provisional		
Subject Matter			
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:

<input type="checkbox"/> Request Early Publication (Fee required at time of Request 37 CFR 1.219)
<input type="checkbox"/> 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.			
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.102
	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			<input type="button" value="Remove"/>
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

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

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).

			<input type="button" value="Remove"/>
Application Number	Country ⁱ	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			<input checked="" type="radio"/> Yes <input type="radio"/> No

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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	<input type="button" value="Remove"/>
If the Assignee is an Organization check here. <input checked="" type="checkbox"/>	
Organization Name	Hale BioPharma Ventures, LLC

Mailing Address Information:

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Address 2	
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Additional Assignee Data may be generated within this form by selecting the **Add** button.

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	/Matthew V. Grumbling/	Date (YYYY-MM-DD)	2011-06-14
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	35401-716.102		
		Application Number			
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS				
First Name	Matthew	Last Name	Grumbling	Registration Number	44427

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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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.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 Remove

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Steve		Cartt	San Carlos	CA	US

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Inventor 3 Remove

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Given Name	Middle Name	Family Name	City	State	Country ;
Andrew		Loxley	Philadelphia	PA	US

Inventor 5 Remove

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Inventor 6 Remove

Given Name	Middle Name	Family Name	City	State	Country ;
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All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Title of Invention Administration of Benzodiazepine Compositions

Attorney Docket Number (if applicable) 35401-716.102

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Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
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Customer Number	21971
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

<input checked="" type="radio"/> No.
<input type="radio"/> Yes, the name of the U.S. Government agency and the Government contract number are:

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Entity Status
 Applicant claims small entity status under 37 CFR 1.27

- Yes, applicant qualifies for small entity status under 37 CFR 1.27
 No

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to 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.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Matthew V. Grumbling/			Date (YYYY-MM-DD)	2011-06-14
First Name	Matthew	Last Name	Grumbling	Registration Number (If appropriate)	44427

This collection of information is required by 37 CFR 1.51. 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 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

Privacy Act Statement

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	10304787
Application Number:	61497017
International Application Number:	
Confirmation Number:	3393
Title of Invention:	Administration of Benzodiazepine Compositions
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Peter R. Munson./Misty Elam (MG/PM/ME)
Filer Authorized By:	Peter R. Munson.
Attorney Docket Number:	35401-716.102
Receipt Date:	14-JUN-2011
Filing Date:	
Time Stamp:	21:21:36
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$110
RAM confirmation Number	7451
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size (KB)	Multi-Part (.zip or appl.)	Pages (if appl.)
		AQUESTIVE EXHIBIT 1040	Message Digest		page 1 of 25

1		716-102ProvisionalApp.pdf	522005	yes	70
			252ed89ccb9dd5b90a395d5f38d89f3d50ff49a1		
Multipart Description/PDF files in .zip description					
		Document Description	Start	End	
		Specification	1	63	
		Claims	64	69	
		Abstract	70	70	
Warnings:					
Information:					
2	Application Data Sheet	716-102ADS.pdf	1031793	no	6
			8fa372058755c5deffaca3f7bbda2b2bd2dd10e4		
Warnings:					
Information:					
3	Provisional Cover Sheet (SB16)	716-102ProvCoverSheet.pdf	1060398	no	4
			49246f205fa45b38c9b226344d03dcefa8f3d27c		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29296	no	2
			48b3b35a86d3dd135a94f3b6d5bb4f3256d1089		
Warnings:					
Information:					
Total Files Size (in bytes):			2643492		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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



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ETATS-UNIS D'AMERIQUE

**For any questions about
this communication:**

Tel.: +31 (0)70 340 45 00

Date

25.10.13

Reference	Application No./Patent No. 12801372.9 - 1453 PCT/US2012042311
Applicant/Proprietor Hale BioPharma Ventures, LLC	

Entry into the European phase before the European Patent Office

The following information describes the procedural steps required for entry into the European phase before the European Patent Office (EPO). You are advised to read it carefully because failure to take the necessary action in due time can lead to a loss of rights.

1. The above mentioned international patent application has been given the **European application No. 12801372.9**.
2. Applicants **without a residence or their principal place of business** in an EPC Contracting State may themselves initiate European processing of their international applications, provided they do so before expiry of the 31st month from the priority date.

During the European phase before the EPO as designated or elected Office, however, such applicants **must** be represented by a professional representative (Art. 133(2) and Art. 134(1) and (8) EPC).

Where, at the expiry of the time period laid down in Rule 163(5) EPC, the requirements of Article 133(2) EPC have not been complied with, the European patent application will be **refused**, pursuant to Rule 163(6) EPC.

Please note that a professional representative authorised to act before the EPO and who acted for the applicant during the international phase does not automatically become the representative for the European phase. Applicants are therefore strongly advised to appoint in good time any representative they wish to initiate the European phase for them; otherwise the EPO has to send all communications directly to the applicant.

3. Applicants **with a residence or their principal place of business** in an EPC Contracting State are not obliged to appoint for the European phase a professional representative authorised to act before the EPO. However, in view of the complexity of the procedure it is recommended that they do so.
4. Applicants and professional representatives are also strongly advised to initiate the European phase using **EPO Form 1200**. It is available free of charge from the EPO or via the EPO website at **www.epo.org**. Similarly, it can be or generated with the Online Filing software, obtainable free of charge from the EPO (**www.epoline.org**) The use of the form is not compulsory.

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5. Where the EPO acts as designated or elected Office (Art. 22(1) and (3) and 39(1) PCT), to enter the European phase before the EPO, the **following acts** must be performed by the applicant within **31 months** from the date of filing of the international application or (where applicable) the earliest priority date:
- a) Supply a translation of the international application into an EPO official language, if the International Bureau did not publish the application in such language (Art. 22(1) PCT and R. 159(1)(a) EPC);
 - b) Specify the application documents, as originally filed or as amended, on which the European grant procedure is to be based (R. 159(1)(b) EPC);
 - c) Pay the filing fee and, where applicable, the additional fee for a European patent application comprising more than 35 pages (R. 159(1)(c) EPC, Art. 2, items 1, 1a Rules relating to Fees);
 - d) Pay the search fee where a supplementary European search report has to be drawn up (R. 159(1)(e) EPC);
 - e) Pay the designation fee if the time limit laid down in Rule 39(1) EPC (i.e. six months after publication of the international search report) has expired before the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(d) EPC);
 - f) File the written request for examination and pay the examination fee if the time limit laid down in Rule 70(1) EPC has expired before the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(f) EPC);
 - g) Pay the renewal fee in respect of the third year, if the fee has fallen due (see Rule 51(1) EPC) before expiry of the 31-month period pursuant to Rule 159(1) EPC (R. 159(1)(g) EPC);
 - h) File, where applicable, the certificate of exhibition referred to in Article 55(2) and Rule 25 EPC (R. 159(1)(h) EPC);
 - i) Pay the claims fees for the sixteenth and each subsequent claim when the application documents on which the European grant procedure is to be based comprise more than fifteen claims (R. 162(1) EPC). For applications entering the European phase on or after 1 April 2009, a higher amount is payable for the 51st and each subsequent claim (Decision of the Administrative Council of 14 December 2007 amending the Rules relating to Fees, OJ EPO 2008, 10).

If either the translation of the international application or the request for examination is not filed in time, or if the filing fee, the additional fee, the search fee, the designation fee or the examination fee is not paid in due time, the application shall be deemed to be withdrawn (R. 160(1) EPC).

6. Payment of fees

An up-to-date guidance for the payment of fees, expenses and prices and a list of the euro accounts of the European Patent Organisation are published in each issue of the Official Journal of the EPO. The guidance includes inter alia a reference to the latest version of the Schedule of fees and expenses where the amounts of fees are set out.

The Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under **www.epo.org/schedule-of-fees**, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Applicants should always check the fee amounts applying at the time of payment.

Payments can be validly made by any person. Permissible methods of payment are laid down in Article 5 Rules relating to Fees. Please note that payment cannot be made by cheque sent to the EPO.

For information on the calculation of the additional fee for applications comprising more than 35 pages, see Notice from the European Patent Office dated 26 January 2009 concerning the 2009 fee structure (OJ EPO 2009, 118), Notice supplementing the notice from the European Patent Office dated 26 January 2009 concerning the 2009 fee structure (OJ EPO 2009, 338) and Guidelines for Examination in the EPO, April 2010, A-III, 13.2.

For an overview of search and examination fees, see Notice from the European Patent Office dated 6 February 2012 (OJ EPO 2012, 212). Fee information is also published on the EPO website under www.epo.org/fees.

7. Restoration of priority right

Where the international application contains a priority claim to an earlier application and it has been filed within two months from the expiration of the 12-month priority period, a request for restoration before the EPO as designated Office (R. 49*ter*.2 PCT) applies under the following circumstances:

- a) No request for restoration filed before the receiving Office (RO) during the international phase (R. 26*bis*.3 PCT)
- b) Negative decision by the RO irrespective of the criterion applied (due care/ unintentionality)
- c) Positive decision by the RO based on the unintentionality criterion.

For a request to be admissible, it must be filed and the requisite fee must be paid (R. 49*ter*.2(b)(iii) and R. 49*ter*.2(d) PCT) within one month from the applicable time limit under Article 22 PCT for entering the regional phase (R. 49*ter*.2(b)(i) PCT). The request for restoration also needs to state the reasons for the failure to file the international application within the priority period (Rule 49*ter*.2(b)(ii) PCT).

8. If the applicant had appointed a representative during the application's international phase, the present Form will be sent to the representative, asking him to inform the applicant accordingly. All subsequent communications will be sent to the applicant, or - if the EPO is informed of his appointment in time - to the applicant's European representative.
9. For more details about time limits and procedural acts before the EPO as designated or elected Office, see the EPO brochure "How to get an European patent", Guide for applicants - Part 2, PCT procedure before the EPO - "Euro-PCT" (EPO PCT Guide). This brochure, the list of professional representatives before the EPO, Form 1200 and details of the latest fees are available on the Internet under <http://www.epo.org>.

10. Programme for accelerated prosecution of European patent applications - "PACE"

Applicants wishing to accelerate proceedings before the EPO as designated or elected Office may request accelerated search and/or examination under the PACE programme (Notice from the European Patent Office dated 4 May 2010 concerning the programme for accelerated prosecution of European patent applications - "PACE", OJ EPO 2010, 352). To be as effective as possible, this should preferably be requested immediately on entry into the European phase.

Receiving Section

