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

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

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

INCORPORATION BY REFERENCE

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

about 95% (w/w); and the one or more alcohols or glycols, or any combinations thereof, in an amount from about 5% to about 70% (w/w). In some embodiments, the benzodiazepine drug is dissolved in a carrier system. In some embodiments, at least part of the benzodiazepine drug is in a form of microparticles, nanoparticles, or combinations thereof. In some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof.

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

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

[037] In some embodiments, one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof. In some embodiments, the alcohol is ethanol (dehydrated, USP). In some embodiments, the one or more glycols are selected from the group consisting of: ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, and any combinations thereof. In some embodiments, the glycol is propylene glycol USP. In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded

or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

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

[039] In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 45% to about 85% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 60% to about 75% (w/w). In some embodiments, the carrier system comprises one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount of about 70% (w/w). In some embodiments, a synthetic tocopherol can include Vitamin E TPGS (Vitamin E polyethylene glycol succinate). In some embodiments, on the other hand, synthetic tocopherols exclude tocopherols covalently bonded or linked (e.g. through a diacid linking group) to a glycol polymer, such as polyethylene glycol). Thus, in some embodiments, the compositions described herein exclude Vitamin E TPGS.

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

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

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

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

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

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

[045] In some embodiments, the composition comprises a benzodiazepine drug that is fully dissolved in a solvent comprising a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. Thus, in some embodiments, the composition is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition

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

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

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

[047] In some embodiments, the composition contains a benzodiazepine drug that at least partially in a particulate form suspended in a carrier system containing a natural or synthetic tocopherol or tocotrienol, one or more alcohols or glycols, and an alkyl glycoside. In some embodiments, substantially all the benzodiazepine drug is in a particulate form. In some embodiments, at least part of the benzodiazepine drug is in a microparticulate or nanoparticulate form. The carrier system is one in which the amount of at least one benzodiazepine present in the composition exceeds its solubility in the carrier system. In some embodiments, a carrier system in such a composition includes water. In some embodiments, such a liquid carrier system contains water and one or more excipients. In some embodiments, one or more excipients are dissolved or suspended in the carrier system. In some embodiments, at least one such excipient stabilizes the suspension of benzodiazepine particulates in

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

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

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

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

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

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

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

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

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

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

[056] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is an alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130, which is incorporated herein by reference in its entirety. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-, decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01 % (w/v) to about 1 % (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05 % (w/v) to about 0.5% (w/v), or about 0.125 % (w/v) to about 0.5% (w/v).

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

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

embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

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

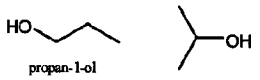
Definitions

[060] As used herein the phrase "therapeutically effective amount" (or more simply "effective amount") includes an amount sufficient to provide a specific therapeutic response for which the drug is administered to a patient in need of particular treatment. The skilled clinician will recognize that the therapeutically effective amount of drug will depend upon the patient, the indication and the particular drug administered.

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

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

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



propan-1-ol propan-2-ol

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

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

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

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

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

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

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

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

Benzodiazepine Drugs

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

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

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

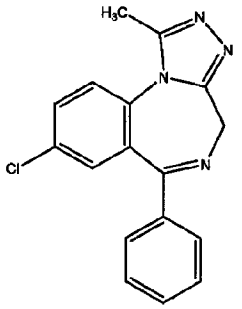
drugs to be administered to one or more mucosal membranes, including to nasal mucosal membranes. This can allow one to administer the drug without hospitalization or unnecessary discomfort. Additionally, in some embodiments of the present invention, such as nasal administration, the digestive system largely may be bypassed. This latter improvement can yield improved bioavailability, faster attainment of therapeutic levels of benzodiazepine in the blood plasma, avoidance of the liver portal vein, and/or concomitant avoidance of first pass effects.

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

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

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

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



[078] Alprazolam is a benzodiazepine drug having sedative, tranquilizing and muscle relaxing properties. It is classified as an anxiolytic. Alprazolam has also been shown to be useful in the treatment of panic disorder. The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6

times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

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

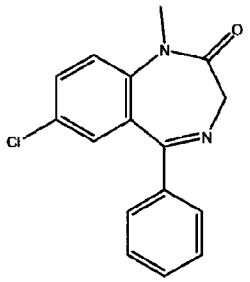
[080] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam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

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

[082] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some

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

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



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

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

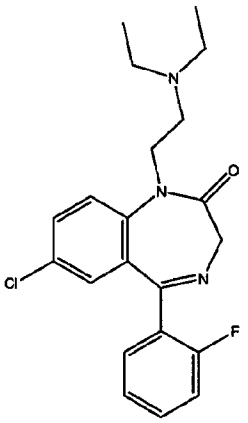
[086] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam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

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

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

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

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



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

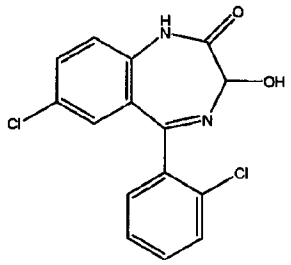
[091] In some embodiments, flurazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

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

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

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

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



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

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

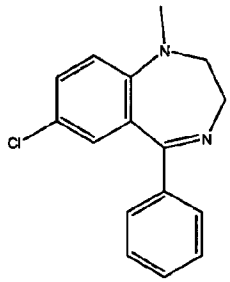
[098] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam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

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

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

[0100] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

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



[0102] Medazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Medazepam has also been shown to be useful in the treatment of nausea. The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427, which is incorporated herein by reference in its entirety.

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

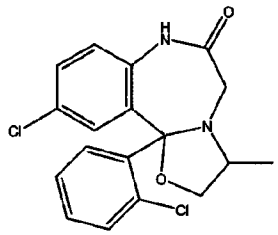
[0104] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam may be administered by the patient or other person (such as a healthcare

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

[0105] Medazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the medazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The medazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0106] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

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



[0108] Mexazolam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Mexazolam has also been shown to be useful in the treatment of nausea. The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371, which is incorporated herein by reference in its entirety.

[0109] In some embodiments, mexazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

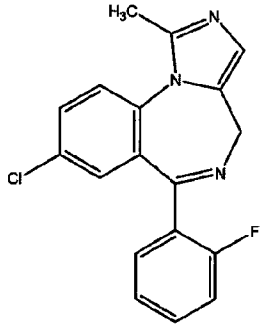
[0110] In some embodiments, mexazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Mexazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of mexazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of mexazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of mexazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with mexazolam to provide a synergistic anticonvulsant effect.

[0111] Mexazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a

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

[0112] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

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



[0114] Midazolam is a tricyclic benzodiazepine having anxiolytic, amnesic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. Midazolam is considered soluble in water at a pH lower than about 4, but is relatively insoluble in most aqueous solutions at neutral pH (e.g. about 6 to 8). Thus it is desirable in some embodiments for aqueous nasal preparations of midazolam to have a pH above about 5.5, preferably above about 6.0, or above about 6.5. In some preferred embodiments, the pH is between about 6 and 9, between about 6 and 8. It is considered that preparations of midazolam are particularly suitable for nasal administration as the lipid-soluble (at approximately

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

[0115] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

[0116] In some embodiments, midazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

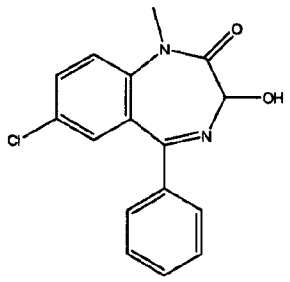
[0117] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection against seizure is not absolute, administration of midazolam may reduce or ameliorate the intensity of seizure and/or reduce or ameliorate the frequency of seizure. In some embodiments, administration of midazolam may prevent occurrence of seizure. In some embodiments, especially where the patient is prone to experiencing serial seizures or status epilepticus, administration of midazolam may aid in interrupting the seizure cycle and may thus prevent the re-occurrence of seizure. In addition to the benzodiazepines (such as diazepam), other anti-convulsant drugs may be combined with midazolam to provide a synergistic anticonvulsant effect.

[0118] Midazolam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the midazolam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less

than about 5 minutes. The midazolam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0119] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

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



[0121] Temazepam is a benzodiazepine drug having sedative, tranquilizing, anticonvulsant, amnesic and muscle relaxing properties. It is classified as an anxiolytic. Temazepam has also been shown to be useful in the treatment of nausea. The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

[0122] In some embodiments, temazepam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

[0123] In some embodiments, temazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of

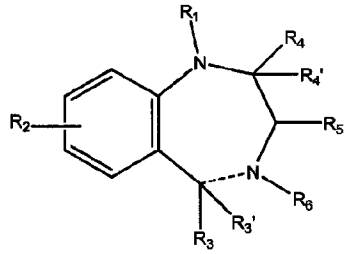
seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Temazepam may be administered by the patient or other person (such as a healthcare professional) while the patient is in a non-seizing state to protect against seizure. Even where protection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

[0124] Temazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability to administer them in an acute therapeutic environment to treat the seizure victim, for example, nasally. Among the beneficial therapeutic effects that may be imparted by acute dosing of benzodiazepine anticonvulsants, such as nasal dosing, are: reduction in the severity of the seizure (*e.g.* general relaxation of the muscles, reduction in seizure-induced anxiety experienced by the patient and a general impartation of a feeling of well-being to the patient), reduction in the duration of the seizure, reduction in the probability that the patient will experience a repeat seizure, an increase in the interval between the current seizure and the next seizure. Thus, the temazepam formulations of the invention, and in particular nasal formulations, provide fast onset of therapeutic benefit – in some instances less than about 30 minutes, less than about 15 minutes, less than about 10 minutes, and in some cases less than about 5 minutes. The temazepam formulations of the invention, and in particular nasal formulations, also provide convenient administration of a therapeutically beneficial drug to a patient that does not require intravenous drug administration or rectal drug administration.

[0125] Often seizures, particularly severe tonic or tonic-clonic seizures, will be presaged by one or more aura events that will be familiar to the patient or those familiar with the patient. These auras are practically *sui generis* for each patient, but may be classified as audible, visual, olfactory or tactile sensations that usually, or typically, precedes a patient's experiencing a seizure. In some embodiments of the invention, the method includes prompt administration of a preparation of a benzodiazepine drug according to the invention during the aura. In some embodiments, such intra-aural administration of benzodiazepine drug, for example by nasal administration, will prevent or at least ameliorate the effects (intensity, duration or both) of the impending seizure. Thus, in the context of this invention, prevention of seizure refers to a temporary forestalling of the onset of seizure, either with or without the benefit of a warning aura.

Pharmaceutically Acceptable Salts

[0126] Benzodiazepines have the generally basic structure of formula I:



Formula I

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

[0127] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4, H_2SO_3, H_3PO_4, H_3PO_3, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. Thus, in some embodiments, the pharmaceutically acceptable acid may be selected from the group consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acidascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acidfumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (- L), malonic acid, mandelic acid (DL), methanesulfonic acid, benzenesulfonic acid (besylic acid), naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid (- L), salicylic acid, sebacic acid, stearic

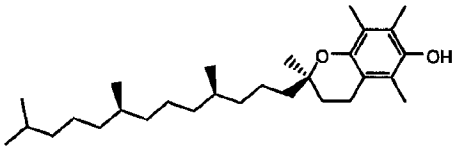
acid, succinic acid, sulfuric acid, tartaric acid (+ L), thiocyanic acid, toluenesulfonic acid (p) and undecylenic acid. Other pharmaceutically acceptable acids may be pharmaceutically acceptable acidic (anionic) polymers or pharmaceutically acceptable amphoteric polymers. One skilled in the art will recognize that other basic active pharmaceutical ingredients may be combined with the foregoing acids to produce acid addition salts. Likewise the person skilled in the art will recognize that in some embodiments it may be advantageous that some or all of the added acid be an active pharmaceutical ingredient in its own right.

[0128] In some embodiments, the invention provides nasal compositions comprising one or more acidic pharmaceutically active ingredients. It is considered well within the ordinary skill in the art to determine which of the compounds set for the above are acidic. Such compounds may be prepared as base addition salts, e.g. by the addition of one or more mineral bases (e.g. NaOH, KOH, $NaHCO_3$, Na_2CO_3, NH_3) or organic bases. It is considered within the skill in the art to choose a pharmaceutically acceptable base.

[0129] Known benzodiazepine compounds have anxiolytic, anticonvulsant, sedative and/or skeletal muscle relaxant effect. The term "anticonvulsant" includes treatment of seizures, protection against seizure, reduction or amelioration of the intensity of seizure, reduction or amelioration of the frequency of seizure, and/or prevention of the occurrence or re-occurrence of seizure. In this regard, treatment of seizure includes cessation of an ongoing seizure, reduction in the severity of an ongoing seizure, reduction in the duration of an ongoing seizure. Protection against seizure includes forestalling an oncoming seizure.

Carrier System

[0130] Vitamin E is a class of fat soluble methylated phenols. There are at least eight naturally-occurring compounds that comprise this class: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β- tocotrienol, γ- tocotrienol, and δ- tocotrienol, all of which may be used in the compositions and methods of the present invention. There are multiple isomers of each of these compounds, all of which may be used in the compositions and methods of the present invention. There are also multiple esters of each of these compounds, including tocophersolan, all of which may be used in the compositions and methods of the present invention. As used herein, Vitamin E refers to any of the natural or synthetic tocopherols, tocotrienols, any isomers thereof, any esters thereof, any analogs or derivatives thereof, or any combinations thereof.



α-tocopherol

[0131] The compounds that comprise Vitamin E are antioxidants. There is also evidence that they can prevent, delay the onset of, or ameliorate the symptoms of heart disease, cancer, cataracts, macular degeneration, glaucoma, Alzheimer's, and Parkinson's disease.

[0132] The inventors have found that Vitamin E can provide an effective carrier for benzodiazepine drugs. In some embodiments, benzodiazepines are soluble, or partially soluble, in Vitamin E. In some embodiments, Vitamin E may be present as microparticles, nanoparticles, or any combination thereof. Furthermore, use of Vitamin E can have the added benefit of either avoiding irritation of sensitive mucosal membranes and/or soothing irritated mucosal membranes.

[0133] Vitamin E is generally classified as hydrophobic, and when used as a carrier may be limited to formulations as an emulsion. However, emulsions can have several drawbacks. For instance, they may be difficult to create and can be highly unstable. Additionally, they can leave an oily film on the surface of the skin. Thus, to avoid the drawbacks of emulsions, some embodiments of the present invention comprise solutions of one or more benzodiazepine drugs in Vitamin E and one or more lower alkyl alcohols or one or more lower alkyl glycols, or any combinations thereof.

[0134] Lower alkyl alcohols are those with six or fewer carbon atoms. Thus, any of ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, or any combinations thereof can be used.

[0135] Lower alkyl glycols are those with six or fewer carbon atoms. Thus, any of ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, any isomers thereof, or any combinations thereof can be used.

Additional Excipients

[0136] In some embodiments, a composition comprises at least one penetration enhancer in addition to a benzodiazepine drug, a natural or synthetic tocopherol or tocotrienol, and an alcohol or glycol. In some embodiments, the penetration enhancer is at least one alkyl glycoside. In some embodiments, the alkyl glycoside refers to any sugar joined to any hydrophobic alkyl, as described in United States patent number 5,661,130, which is incorporated herein by reference in its entirety. The hydrophobic alkyl can be any suitable length, for example about 9 to about 24 carbons in length, especially about 10 to about 14 carbons in length. The hydrophobic alkyl can be branched and/or partially or wholly unsaturated. The alkyl may be joined to the saccharide core for example through a carbonyl group, whereby an ester group may be formed. A suitable alkyl glycoside will have the characteristics of being nontoxic, nonionic, and capable of increasing the absorption of a benzodiazepine drug when it is administered intranasally as described herein. Exemplary saccharides that may be covalently joined to an alkyl according to the present invention include glucose, maltose, maltotriose, maltotetrose, sucrose and trehalose. Exemplary alkyl glycosides that may be employed include octyl-, nonyl-,

decyl-, undecyl-, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl α- or β-D-maltoside, -glucoside or sucroside. In some embodiments, the preferred glycosides include maltose, sucrose or glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12, 14, 16, 18 or 20 carbon atoms. Specific excipients that may be employed in a nasal composition according to the invention include alkylsaccharide is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof. Alkyl glycosides that are particularly considered useful in embodiments of the invention include those marketed under the name Intravail® by Aegis Therapeutics, LLC, San Diego, CA. Other alkyl glycosides may be selected from those having a hydrophile-lipophile balance (HLB) number of from about 10-20, especially about 11-15. The HLB number may be determined as set forth in the publication US2009/0047347, published on 19 February 2009, the entirety of which, and especially paragraphs [0075]-[0079], is incorporated herein by reference. Where present, the amount of alkyl glycoside in the composition is sufficient to enhance the absorption of a benzodiazepine drug administered by the intranasal route. In some embodiments, the amount of alkyl glycoside in the composition is selected so as to enhance absorption of the benzodiazepine drug, while at the same time not significantly irritating the nasal mucosa. In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.01 % (w/v) to about 1 % (w/v). In some embodiments, the amount of alkyl glycoside in the composition is in a range of about 0.05 % (w/v) to about 0.5% (w/v), or about 0.125 % (w/v) to about 0.5% (w/v).

[0137] The term "penetration enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[0138] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% w/v.

[0139] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids

and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

[0140] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

[0141] Thus, in some embodiments, the invention provides a pharmaceutical composition for nasal administration comprising: a benzodiazepine drug, which benzodiazepine drug comprises microparticles, nanoparticles or both, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w); one or more alkyl glycosides; and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w), in a pharmaceutically-acceptable formulation for administration to one or more nasal mucosal membranes of a patient. In some embodiments, the alkyl glycoside is an Intravail® brand alkyl glycoside. In some embodiments, the alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or a combination of two or more thereof. In some embodiments, the alkyl glycoside is dodecyl maltoside. In some embodiments, the alkyl glycoside is tetradecyl maltoside. In some embodiments, the alkyl glycoside is sucrose dodecanoate. In some embodiments, the alkyl glycoside is sucrose monostearate. In some embodiments, the alkyl glycoside is sucrose distearate. In some embodiments, the alkyl glycoside is a combination of two or more of dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, or sucrose distearate.

Mucosal Membrane Preparations

[0142] Mucosal membrane preparations are generally administered in metered sprays having volumes of less than 250 μL, preferably less than 150 μL, and ideally from 25 to 100 μL. Although not prohibited in this invention, administration of volumes larger than about 300 μL per dose usually exceeds the absorption capacity of the membranes. This results in a large portion of the pharmaceutically-active ingredient being lost.

[0143] The dosage volume of preparations, in particular nasal preparations, preferably ranges from 25 to 100 μL. Volumes in excess of the aforementioned ranges may bypass the sinuses and flow down the back of the throat where the excess is swallowed.

Alprazolam

[0144] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

[0145] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays

Diazepam

[0146] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

[0147] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Flurazepam

[0148] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053, each of which is incorporated herein by reference in its entirety.

[0149] As a nasal formulation, flurazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Lorazepam

[0150] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249, which is incorporated herein by reference in its entirety.

[0151] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays.

Medazepam

[0152] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427, which is incorporated herein by reference in its entirety.

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

Mexazolam

[0154] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371, which is incorporated herein by reference in its entirety.

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

Midazolam

[0156] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

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

Temazepam

[0158] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

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

Formulation

[0160] Some embodiments comprise administering to one or more mucosal membranes of a patient a therapeutically effective amount of one or more benzodiazepine drugs, or pharmaceutically-acceptable salts thereof. Some embodiments of the composition disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration up to about 600 mg/mL. Other compositions disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 10 mg/mL up to about 250 mg/mL. Further, some embodiments disclose a composition comprising one or more benzodiazepine drugs or pharmaceutically-acceptable salts thereof in a concentration of about 20 mg/mL up to about 50 mg/mL.

[0161] Some embodiments disclose a carrier system that is about 50% to about 90% (w/w) Vitamin E and about 10% to about 50% (w/w) lower alcohol or lower alkyl glycol, or any combinations thereof. Some embodiments disclose a carrier system that is about 65% to about 75% (w/w) Vitamin E and about 25% to about 35% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof. Further, some embodiments disclose a carrier system that is about 70% (w/w) Vitamin E and about 30% (w/w) lower alkyl alcohol or lower alkyl glycol, or any combinations thereof.

[0162] Some embodiments of the invention provide a method of administering the benzodiazepine drug composition to a patient. The preferred embodiment comprises use of diazepam. Some embodiments of the method disclose a dosage level of diazepam of about 1.0 mg to about 20.0 mg until achievement of the desired result. Other dosage levels disclose a dosage level of about 2.0 mg to about 15.0 mg until the desired result is achieved. Some embodiments disclose a dosage level of about 5.0 mg to about 10.0 mg until the desired result is achieved.

[0163] In some embodiments of the method, the dosage volume ranges from about 10 μL to about 200 μL. In some embodiments, the dosage volume ranges from about 20 μL to about 180 μL. Further, some embodiments disclose a dosage volume of about 50 μL to about 140 μL.

Formulation Process

[0164] In some embodiments, the composition for nasal administration is substantially free of benzodiazepine microparticles, nanoparticles or combinations thereof. In some embodiments, the composition is made by slowly warming or heating the Vitamin E until it is liquefied. Next, the one or more benzodiazepine drugs are added. The mixture is stirred and heated until the one or more benzodiazepine drugs dissolve or are substantially dissolved. Next, the one or more alcohols or glycols, or any combinations thereof, are added to the composition. This composition is stirred until a less viscous composition is achieved.

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

[0166] In some embodiments, the benzodiazepine drug is formulated as a microparticulate and/or nanoparticulate suspension of the benzodiazepine. Preparation of microparticulate and nanoparticulate benzodiazepine may be accomplished by methods such as milling, etc. Such methods are known to those skilled in the art.

[0167] In some embodiments, the benzodiazepine drug is formulated as a solution. It is considered an aspect of the invention that employment of microparticulate and/or nanoparticulate benzodiazepine drug during the process of preparing the formulation, can improve the overall solubility of the benzodiazepine drug in the solvent system.

Additional Active and Inactive Ingredients

[0168] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from active ingredients. By way of non-limiting example, such active ingredients include insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof, enkephalins, LHRH and analogues (Nafarelin, Buserelin, Zolidex), GHRH (growth hormone releasing hormone), nifedipin, THF (thymic humoral factor), CGRP (calcitonin gene related peptide), atrial natriuretic peptide, antibiotics, metoclopramide, ergotamine, Pizotizin, nasal vaccines (particularly HIV vaccines, measles, rhinovirus Type 13 and respiratory syncitial virus), pentamidine, CCK (Cholecystikinine), DDVAP, Interferons, growth hormone (solatotropir polypeptides or their derivatives (preferably with a molecular weight from 1000 to 300000), secretin, bradykinin antagonists, GRF (Growth releasing factor), THF, TRH (Thyrotropin releasing hormone), ACTH analogues, IGF (Insulin like growth factors), CGRP (Calcitorin gene related peptide) Atrial Natriuretic peptide, Vasopressin and analogues (DDAVP, Lypressin), Metoclopramide, Migraine treatment (Dihydroergotamine, Ergometrine, Ergotamine, Pizotizin), Nasal Vaccines (Particularly AIDS vaccines) FACTOR VIII, Colony Stimulating factors, G-CSF (granulocyte-colony stimulating factor), EPO (Erythropoitin) PTH (Parathyroid hormone) or pharmaceutically acceptable salts or combinations thereof.

[0169] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: paraldehyde; aromatic allylic alcohols (such as stiripentol); barbiturates (e.g. phenobarbitol, primidone, methylphenobarbital, metharbital and barbexaclone); bromides (such as potassium bromide); carbamates (such as felbamate); carboxamides (such as carbamazepine and oxcarbazepine); fatty acids (such as valproic acid, sodium valproate, and divalproex sodium, vigabatrin, progabide, tiagabine); fructose, topiramate, Gaba analogs (e.g. gabapentin and pregabalin); hydantoins (e.g. ethotoin, phenytoin, mephenytoin and fosphenytoin); oxazolidinediones (such as paramethadione, trimethadione, ethadione); propionates (e.g. beclamide), pyrimidinediones (e.g. primidone); pyrrolidines (e.g. brivaracetam, levetiracetam and seletracetam); succinimides (e.g. ethosuximide, phensuximide and mesuximide); sulfonamides (e.g. acetazolamide, sulthiame, methazolamide and zonisamide); triazines (such as lamotrigine); ureas (such as pheneturide, phenacemide); valproylamides (such as valpromide and valnoctamide); as well as other anticonvulsants or pharmaceutically acceptable salts or combinations thereof.

[0170] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, gentamicin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and ethacridine; enzymes such as lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, active vitamin D and vitamin C; sex hormones; hypotensives; sedatives; anti-tumor agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen, diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

[0171] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional inactive ingredient in the composition. By way of non-limiting example,

minor amounts of ingredients such as stabilizers, coloring agents, pH adjusters, buffering agents, preservatives such as agents which may prevent degradation, wetting agents, and flavoring agents may also be present. Examples of coloring agents include β-carotene, Red No. 2 and Blue No. 1. Examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid. Examples of corrigents include menthol and citrus perfume.

[0172] In some embodiments, the drug delivery system of the invention may advantageously comprise an absorption enhancer. The term "enhancer", means any material which acts to increase absorption across the mucosa and/or increases bioavailability. In some embodiments, such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an in vivo or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because in vivo the enhancer should be non-irritant and/or rapidly metabolized to a normal cell constituent that does not have any significant irritant effect.

[0173] In some embodiments, preferred enhancing materials lysophospholipids, for example lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl-carnitine-chloride) is an alternative. In some embodiments, a suitable concentration is from 0.02 to 20% w/v.

[0174] In some embodiments, enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-321 (which is incorporated herein by reference). Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethylacetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 20% w/v.

[0175] In some embodiments, the invention takes advantage of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, bestatin, chloroacetyl-HOLeu-Ala-Gly-NH.sub.2, diprotin A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin, kallikrein, chymostatin,

benzamidine, chymotrypsin and trypsin. Suitable concentrations are from 0.01 to 10% w/v. The person skilled in the art will readily be able to determine whether an enhancer should be included.

Administration

[0176] In some embodiments, the administration of the composition comprises administering at least a portion of the therapeutically effective amount of the composition onto at least one mucosal membrane. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into at least one nostril. In some embodiments, the administration of the composition comprises spraying at least a portion of the therapeutically effective amount of the composition into each nostril. In some embodiments, the administration of the composition comprises spraying a first quantity of the composition into the first nostril, spraying a second quantity of the composition into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of the composition into the first nostril. Some embodiments further comprise, optionally after a pre-selected time delay, administering at least a fourth quantity of the composition to the second nostril.

Alprazolam

[0177] The dosage of alprazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.5 to about 4, preferably about 1 to about 2 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Alprazolam may be manufactured using the process disclosed in United States patent 3,987,052, which is incorporated herein by reference in its entirety.

[0178] As a nasal formulation, alprazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, alprazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Diazepam

[0179] The dosage of diazepam may vary by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 20, preferably about 2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Diazepam may be manufactured using the process disclosed in one of United States patents 3,371,085, 3,109,843, 3,136,815 or 3,102,116, each of which is incorporated herein by reference in its entirety.

[0180] As a nasal formulation, diazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, diazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Flurazepam

[0181] The dosage of flurazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 5 to 40, preferably about 20 to about 35 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Flurazepam may be manufactured using the process disclosed in United States patent 3,567,710 or 3,299,053, each of which is incorporated herein by reference in its entirety.

[0182] As a nasal formulation, flurazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, flurazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a

full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Lorazepam

[0183] The dosage of Lorazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Lorazepam may be manufactured using the process disclosed in United States patent 3,296,249, which is incorporated herein by reference in its entirety.

[0184] As a nasal formulation, lorazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, lorazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Medazepam

[0185] The dosage of medazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Medazepam may be manufactured using the process disclosed in United States patent 3,243,427, which is incorporated herein by reference in its entirety.

[0186] As a nasal formulation, medazepam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, medazepam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This

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

Mexazolam

[0187] The dosage of mexazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 10, preferably about 0.2 to about 1 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Mexazolam may be manufactured using the process disclosed in United States patent 3,722,371, which is incorporated herein by reference in its entirety.

[0188] As a nasal formulation, mexazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, mexazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Midazolam

[0189] The dosage of midazolam varies by indication, however it is expected that a therapeutic dose will be in the range of about 0.1 to about 20, preferably about 0.2 to about 10 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Midazolam may be manufactured using the process disclosed in one of United States patents 4,280,957 or 5,831,089, each of which is incorporated herein by reference in its entirety.

[0190] As a nasal formulation, midazolam may be administered in 25 to 250 μL metered sprays. In some preferred embodiments, midazolam is administered in 50 to 150 μL, especially about 100 μL, metered sprays. In some embodiments, a first metered spray is applied to a first nostril and if necessary a second metered spray is applied to a second nostril. In some optional embodiments, a third metered spray is applied to the first nostril. In some embodiments, a fourth metered spray is applied to the second nostril. In some embodiments, additional metered sprays are applied to alternating nostrils until the full target therapeutic dose has been administered to the patient. In some

embodiments, there is a time increment of from several seconds to 5 minutes, preferably about 10 seconds to about 1 minute, between applications of benzodiazepine drug to the same nostril. This allows time for the drug to cross the nasal mucosa and enter the blood stream. Multiple applications of metered sprays to each nostril, optionally separated by a time interval, allows administration of a full therapeutic dose in increments small enough to permit full absorption of the benzodiazepine drug into the blood stream and avoid loss of drug down the back of the throat.

Temazepam

[0191] The dosage of temazepam varies by indication, however it is expected that a therapeutic dose will be in the range of about 1 to about 50, preferably about 5 to about 30 mg per dose, from 1 to 8, preferably from 2 to 8, and in some preferred embodiments about 4 to about 6 times per day. Temazepam may be manufactured using the process disclosed in United States patent 3,340,253 or 3,374,225, each of which is incorporated herein by reference in its entirety.

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

[0193] Those skilled in the art will be aware that a systematic, therapeutically effective amount of benzodiazepine drugs for treating the aforementioned disorders will vary with age, size, weight, and general physical condition of the patient as well as the severity of the disease. Frequency of administration will likewise vary with the formulation of the composition and it can be adjusted so that any suitable number of doses per day may be used.

Examples

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

Example 1

[0195] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in adults. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 5.0 mg/puff (5.0 mg/0.1 mL and 0.1 mL/puff)) every 5 minutes until cessation of the seizure. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 2.5 mg/puff (5.0 mg/0.1 mL and 0.05 mL/puff)) every 5 minutes until cessation of the seizure. The composition according to this example is set forth in the following table.

Table 1-1

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

Example 2

[0196] A pharmaceutical composition comprising diazepam is prepared. It is formulated as a solution to be delivered via a nasal delivery device. The composition is used to treat or prevent seizures associated with epilepsy in children. Treatment is administered either before or after a seizure has begun. If the patient is seizing, it is administered as 1 puff from any nasal delivery device (1 puff at 2.0 mg/puff (2.0 mg/0.1 mL and 0.1 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. However, it can be given as 1 puff per nostril in each nostril (2 puffs at 1.0 mg/puff (2.0 mg/0.1 mL and 0.05 mL/puff)). If the seizure fails to stop another dose may be administered after 5 minutes. The composition according to this example is set forth in the following table.

Table 2-1

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

Example 3 – Formulation of Diazepam Solutions

[0197] In general, benzodiazepine solutions may be formulated by combining one or more natural or synthetic tocopherols or tocotrienols and one or more lower alcohols or glycols and mixing until a homogeneous mixture is formed, adding the benzodiazepine drug to the homogeneous mixture, heating and mixing the ingredients until the benzodiazepine is fully dissolved in the homogeneous

mixture, cooling the mixture, and bringing the mixture to its final mass or volume with lower alcohol or glycol.

[0198] Two different diazepam solutions were formulated by the foregoing process. Vitamin E USP and dehydrated ethanol USP were combined in the amounts set forth in the following table and mixed to form a homogeneous mixture. Diazepam in the amounts set forth in the following table was then added to the homogeneous mixture. The ingredients were heated to 40-45°C with mixing until the diazepam was fully dissolved, thereby forming a solution. The solution was cooled to 20-25°C, whereupon the solution was brought to its final target weight with dehydrated ethanol USP and the solution was mixed thoroughly to assure homogeneity. The solution was then sampled for in-process testing and packaged in 3 mL amber glass vials.

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

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

[0199] Additional solutions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and the relative amounts of Vitamin E and ethanol. Other benzodiazepine solutions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process (e.g. before or concurrently with the addition of benzodiazepine).

Example 4 -- Formulation of Diazepam Suspensions

[0200] In general, benzodiazepine suspensions are formulated by micronizing benzodiazepine and combining the benzodiazepine with a carrier. The carrier is prepared by combining one or more lower alcohols or glycols with water, adding a natural or synthetic tocopherol or tocotrienol, heating the mixture until the tocopherol or tocotrienol is dissolved, adding one or more parabens and mixing until the parabens are dissolved and cooling the carrier. Once the benzodiazepine is added to the carrier, additional excipients, such as surfactants, can optionally be added and dissolved in the carrier. The suspension is then brought up to its final mass or volume with water.

[0201] Two different diazepam suspensions were formulated by the foregoing general process. Two different diazepam particle sizes were prepared – A: a small particle size by prepared by high pressure micronization, and B: a large particle size prepared by low pressure micronization. The carrier was prepared by combining propylene glycol USP and purified water USP, then adding Vitamin E Polyethylene Glycols Succinate NF, then mixing and heating the combined ingredients to

about 45°C. Mixing was continued until the Vitamin E Polyethylene Glycol Succinate was fully dissolved. The carrier was then cooled to 20-25°C. The micronized diazepam (A and B) was then added to the carrier with vigorous mixing until the diazepam was fully dispersed in the carrier. Polyvinylpyrrolidone Povidone USP/NF was then added to the mixture and mixed until fully dissolved. The suspension was then brought up to weight with purified water USP. The suspension was then mixed until homogeneous, sampled for in-process testing, and packaged in 3 mL amber glass bottles.

Table 4-1: Diazepam Suspension Formulations

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

[0202] Additional suspensions of diazepam at varying concentrations are made in a similar manner, by varying the amount of diazepam and optionally other excipients. Other benzodiazepine suspensions are made by substituting one or more benzodiazepines for diazepam. Other ingredients, such as alkyl glycoside, can be added at a suitable step in the process. For example, an alkylglycoside may be added to the carrier during compounding of the carrier, or may be added to the suspension mixture concurrently with or after addition of the povidone.

Example 5 -- Stability of Diazepam Solutions and Suspensions

[0203] Solutions 00 and 02 (Example 3) and Suspensions 01 and 03 (Example 4) were set up on stability at 25°C / 60% RH, 30°C / 65% RH and 40°C / 75% RH. One batch each of four different formulations, packaged in 3-ml vials with screw-top closures, along with corresponding actuators, were set up at three storage conditions. They are listed in Table 1 with their corresponding Particle Sciences initial sample control numbers.

Table 5-1: Summary of PSI sample control numbers

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

[0204] Samples were tested for spray content uniformity, spray volume, diazepam content, diazepam related substances, and methylparaben and propylparaben assay (suspension samples only). Unit weights were determined as per USP <755>.

[0205] Summaries of the average assay values and all other results are given in Tables 5-4, 5-5, 5-6 and 5-7. The results for the initial, 1-month and 3-month time points are also shown for comparison. Individual spray content uniformity results are given in Tables 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, and 5-15.

[0206] In general, all of the assays and the other results are similar to the initial data, with the exceptions of diazepam related compounds A and B.

[0207] Related compound A did not meet the specification of not more than (NMT) 0.01% for some samples (see Table 2). Related compound A has increased with time and temperature.

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

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

[0208] Related compound B is also increasing with time and temperature, and now fails specification of NMT 0.1% at 40°C condition for both suspension and one solution formulation. Only formulation 2602 meets all impurity specifications.

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

Solution/Suspension #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00	Meets specification	Meets specification	0.398%

Solution 02	Meets specification	Meets specification	Meets specification
Suspension 01	Meets specification	Meets specification	0.289%
Suspension 03	Meets specification	Meets specification	0.123%

Table 5-4: Summary of Solution 00 results

Solution 00, 70mg/mL, 65% Vitamin E	Specifications	Initial	1 month 25°C/60 %RH	1 month 30°C/65 %RH	1 month 40°C/75 %RH	3 month 25°C/60 %RH	3 month 30°C/65 %RH	3 month 40°C/75 %RH	6 month 25°C/60 %RH	6 month 30°C/65 %RH	6 month 40°C/75 %RH
		Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution
Description	Yellow to orange 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 month 25°C/60 %RH**	**1 month 30°C/65 %RH**	**1 month 40°C/75 %RH**	**3 month 25°C/60 %RH**	**3 month 30°C/65 %RH**	**3 month 40°C/75 %RH**	**6 month 25°C/60 %RH**	**6 month 30°C/65 %RH**	**6 month 40°C/75 %RH**
Description	Yellow to orange solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution	Amber solution
Identification – UV	Conforms to reference std. UV and RT	pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

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

Table 5-6: Summary of Suspension 01 results

Suspension 01, 100 mg/ml	Specifications	Initial	1 month 25°C/60 %RH	1 month 30°C/65 %RH	1 month 40°C/75 %RH	3 month 25°C/60 %RH	3 month 30°C/65 %RH	3 month 40°C/75 %RH	6 month 25°C/60 %RH	6 month 30°C/65 %RH	6 month 40°C/75 %RH
Description	Cloudy to white solution	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	pale yellow dispersion	yellow dispersion
Identification – UV	Conforms to reference std. UV and RT	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Assay Diazepam (%)	90.0 to 110.0%	102.8	102.6	100.9	104.3	101.3	101.8	103.6	100.7	104.3	99.4
Impurities (%) (1)											
Nordazepam	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Related Compound B	NMT 0.1%	ND	ND	ND	0.004	ND	0.004	0.053	0.005	0.013	0.289
Related Compound A	NMT 0.01%	ND	0.01	0.02	0.034	0.026	0.036	0.08	0.038	0.046	0.157
Unknown	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.007	0.007	0.008	0.007	0.018
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.5
Methylparabe n (%)	80.0%-115.%	97.7	100.2	92.1	100.3	101.4	100.6	101.6	106.0	103.2	103.2

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

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

Table 5-7: Summary of Suspension 03 results

Suspension 03, 200mg/mL	**Specifications**	**Initial**	**1 month 25°C/60 %RH**	**1 month 30°C/65 %RH**	**1 month 40°C/75 %RH**	**3 month 25°C/60 %RH**	**3 month 30°C/65 %RH**	**3 month 40°C/75 %RH**	**6 month 25°C/60 %RH**	**6 month 30°C/65 %RH**	**6 month 40°C/75 %RH**
Description	Cloudy to white dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	pale yellow dispersion	yellow dispersion
Identification – UV	Conforms to reference std. UV and RT	Pass	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Assay Diazepam (%)	90.0 to 110.0%	100.7	101.2	98.9	101.6	102.6	103.6	103.1	100.5	98.9	100.1	
Impurities (%) [1]												
Nordazepam	NMT 0.3%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
Related Compound B	NMT 0.1%	ND	ND	ND	ND	0.002	ND	0.023	0.002	0.008	0.123	
Related Compound A	NMT 0.01%	ND	0.005	0.01	0.017	0.017	0.012	0.039	0.019	0.029	0.081	
Unknown	NMT 0.1%	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.007	0.008	
Total	NMT 1.0%	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.2	
Methylparaben (%)	80.0%-115.%	93.4	101.1	93.8	99.7	101.5	101.6	101.2	103.5	97.2	102.1	
Propylparaben (%)	80.0% 115.0%	95.6	100.2	94	98.4	100.1	101.3	99.2	97.1	91.9	95.9	
Microbial Limits	Meets USP {61}	Pass	N/A	N/A	N/A	N/A	N/A	N/A	pass	not tested	not tested	
Fill weight (g)	report results	1.276	1.28	1.259	1.272	1.279	1.279	1.276	1.280	1.262	1.260	
Fill volume (ml)	report results	1.186	1.19	1.171	1.183	1.19	1.19	1.187	1.190	1.173	1.172	
Spray delivered (µl)	report results	112.4	137.4	134.3	119.9	138.9	139.3	134.3	149.4	not tested	138.0	

Average Spray Content (%)	report results	82.8	99.3	97.3	86.7	98.6	102.3	96.2	98.2	not tested	98.7
Viscosity (Pa*s)	report results	0.021	0.017	0.017	0.019	0.016	0.016	0.018	0.014	0.013	0.015

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

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

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

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.14139	0.15111	10.57237	107.88
2	0.14731	0.15146	11.62831	118.66
3	0.14489	0.14684	10.94206	111.65
4	0.14237	0.14873	11.94883	121.93
5	0.12188	0.13415	9.78103	99.81
6	0.12756	0.13047	9.78347	99.83
7	0.13549	0.13841	10.45221	106.66
8	0.12323	0.12543	9.41177	96.04
9	0.14299	0.14517	11.35701	115.89
Average	0.13635	0.14131	10.653	108.70
St. Dev.	0.0097	0.0095	0.8884	9.0649
% RSD	7.14	6.76	8.34	8.34

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

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

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.12336	0.12563	9.02005	92.04
2	0.05723	0.05792	9.43076	96.23
3	0.13554	0.13908	9.93829	101.41
4	0.13619	0.13679	9.87755	100.79
5	0.13227	0.13414	9.64403	98.41
6	0.13331	0.13515	9.80808	100.08
7	0.13455	0.13844	9.31952	95.10
8	0.13314	0.13736	9.28106	94.70
9	0.13249	0.13387	9.32935	95.20
Average	0.12423	0.12649	9.517	97.11
St. Dev.	0.0254	0.0260	0.3148	3.2119
% RSD	20.45	20.57	3.31	3.31

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

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

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

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Diazepam Recovered
1	0.14411	0.14869	13.04770	93.20
2	0.14066	0.14151	13.23277	94.52
3	0.13012	0.13485	13.78126	98.44
4	0.14667	0.14879	13.36970	95.50
5	0.14294	0.14338	12.54309	89.59
6	0.13797	0.14253	13.25396	94.67
7	0.13374	0.13594	13.41984	95.86
8	0.12388	0.12559	14.34944	102.50
9	0.13790	0.14011	13.88564	99.18
Average	0.13755	0.14015	13.431	95.94
St. Dev.	0.0073	0.0073	0.5223	3.7310
% RSD	5.28	5.19	3.89	3.89

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
1	0.13604	0.13897	25.93418	92.62
2	0.14608	0.14792	26.21721	93.63

3	0.15294	0.15425	30.05570	107.34
4	0.14728	0.14910	25.78804	92.10
5	0.15352	0.15493	26.60721	95.03
6	0.15242	0.15401	29.51030	105.39
7	0.15118	0.15254	28.43104	101.54
8	0.15322	0.15556	28.03664	100.13
9	0.15197	0.15393	26.82906	95.82
Average	0.14941	0.15125	27.490	98.18
St. Dev.	0.0057	0.0053	1.5812	5.6472
% RSD	3.79	3.50	5.75	5.75

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

Sample	Weight Collected, g	Weight Actuated, g	Diazepam Recovered, mg	% Disazepam Recovered
1	0.13574	0.13797	28.14588	100.52
2	0.13639	0.13803	27.04437	96.59
3	0.14082	0.14195	26.78985	95.68
4	0.12962	0.13249	29.07192	103.83
5	0.12518	0.12683	27.39785	97.85
6	0.14423	0.14541	28.50133	101.79
7	0.13922	0.14096	27.34617	97.66
8	0.14146	0.14313	27.17415	97.05
9	0.14902	0.15344	27.20939	97.18
Average	0.13796	0.14002	27.631	98.68
St. Dev.	0.0073	0.0076	0.7642	2.7294
% RSD	5.28	5.43	2.77	2.77

Example 6

[0209] All of the solutions and suspensions described in Examples 3 and 4 are formulated as described in Examples 3 and 4, with the addition of a suitable amount of an alkyl glycoside, as described herein, such as dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, and/or combinations of two or more thereof, or marketed as Intravail® by Aegis Therapeutics, San Diego, CA. The solutions and suspensions with added alkyl glycoside may then be put up on stability as described in Example 5, *mutatis mutandis*.

Example 7

[0210] The solutions and suspensions of Examples 3, 4 and 6 are evaluated for pharmacokinetics in a suitable animal model, such as in mice, rats, rabbits or dogs. First each animal (e.g. rabbit) is administered an amount of a benzodiazepine drug intravenously. The amount of intravenously dosed benzodiazepine drug is selected to be less, e.g. roughly half, of what is considered an effective dose administered nasally. For example, the intravenous dose of diazepam administered to rabbits is about 0.05 to about 0.2 mg/kg, e.g. about 0.1 mg/kg. Blood is collected immediately before administration and at specific time points post-administration. Plasma blood levels of the drug are assayed for each of the blood samples. After at least a one day washout period, each animal is administered, intranasally, an amount of a solution or suspension as described in Examples 3, 4 and 6. Blood is collected immediately before administration and at substantially the same specific time points as the IV dose post-administration. Pharmacokinetic curves (blood plasma concentration of drug versus time) are constructed for the intravenous route of administration and for each of the solutions and suspensions administered by the intranasal administration route.

[0211] Toxicity is assessed by known means. In particular, histological samples are collected from the nasal mucosal tissues of the test animals. Other toxological methods are optionally employed as well.

Example 8

[0212] The solutions and suspensions of Examples 3, 4 and 6 are evaluated for their ability to deliver drug across the blood brain barrier in a suitable animal model, such as in mice, rats, rabbits or dogs. Each animal is administered, intranasally, an amount of a solution or suspension as described in Examples 3, 4 and 6, with the solution or suspension optionally containing an imaging agent, such as a dye, that may be used as a proxy for determining the ability of the drug to cross the blood brain barrier. The drug or imaging agent is detected at selected time points after administration of the suspension or solution to determine how well the drug or imaging agent crosses the blood brain barrier. These results may be compared with analogous result obtained with an intravenous solution containing the drug or imaging agent.

Example 9

[0213] The above-described solutions and/or suspensions can be evaluated for pharmacokinetics in humans. Normal, healthy human test subjects are administered an amount of the drug intravenously. The amount chosen for intravenous administration may be any amount, but is conveniently a dose that is considered effective in treating seizure in humans. For example, an IV dose of diazepam administered to humans may be in the range of 1 to 15 mg, e.g. about 7.5 mg. Blood is collected immediately before administration and at selected time points after administration. Plasma blood levels of the drug are assayed for each of the blood samples. After at least a one day washout period, each subject is administered, intranasally, an amount of a solution or suspension as described

herein. Blood is collected immediately before administration and at substantially the same time points after administration as the intravenous time points. Pharmacokinetic curves (blood plasma concentration of drug versus time) are constructed for the intravenous and intranasal administration routes.

Example 10

[0214] The above-described solutions and/or suspensions can be evaluated for efficacy in a suitable animal model. Briefly, for each dose of suspension or solution to be tested, a test animal is stimulated with a seizure inducing stimulus. The stimulus may be light, sound, chemical or other stimulus effective to induce seizure in the model animal. Once the animal has begun to seize, a solution or suspension as described herein is administered intranasally to the animal. The efficacy of the dose of the solution and/or suspension is evaluated based upon the animal's response to the test dose. This procedure is repeated through sufficient iterations, and at sufficient numbers of doses, to identify a dose that is considered effective to treat seizure by intranasal administration of the drug.

[0215] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for nasal administration comprising:

(a) a benzodiazepine drug,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14. The pharmaceutical composition of claim 13, wherein the one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, is in an amount from about 60% to about 75% (w/w).

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

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

17. The composition of one of claims 1 - 16, further comprising at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

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

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

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

(a) administering to one or more nasal mucosal membranes of a patient a pharmaceutical composition for nasal administration comprising a benzodiazepine drug, one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, in an amount from about 30% to about 95% (w/w), and one or more alcohols or glycols, or any combinations thereof, in an amount from about 10% to about 70% (w/w).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

37. The method of claim 20, wherein the composition comprises at least one additional ingredient selected from the group consisting of: active pharmaceutical ingredients; enhancers; excipients; and agents used to adjust the pH, buffer the composition, prevent degradation, and improve appearance, odor, or taste.

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

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

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

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

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

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

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

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

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

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

Alprazolam nasal spray

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ABSTRACT

A kind of benyl diazopines medicine-alprazolam nasal spray is comprised of alprazolam as main medicine, medicinal solvent and medicinal auxiliary materials. Said invention can be divided into solution type, suspension type, gel type and emulsion type, and can be used for curing status epilepticus (SE) and epilepsy.

DESCRIPTION translated from Chinese

Alprazolam nasal spray

The present invention relates □ benzodiazepine class of drugs - alprazolam nasal spray, belongs to the field of chemical and pharmaceutical preparations.

Epilepsy is a recurrent phenomenon of a brain dysfunction caused by a variety of different factors, also known as convulsions, epilepsy, generally can be divided into generalized seizures and partial seizures categories. Status epilepticus (SE) refers to the time of onset of frequent seizures more than 30 minutes or in the interim period has been unable to fully return to normal awareness of the disease, one case of severe disease of the nervous system. Onset often appear hypoxia, high fever, brain edema, cardiovascular system disorders, hypoglycemia and respiratory infections further aggravate convulsions and even life-threatening physiological and pathological changes, if not treated, the patient died of illness and disability that is possible, it should be take decisive and effective treatment as soon as possible just scared. Current clinical think the ideal drug only surprise should have the following properties: (1) high fat-soluble, easily through the blood-brain barrier, the brain quickly reached a peak of drugs; (2) the role of a strong and does not significantly inhibit respiration and blood pressure; (3) long half-life, without having to repeatedly medication; convenient (4) the route of administration, rapid onset of drug; (5) other just scared and no adverse drug interactions; (6) wake up fast; (7) non-contradictory reaction that a need to increase the dose of the drug ineffective or change occurs with similar drugs actually worsened the SE. SE currently controls generally preferred benzodiazepine □ drugs, such as intravenous diazepam (Valium), lorazepam (lorazepam) clonazepam (clonazepam) and so on.

Intramuscular injection, enema and other routes of administration compared to oral administration, intravenous drug absorption, rapid onset, etc., but for SE patients, especially more severe tonic-clonic SE patients, due to the incidence of limb or constantly twitching or stupor, intravenous injection will be difficult, at this time also using case enema or intramuscular injection or sublingual administration of treatment, but the former is due to the absorption of slow, difficult to quickly just scared, which most patients rigidity, can not be placed in sublingual drug fails, so in addition to the above-described methods of treatment intravenous other methods are difficult to achieve a better therapeutic effect.

Object of the present invention is to solve the above problems, an invention benzodiazepine □ drug - alprazolam nasal spray, so as to achieve rapid treatment, facilitate administration purposes.

The present invention is implemented as follows: alprazolam nasal spray is the main drug alprazolam, solvents and other pharmaceutical excipients pharmaceutical composition, the type and amount of pharmaceutical excipients can be adjusted according to the type of formulation. In 1000ml of liquid, the alprazolam dosage 0.5 ~ 10g, the amount of other auxiliary branch of 0.01 ~ 500g. The solvent used in the present invention is water, polyethylene glycol, ethanol, propylene glycol and glycerol, which can be one or more, in an amount of 5-1000ml; Other pharmaceutical excipients include: co-solvents, bioadhesive high molecular materials, suspending agents, oils, emulsifiers, osmotic pressure adjusting agents, aromatic flavoring agents and antimicrobial preservatives, which may comprise one or several. Wherein the co-solvent is a cyclodextrin, including α- cyclodextrin, β- cyclodextrin, hydroxyethyl -β- cyclodextrin, hydroxypropyl -β- cyclodextrin, 3-hydroxypropyl -β- ring dextrin and the like, which may be one or more, in an amount of 0.1 ~ 20g; bioadhesive polymer materials include polyacrylic acid, polyvinyl pyrrolidone, polyethylene glycol, cellulose and derivatives thereof, wherein the poly acrylate, including a variety of types of cards perm, cellulose and its derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose, etc., can be one of them or Several, in an amount of 0.1 ~ 25g; suspending agents include polyacrylic acid, polyvinyl pyrrolidone, cellulose and derivatives thereof, natural rubber, etc., wherein a polyacrylic acid include a variety of types of cards perm, etc., cellulose and its derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and the like; natural gums include gelatin, acacia, sodium alginate, etc., which may be one or more in an amount of 0.5 ~ 50g; fats include oleic acid, nutmeg acid and isopropyl, which may be one or more, in an amount of 20 ~ 500g; emulsifiers include glycerol esters, sucrose esters, Tween , poloxamer, cards perm etc., which may be one or more, in an amount of 1.5-80g; osmolality adjusting agents include sodium chloride, dextrose, mannitol, sodium lactate, etc., may be one of a species or more, in an amount of 0.5 ~ 55g; aromatic flavoring agents include sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, which may be one or several, aromatic agents include natural and synthetic fragrances, which may be one or more, in an amount of 0 ~ 1g; PH adjusting agents include inorganic acid and organic acid, for adjusting the PH value of the solution in an amount few, can According to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzyl alcohol, benzyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal, etc., can be one of them or a few species, in an amount of 0.01 ~ 10g.

Effect of the drug according to the characteristics and physical and chemical properties, and the characteristics of nasal administration, the present invention can be classified into solution type, suspension type, gel type, emulsion type.

Solution-based nasal spray alprazolam alprazolam by primary drug, medicinal solvent, solvent, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml of liquid, the alprazolam dosage 0.5 ~

10g, medicinal solvent is water, polyethylene glycol, including 200,300,400 other models, ethanol, propylene glycol and glycerin, which can be one or a few species, an amount of 5-950ml; cosolvent as cyclodextrins, cyclodextrin include α-, β- cyclodextrin, hydroxyethyl -β- cyclodextrin, hydroxypropyl -β- cyclodextrin, 3 - hydroxypropyl -β- cyclodextrin, which can be one or more, in an amount of 0.1 ~ 20g, but in the liquid in the lower alprazolam concentration may not be added; aromatic flavoring agents sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, which can be one or more an amount of from 0 ~ 1g; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzyl alcohol, benzyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal, etc., can be one of them species or more, in an amount of 0.01 ~ 10g. The preparation process for the main drug alprazolam mixed with a variety of suitable pharmaceutical excipients, to prepare a solution to obtain liquor.

Alprazolam gel nasal spray is the main drug alprazolam, a pharmaceutically acceptable solvent, solvent, bioadhesive polymer materials, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml drug solution, the amount of alprazolam 0.5 ~ 10g, the solvent used is water, polyethylene glycol, comprising 200,300,400 models, ethanol, propylene glycol and glycerol, which can be one or several species, an amount 5-1000ml; cosolvent as cyclodextrins, cyclodextrin include α-, β- cyclodextrin, hydroxyethyl -β- cyclodextrin, hydroxypropyl -β- cyclodextrin, 3 - hydroxypropyl -β- cyclodextrin, which can be one or more, in an amount of 0.1 ~ 20g, but in the liquid may not be added at low concentration of alprazolam; bioadhesive polymer materials include: polyacrylic acid, polyvinyl pyrrolidone, polyethylene glycol, cellulose and derivatives thereof, wherein the polyacrylic acid comprises a card perm -934,974,941,981, TR-2 and other models, cellulose and derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and other claims, which can be one or more, in an amount of 0.1 ~ 25g; aromatic flavoring agents include sweet flavoring and perfuming agents, sweetening agents include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, which can be one or several, of its the amount of 0 ~ 1g; PH regulators include inorganic acid and organic acid, used to adjust the PH value of the gel solution, the amount of rare, according to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzene methanol, benzyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal and the like, which may be one or more, in an amount of 0.01 ~ 10g. With polyacrylic acid made hydrophilic gel nasal sprays, drugs can prolong the contact time with the nasal mucosa, help to improve bioavailability. The preparation process for a variety of primary drug is mixed with a suitable pharmaceutical excipients, made of hydrophilic gel solution to obtain the drug gel fluid.

Suspension type alprazolam nasal spray is the main drug alprazolam, a pharmaceutically acceptable solvent, suspending agents, osmotic pressure regulator, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml drug solution, the amount of alprazolam 0.5 ~ 10g, the solvent used is water, polyethylene glycol, comprising 200,300,400 models, ethanol, propylene glycol and glycerol, which can be one or several species, an amount 5-1000ml; suspending agents include polyacrylic acid, polyvinyl

pyrrolidone, cellulose and derivatives thereof, natural rubber, etc., wherein a polyacrylic acid include a variety of types of cards perm, etc., cellulose and its derivatives include methyl cellulose, sodium hydroxymethyl cellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and the like; natural gums such as gelatin, acacia, sodium alginate, etc., which may be one or several, in an amount of 0.5 ~ 50g; osmolality adjusting agents include: sodium chloride, dextrose, mannitol, sodium lactate, etc., which may be one or more, in an amount of 0.5 ~ 55g; aromatic flavoring agents include sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, which can be one or more, an amount of 0 ~ 1g; PH regulators include inorganic acid and organic acid, used to adjust the PH value of the solution, the amount of very few, according to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium bromide, benzyl alcohol, benzyl alcohol , cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal and the like, which may be one or more, in an amount of 0.01 ~ 10g. The preparation process for the main drug alprazolam variety of suitable pharmaceutical excipients mixed with a solution that is made to get spray liquid suspension.

Emulsion alprazolam nasal spray is the main drug alprazolam, a pharmaceutically acceptable solvent, suspending agents, oils, emulsifiers, osmotic pressure regulator, aromatic flavoring agents and antimicrobial preservative composition. In 1000ml of liquid, the alprazolam dosage 0.5 ~ 10g. The solvent used in the present invention is water, polyethylene glycol (200,300,400), ethanol, propylene glycol and glycerol, which can be one or more, in an amount of 5-1000ml; suspending agents include polyacrylic acid, slightly polyvinyl pyrrolidone, cellulose and its derivatives, natural rubber, etc., wherein a polyacrylic acid include a variety of types of cards perm, etc., cellulose and its derivatives include methyl cellulose, sodium carboxymethylcellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and the like; natural gums include gelatin, acacia, sodium alginate, etc., which may be one or more, in an amount of 0.5 ~ 50g; fats include oleic acid, meat Kou acid and isopropyl, which may be one or more, in an amount of 20 ~ 500g; emulsifiers include glycerol esters, sucrose esters, polysorbate, poloxamer, cards perm etc., which can be one or more, in an amount of 1.5-80g; osmolality adjusting agents include sodium chloride, dextrose, mannitol, sodium lactate, etc., which may be one or more, in an amount of 0.5 ~ 55g; aromatic straightening flavoring agents including sweeteners and flavoring agents, sweeteners include aspartame, stevioside, saccharin, etc., which may be one or more, flavoring agents including natural and synthetic flavors, can be one of them or Several, in an amount of 0 ~ 1g; PH regulators include inorganic acid and organic acid, used to adjust the PH value of the solution, the amount of rare, according to the actual need to add; antimicrobial preservatives include benzalkonium chloride, benzalkonium , benzyl alcohol, phenylethyl alcohol, cresol, chlorocresol, sodium benzoate, sorbic acid, sodium sorbate, thimerosal and the like, which may be one or more, in an amount of 0.01 ~ 10g, process for the preparation thereof main drug alprazolam mixed with various suitable pharmaceutical excipients, suspending solution using adhesive or wet glue into the legal system to obtain a spray solution.

Alprazolam is a benzodiazepine □ new drugs, and diazepam have similar pharmacological effects, anxiolytic, anticonvulsant, antidepressant, sedative, hypnotic and muscle relaxation and so on, which is stronger than diazepam 10 times. The nasal spray is made alprazolam, after absorption of the drug through the nasal capillaries directly into the systemic circulation, rather than through the door - liver system, avoiding first-pass effect of the liver, and high bioavailability, plasma concentration and intravenous similar, alprazolam SE nasal spray treatment compared with intravenous and rectal administration, the administration is not only convenient, but also rapid onset of absorption is complete, you can achieve better therapeutic effect.

The following are examples of the present invention, but are not limited to the embodiments of the subject.

Formulation Example 1 (with a volume of solution dubbed 1000ml of dollars) alprazolam 5g ethanol diluted to 1000ml operation: the main prescription drugs mixed with excipients proportion spray liquid preparation, the filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 2

Prescription (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam sweetener 2g 1.0g 0.1g vanilla 5ml ethanol, benzyl alcohol polyethylene glycol 600ml water 200ml to 1000ml operation: the main prescription drugs and excipients proportion mixed to prepare a spray liquid, the filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 3 prescription (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam chlorocresol 2g 1g ethanol glycerol 200mL water 300ml to 1000ml operation: the main mixing prescription drugs and excipients proportion, preparation spray liquid filtration filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Diluted to 1000ml Formulation Example 4 (dubbed the volume of solution to 1000ml of dollars) alprazolam Bromogeramine 2g 1g ethanol glycol 250mL water 250ml

Operation: The main prescription drugs and excipients proportions, preparation spray liquid, the filtrate Determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 5 (dubbed the volume of solution to 1000ml of dollars) alprazolam 4g card perm -934 5gβ- diluted cyclodextrin 6g0.1N NaOH appropriate amount of propylene glycol, benzyl alcohol 5g water 250ml to 1000ml: Press prescription proportion the main drug and β- cyclodextrin was dissolved in propylene glycol to produce a solution (1), the card perm, benzyl alcohol, and 500ml of pure water were mixed to prepare a hydrogel solution (2), the solution (1) and (2) diluted mix, add water to 1000ml, adding NaOH solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation gel spray pumps, packaging, testing, storage.

Formulation Example 6 (dubbed volume of solution to 1000ml of dollars) alprazolam 2g card perm 941 1.5gβ- cyclodextrin diluted 4g 5g triethanolamine right amount of benzyl alcohol polyethylene glycol water 350ml to 1000ml

Operation: According to the proportion of the main drug prescription with β- cyclodextrin was dissolved in polyethylene glycol, to prepare a solution (1), the card perm, benzyl alcohol and purified water 500ml, prepared hydrogel solution (2), the diluted solution (1) and (2) mixing, add water to 1000ml, adding NaOH solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 7 (dubbed volume of solution to 1000ml of dollars) alprazolam 1g card perm -974 10g0.1N NaOH appropriate amount of benzyl alcohol, propylene glycol 5g ethanol 280ml 200ml to 1000ml water dilution: Press prescription drugs and the proportion of the primary β- cyclodextrin was dissolved in a mixture of ethanol and propylene glycol, to prepare a solution (1), the card perm, benzyl alcohol and purified water 500ml, prepared hydrogel solutions (2), the solution (1) and dilution (2) mixing, add water to 1000ml, adding NaOH solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 8 (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam 8g methylcellulose 15gβ- cyclodextrin 10g0.1NHCl or NaOH appropriate amount of propylene glycol, benzyl alcohol 5g water 250ml to 1000ml: Press prescription proportion the main drug and β- cyclodextrin was dissolved in propylene glycol to produce a solution (1), methyl cellulose, EDTA-2Na, benzyl alcohol, and 500ml of pure water were mixed to prepare a hydrogel solution (2), and the solution dilution (1) and (2) mixing, add water to 1000ml, adding acid or alkali solution was adjusted to 5.0-7.0 PH, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 9 Formulation example (with a volume of solution dubbed the meter 1000ml) alprazolam 10g sodium carboxymethyl cellulose 2.5gβ- cyclodextrin 10g0.1N HCl or NaOH 5g appropriate amount of benzyl alcohol glycol polyethylene glycol 350ml water 150ml diluted to 1000ml: Press the mixture ratio of the main drug prescription with β- cyclodextrin was dissolved in polyethylene glycol and propylene glycol to prepare a solution (1), and the mixture of sodium carboxymethyl cellulose, benzyl alcohol and purified water 500ml to prepare a hydrogel solution (2), the diluted solution (1) and (2) were mixed with water to 1000ml, the addition of acid or alkali solution to adjust the PH to 5.0-7.0, determination, filling, sealing, installation spray pump , packaging, testing, storage.

Formulation Example 10 (dubbed the volume of solution to 1000ml of dollars) alprazolam 8g card perm TR-2 1.5gβ- cyclodextrin 10g right amount of benzyl alcohol, triethanolamine diluted 5g propylene glycerol 100 Water 250ml to 1000ml

Operation: According to the proportion of the main drug prescription with β- cyclodextrin was dissolved in a mixture of propylene glycol and glycerol, to make a solution (1), the card perm TR-2, benzyl alcohol, and 500ml of pure water were mixed to prepare a hydrogel gum solution (2), the diluted solution (1) and (2) mixing, add water to 1000ml, plus triethanolamine adjust the PH of 5.0-7.0, determination, filling, sealing, installation of spray pumps, packaging, testing, storage .

Prescription Example 11 (dubbed the volume of solution in the meter 1000ml) alprazolam 10g sodium carboxymethyl cellulose 2.5gβ- cyclodextrin 10g0.1N HCl or dilute NaOH 5g appropriate amount of benzyl alcohol polyethylene glycol to 250ml water 1000ml operation: the ratio of the main drug prescription with β-cyclodextrin was dissolved in polyethylene glycol, to prepare a solution (1), and the mixture of sodium carboxymethyl cellulose, benzyl alcohol, and 500ml of pure water to prepare a hydrogel gum solution (2), the diluted solution (1) and (2) were mixed with water to 1000ml, the addition of acid or alkali solution to adjust the PH to 5.0-7.0, determination, filling, sealing, installation spray pumps, packaging, testing, storage.

Formulation Example 12 (dubbed the volume of solution to 1000ml of dollars) alprazolam 1.0g sodium carboxymethyl cellulose, microcrystalline cellulose 2.5g 3g 9g0.1N HCl or NaOH appropriate amount of sodium chloride benzalkonium 5g dilution water to 1000ml

Operation: The main drug be micronized (5μm or less), the standby; prescription mixing proportions of sodium carboxymethyl cellulose, microcrystalline cellulose, sodium chloride, benzalkonium chloride and 800ml of pure water, swell, and dissolved to prepare an aqueous solution will be diluted with micronized drug master mix, add water to 1000ml, adding acid or alkali solution was adjusted to 5.0-7.0 PH, mix, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Example 13 Formulation example (with a volume of solution dubbed the meter 1000ml) alprazolam 10g sodium carboxymethyl cellulose 2.5g card perm -941 2g glucose 55g0.1N HCl or NaOH appropriate amount of benzyl alcohol, polyethylene glycol 5g 250ml diluted with water to 1000ml operation: the primary agents for the micronized (5μm or less), the standby; prescription proportion of sodium carboxymethyl cellulose, card perm -941, glucose, benzyl alcohol and 800ml of purified water, the swelling, dissolution system into the aqueous solution, the diluted with micronized drug master mix, add water to 1000ml, adding acid or alkali solution to adjust PH 5.0-7.0, mixing, determination, filling, sealing, installation of spray pumps, packaging, testing, into library.

Diluted to 1000ml Formulation Example 14 (dubbed the volume of solution to 1000ml of dollars) alprazolam 4g oleic acid 80g card perm TR-2 2g0.1N HCl or NaOH appropriate amount of benzyl alcohol, polyethylene glycol 5g 350ml water

Operation: The main drug prescription proportion, oleic acid, card perm TR-2, benzyl alcohol were mixed and dissolved in a water bath, was added slowly with stirring at a high speed mixing of pure water, diluted to

1000ml, homogenized for 30 minutes, adding acid or base PH was adjusted to 5.0-7.0, mixing, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

Formulation Example 15 (dubbed the volume of solution to 1000ml of dollars) diluted alprazolam 4g nutmeg 90g sucrose isopropyl ester 2g0.1N HCl or NaOH appropriate amount of benzyl alcohol, polyethylene glycol 5g 350ml to 1000ml water operations: The main drug prescription proportion, nutmeg isopropyl, sucrose esters, benzyl alcohol were mixed and dissolved in a water bath, was added slowly with stirring at a high speed mixing of pure water, diluted to 1000ml, homogenized for 30 minutes, the addition of acid or alkali solution is adjusted PH is 5.0-7.0, mixing, determination, filling, sealing, installation of spray pumps, packaging, testing, storage.

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[71]申请人 山东省医药工业研究所
地址 250100 山东省济南市山大北路52号
[72]发明人 王文菊 孙 玲 杨珮琨

[74]专利代理机构 山东省专利事务所
代理人 邹 燕

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[54]发明名称 阿普唑仑鼻喷剂

[57]摘要

一种苯二氮䓬类药物——阿普唑仑鼻喷剂，由主药阿普唑仑、药用溶剂和其它药用辅料组成。根据药物的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。本发明给药方便，起效快，吸收完全，可用于癫痫持续状态(SE)及癫痫的治疗。

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权利要求书

1.阿普唑仑的鼻喷剂，其特征在于由主药阿普唑仑、溶剂和其它药用辅料组成，在1000ml药液中，阿普唑仑的用量为0.5~10g，其它辅料的用量为0.01~500g。

2.权利要求 1 中所述的鼻喷剂，其特征在于其溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，其用量为5-1000ml。

3.权利要求 1 中所述的鼻喷剂，其特征在于权利要求 1 中所述的其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂和乳化剂，其中助溶剂为环糊精，其用量为0.1～20g；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇和纤维素，其用量为0.1～25g；助悬剂为聚丙烯酸、聚乙烯吡咯烷酮、纤维素和天然胶，其用量为0.5～50g；油脂为油酸和肉蔻酸异丙酯，其用量为20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆和卡泊姆，其用量为1.5-80。

4.权利要求 1 中所述的鼻喷剂，其特征在于它可制备成溶液型、混悬型、凝胶型、乳液型四种类型；

5.权利要求 4 中所述的鼻喷剂，其特征在于溶液型的主要成分是阿普唑仑和溶剂；在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-950ml。

6.权利要求 4 中所述的鼻喷剂，其特征在于凝胶型的主要成分是阿普唑仑、溶剂、生物粘附性高分子材料，在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-1000ml；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素，可以是其中的一种或几种，其用量为0.1～25g。

7.权利要求 4 中所述的鼻喷剂，其特征在于混悬型的主要成分是阿普唑仑、溶剂、助悬剂，在1000ml药液中，阿普唑仑的用量为0.5~10g，所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素、天然

胶， 可以是其中的一种或几种，其用量为 0.5～50g。

8.权利要求 4 中所述的鼻喷剂，其特征在于乳液型的主要成分是阿普唑仑、溶剂、油脂、乳化剂,在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；油脂为油酸和肉蔻酸异丙酯，可以是其中的一种或几种，其用量为 20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆，可以是其中的一种或几种，其用量为 1.5-80g。

说 明 书

阿普唑仑鼻喷剂

本发明涉及苯二氮䓬类药物——阿普唑仑鼻喷剂，属于化学和药物制剂领域。

癫痫是一种可由多种不同因素引起的反复发作性的脑功能紊乱现象，又称抽风、羊角风，一般大致可分为全身性发作和部分性发作两类。癫痫持续状态（SE）是指发作时间超过 30 分钟或者发作频繁而在间歇期意识始终未能完全恢复正常的病症，属神经系统危重症之一。发病时常出现缺氧、高热、脑水肿、心血管系统紊乱、低血糖以及呼吸道感染等进一步加重惊厥甚至危及生命的病理生理改变，如不及时治疗，病人即有病死和致残的可能，故应采取果断而有力的治疗措施尽快止惊。目前临床认为理想的止惊药应具备下列性能：（1）脂溶性高，易透过血脑屏障，迅速达到脑内药物峰值；（2）作用强而不会显著抑制呼吸和血压；（3）半衰期长，不必多次用药；（4）用药途径方便，药物起效迅速；（5）与其它止惊药之间无不利的相互作用；（6）苏醒较快；（7）无矛盾反应，即某药效果不佳需加大剂量或换用同类药物时 SE 反而加重的情况。目前控制 SE 一般首选苯二氮䓬类药物，如静脉注射地西泮（安定）、劳拉西泮（氯羟安定）氯硝西泮（氯硝安定）等。

与口服给药、肌肉注射、保留灌肠等给药途径相比，静脉注射药物有吸收好、起效快等特点，但对于 SE 病人，尤其是较严重的强直—阵挛性 SE 病人，由于发病期肢体或不断抽动或木僵，静脉注射有一定困难，此时亦有采用保留灌肠或肌肉注射或舌下给药治疗的情况，但前者由于吸收慢，难以迅速止惊，而后者多数病人强直，无法将药放入舌下而失败，因此上述治疗方法中除静脉注射外其它方法均难以达到较好的治疗效果。

本发明的目的在于针对上述问题,发明一种苯二氮䓬类药物——阿普唑仑鼻喷剂，从而达到治疗迅速、用药方便的目的。

本发明是这样实现的：阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂和其它药用辅料组成,所使用的药用辅料的种类和数量可根据制剂类型进行调整。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，其它辅料的用量为

0.01~500g。本发明所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂，可以包括其中的一种或几种。其中助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20g；生物粘附性高分子材料包括聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及其衍生物，其中聚丙烯酸包括多种型号的卡泊姆，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。

根据药物的的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。

溶液型的阿普唑仑鼻喷剂由主药阿普唑仑、药用溶剂、助溶剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，药

用溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-950ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成溶液即得到药液。

凝胶型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助溶剂、生物粘附性高分子材料、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；生物粘附性高分子材料包括：聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及衍生物，其中聚丙烯酸包括卡泊姆-934、974、941、981、TR-2 等型号，纤维素及衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节凝胶溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。用聚丙烯酸等制成亲水凝胶型鼻喷剂，

可以延长药物与鼻腔粘膜的接触时间，有利于提高生物利用度。其制备过程为将主药与各种适宜的药用辅料混合，制成亲水凝胶溶液即得到药物凝胶液。

混悬型的阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶如明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；渗透压调节剂包括：氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成混悬溶液即得到喷雾药液。

乳液型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g。本发明所用的溶剂为水、聚乙二醇（200、300、400）、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂

包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g，其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，采用干胶法或湿胶法制成混悬溶液即得到喷雾溶液。

阿普唑仑为新的苯二氮䓬类药物，有与地西泮相似的药理作用，有抗焦虑、抗惊厥、抗抑郁、镇静、催眠及肌肉松弛等作用，其作用比地西泮强 10 倍。将阿普唑仑制成鼻喷剂，药物经鼻腔毛细血管吸收后，直接进入体循环，而不经门—肝系统，避免了肝脏的首过效应，生物利用度高，血药浓度与静脉注射相似，因此阿普唑仑喷鼻治疗 SE 与静脉注射和直肠给药相比，不仅给药方便，而且起效快，吸收完全，可以达到较好的治疗效果。

下面是本发明的实施例，但并不受实施例的限制。

实施例 1

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	5g
乙醇	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 2

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
甜味剂	1.0g
香草香精	0.1g
苯甲醇	5 ml
乙醇	200ml
聚乙二醇	600ml
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 3

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
氯甲酚	1 g
乙醇	300ml
甘油	200mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 4

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
新洁尔灭	1g
乙醇	250ml
丙二醇	250mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 5

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
卡泊姆-934	5 g
β-环糊精	6g
0.1N NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装凝胶喷泵，包装，检验，入库。

实施例 6

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
卡泊姆 941	1.5g
β-环糊精	4g
三乙醇胺	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 7

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	1 g
卡泊姆-974	10 g
0.1N NaOH	适量
苯甲醇	5 g
乙醇	280ml
丙二醇	200ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于乙醇和丙二醇的混合物中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液(1)和(2)混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 8

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8 g
甲基纤维素	15 g
β-环糊精	10g
0.1NHCl 或 NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将甲基纤维素、EDTA-2Na、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），

将溶液(1)和(2)混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 9

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
丙二醇	150ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇和丙二醇的混合物中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 10

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8g
卡泊姆 TR-2	1.5 g
β-环糊精	10g
三乙醇胺	适量
苯甲醇	5 g
丙二醇	250ml
甘油	100
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇和甘油的混合物中，制成溶液（1），将卡泊姆 TR-2、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加三乙醇胺调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 11

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 12

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
微晶纤维素	3 g
氯化钠	9 g
0.1N HCl 或 NaOH	适量
洁尔灭	5 g
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、微晶纤维素、氯化钠、洁尔灭及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 13

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
卡泊姆-941	2 g
葡萄糖	55 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、卡泊姆-941、葡萄糖、苯甲醇及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 14

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4g
油酸	80 g
卡泊姆 TR-2	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、油酸、卡泊姆 TR-2、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 15

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
肉蔻酸异丙酯	90 g
蔗糖酯	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、肉蔻酸异丙酯、蔗糖酯、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

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[71]申请人 山东省医药工业研究所
地址 250100 山东省济南市山大北路 52 号
[72]发明人 王文菊 孙 玲 杨珮瑶
[74]专利代理机构 山东省专利事务所
代理人 邹 燕

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[57]摘要

一种苯二氮䓬类药物——阿普唑仑鼻喷剂，由主药阿普唑仑、药用溶剂和其它药用辅料组成。根据药物的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。本发明给药方便，起效快，吸收完全，可用于癫痫持续状态(SE)及癫痫的治疗。

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权利要求书

1.阿普唑仑的鼻喷剂，其特征在于由主药阿普唑仑、溶剂和其它药用辅料组成，在1000ml药液中，阿普唑仑的用量为0.5~10g，其它辅料的用量为0.01~500g。

2.权利要求 1 中所述的鼻喷剂，其特征在于其溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，其用量为5-1000ml。

3.权利要求 1 中所述的鼻喷剂，其特征在于权利要求 1 中所述的其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂和乳化剂，其中助溶剂为环糊精，其用量为0.1～20g；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇和纤维素，其用量为0.1～25g；助悬剂为聚丙烯酸、聚乙烯吡咯烷酮、纤维素和天然胶，其用量为0.5～50g；油脂为油酸和肉蔻酸异丙酯，其用量为20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆和卡泊姆，其用量为1.5-80。

4.权利要求 1 中所述的鼻喷剂，其特征在于它可制备成溶液型、混悬型、凝胶型、乳液型四种类型；

5.权利要求 4 中所述的鼻喷剂，其特征在于溶液型的主要成分是阿普唑仑和溶剂；在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-950ml。

6.权利要求 4 中所述的鼻喷剂，其特征在于凝胶型的主要成分是阿普唑仑、溶剂、生物粘附性高分子材料，在1000ml药液中，阿普唑仑的用量为0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为5-1000ml；生物粘附性高分子材料为聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素，可以是其中的一种或几种，其用量为0.1～25g。

7.权利要求 4 中所述的鼻喷剂，其特征在于混悬型的主要成分是阿普唑仑、溶剂、助悬剂，在1000ml药液中，阿普唑仑的用量为0.5~10g，所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为6-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素、天然

胶， 可以是其中的一种或几种，其用量为 0.5～50g。

8.权利要求 4 中所述的鼻喷剂，其特征在于乳液型的主要成分是阿普唑仑、溶剂、油脂、乳化剂,在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；油脂为油酸和肉蔻酸异丙酯，可以是其中的一种或几种，其用量为 20～500g；乳化剂为甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆，可以是其中的一种或几种，其用量为 1.5-80g。

说 明 书

阿普唑仑鼻喷剂

本发明涉及苯二氮䓬类药物——阿普唑仑鼻喷剂，属于化学和药物制剂领域。

癫痫是一种可由多种不同因素引起的反复发作性的脑功能紊乱现象，又称抽风、羊角风，一般大致可分为全身性发作和部分性发作两类。癫痫持续状态（SE）是指发作时间超过 30 分钟或者发作频繁而在间歇期意识始终未能完全恢复正常的病症，属神经系统危重症之一。发病时常出现缺氧、高热、脑水肿、心血管系统紊乱、低血糖以及呼吸道感染等进一步加重惊厥甚至危及生命的病理生理改变，如不及时治疗，病人即有病死和致残的可能，故应采取果断而有力的治疗措施尽快止惊。目前临床认为理想的止惊药应具备下列性能：（1）脂溶性高，易透过血脑屏障，迅速达到脑内药物峰值；（2）作用强而不会显著抑制呼吸和血压；（3）半衰期长，不必多次用药；（4）用药途径方便，药物起效迅速；（5）与其它止惊药之间无不利的相互作用；（6）苏醒较快；（7）无矛盾反应，即某药效果不佳需加大剂量或换用同类药物时 SE 反而加重的情况。目前控制 SE 一般首选苯二氮䓬类药物，如静脉注射地西泮（安定）、劳拉西泮（氯羟安定）氯硝西泮（氯硝安定）等。

与口服给药、肌肉注射、保留灌肠等给药途径相比，静脉注射药物有吸收好、起效快等特点，但对于 SE 病人，尤其是较严重的强直—阵挛性 SE 病人，由于发病期肢体或不断抽动或木僵，静脉注射有一定困难，此时亦有采用保留灌肠或肌肉注射或舌下给药治疗的情况，但前者由于吸收慢，难以迅速止惊，而后者多数病人强直，无法将药放入舌下而失败，因此上述治疗方法中除静脉注射外其它方法均难以达到较好的治疗效果。

本发明的目的在于针对上述问题,发明一种苯二氮䓬类药物——阿普唑仑鼻喷剂，从而达到治疗迅速、用药方便的目的。

本发明是这样实现的：阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂和其它药用辅料组成,所使用的药用辅料的种类和数量可根据制剂类型进行调整。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，其它辅料的用量为

0.01~500g。本发明所用的溶剂为水、聚乙二醇、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；其他药用辅料包括：助溶剂、生物粘附性高分子材料、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂，可以包括其中的一种或几种。其中助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20g；生物粘附性高分子材料包括聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及其衍生物，其中聚丙烯酸包括多种型号的卡泊姆，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。

根据药物的的作用特点和理化性质，以及鼻腔给药的特点，本发明可分为溶液型、混悬型、凝胶型、乳液型。

溶液型的阿普唑仑鼻喷剂由主药阿普唑仑、药用溶剂、助溶剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，药

用溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-950ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成溶液即得到药液。

凝胶型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助溶剂、生物粘附性高分子材料、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助溶剂为环糊精，包括α-环糊精、β-环糊精、羟乙基-β-环糊精、羟丙基-β-环糊精、3-羟丙基-β-环糊精等，可以是其中的一种或几种，其用量为 0.1～20 g，但在药液中阿普唑仑浓度较低时可以不添加；生物粘附性高分子材料包括：聚丙烯酸、聚乙烯吡咯烷酮、聚乙二醇、纤维素及衍生物，其中聚丙烯酸包括卡泊姆-934、974、941、981、TR-2 等型号，纤维素及衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等，可以是其中的一种或几种，其用量为 0.1～25g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节凝胶溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。用聚丙烯酸等制成亲水凝胶型鼻喷剂，

可以延长药物与鼻腔粘膜的接触时间，有利于提高生物利用度。其制备过程为将主药与各种适宜的药用辅料混合，制成亲水凝胶溶液即得到药物凝胶液。

混悬型的阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g，所用的溶剂为水、聚乙二醇包括 200、300、400 等型号、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶如明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；渗透压调节剂包括：氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g。其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，制成混悬溶液即得到喷雾药液。

乳液型阿普唑仑鼻喷剂是由主药阿普唑仑、药用溶剂、助悬剂、油脂、乳化剂、渗透压调节剂、芳香矫味剂和抗菌防腐剂组成。在 1000ml 药液中，阿普唑仑的用量为 0.5~10g。本发明所用的溶剂为水、聚乙二醇（200、300、400）、乙醇、丙二醇和甘油，可以是其中的一种或几种，其用量为 5-1000ml；助悬剂包括聚丙烯酸、聚乙烯吡咯烷酮、纤维素及其衍生物、天然胶等，其中聚丙烯酸包括多种型号的卡泊姆等，纤维素及其衍生物包括甲基纤维素、羟甲基纤维素钠、羧甲基纤维素钠、羟乙基纤维素等；天然胶包括明胶、阿拉伯胶、海藻酸钠等，可以是其中的一种或几种，其用量为 0.5～50g；油脂

包括油酸、肉蔻酸异丙酯等，可以是其中的一种或几种，其用量为 20～500g；乳化剂包括甘油酸酯、蔗糖酯、吐温、泊洛沙姆、卡泊姆等，可以是其中的一种或几种，其用量为 1.5-80g；渗透压调节剂包括氯化钠、葡萄糖、甘露醇、乳酸钠等，可以是其中的一种或几种，其用量为 0.5～55g；芳香矫味剂包括甜味剂和芳香剂，甜味剂包括天冬甜素、甜菊甙、糖精等，可以是其中的一种或几种，芳香剂包括天然及合成香料，可以是其中的一种或几种，其用量为 0～1g；PH 调节剂包括无机酸碱和有机酸碱，用于调节溶液的 PH 值，其用量极少，可根据实际需要加入；抗菌防腐剂包括洁尔灭、新洁尔灭、苯甲醇、苯乙醇、苯甲酚、氯甲酚、苯甲酸钠、山梨酸、山梨酸钠、硫柳汞等，可以是其中的一种或几种，其用量为 0.01～10g，其制备过程为将主药阿普唑仑与各种适宜的药用辅料混合，采用干胶法或湿胶法制成混悬溶液即得到喷雾溶液。

阿普唑仑为新的苯二氮䓬类药物，有与地西泮相似的药理作用，有抗焦虑、抗惊厥、抗抑郁、镇静、催眠及肌肉松弛等作用，其作用比地西泮强 10 倍。将阿普唑仑制成鼻喷剂，药物经鼻腔毛细血管吸收后，直接进入体循环，而不经门—肝系统，避免了肝脏的首过效应，生物利用度高，血药浓度与静脉注射相似，因此阿普唑仑喷鼻治疗 SE 与静脉注射和直肠给药相比，不仅给药方便，而且起效快，吸收完全，可以达到较好的治疗效果。

下面是本发明的实施例，但并不受实施例的限制。

实施例 1

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	5g
乙醇	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 2

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
甜味剂	1.0g
香草香精	0.1g
苯甲醇	5 ml
乙醇	200ml
聚乙二醇	600ml
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 3

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
氯甲酚	1 g
乙醇	300ml
甘油	200mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 4

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
新洁尔灭	1g
乙醇	250ml
丙二醇	250mL
水	稀释至 1000ml

操作：将主药与辅料按处方比例混合，配制喷雾药液，过滤，滤液测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 5

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
卡泊姆-934	5 g
β-环糊精	6g
0.1N NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装凝胶喷泵，包装，检验，入库。

实施例 6

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	2 g
卡泊姆 941	1.5g
β-环糊精	4g
三乙醇胺	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 7

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	1 g
卡泊姆-974	10 g
0.1N NaOH	适量
苯甲醇	5 g
乙醇	280ml
丙二醇	200ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于乙醇和丙二醇的混合物中，制成溶液（1），将卡泊姆、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液(1)和(2)混合，加水稀释至 1000ml，加 NaOH 溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 8

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8 g
甲基纤维素	15 g
β-环糊精	10g
0.1NHCl 或 NaOH	适量
苯甲醇	5 g
丙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇中，制成溶液（1），将甲基纤维素、EDTA-2Na、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），

将溶液(1)和(2)混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 9

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
丙二醇	150ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇和丙二醇的混合物中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 10

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	8g
卡泊姆 TR-2	1.5 g
β-环糊精	10g
三乙醇胺	适量
苯甲醇	5 g
丙二醇	250ml
甘油	100
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于丙二醇和甘油的混合物中，制成溶液（1），将卡泊姆 TR-2、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加三乙醇胺调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 11

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
β-环糊精	10g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：按处方比例将主药与β-环糊精溶于聚乙二醇中，制成溶液（1），将羧甲基纤维素钠、苯甲醇及 500ml 纯水混合，制成水凝胶溶液（2），将溶液（1）和（2）混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 12

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
微晶纤维素	3 g
氯化钠	9 g
0.1N HCl 或 NaOH	适量
洁尔灭	5 g
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、微晶纤维素、氯化钠、洁尔灭及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 13

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	10g
羧甲基纤维素钠	2.5 g
卡泊姆-941	2 g
葡萄糖	55 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	250ml
水	稀释至 1000ml

操作：将主药进行微粉化（5μm 以下），备用；按处方比例将羧甲基纤维素钠、卡泊姆-941、葡萄糖、苯甲醇及 800ml 纯水混合，溶胀、溶解制成水溶液，将微粉化的主药与之混合，加水稀释至 1000ml，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 14

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4g
油酸	80 g
卡泊姆 TR-2	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、油酸、卡泊姆 TR-2、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

实施例 15

处方(以配成体积为 1000ml 的溶液计)

阿普唑仑	4 g
肉蔻酸异丙酯	90 g
蔗糖酯	2 g
0.1N HCl 或 NaOH	适量
苯甲醇	5 g
聚乙二醇	350ml
水	稀释至 1000ml

操作：按处方比例将主药、肉蔻酸异丙酯、蔗糖酯、苯甲醇于水浴中混合溶解，在高速搅拌下缓慢加入纯水混合，稀释至 1000ml，均质 30 分钟，加酸或碱溶液调节 PH 为 5.0-7.0，混匀，测定含量，灌装，封口，安装喷雾泵，包装，检验，入库。

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	CARTT; Steve et al.	Group Art Unit:	1612
Serial Number:	12/413,439	Examiner:	Milligan, Adam
Filing or 371 (c) Date:	2009-03-27	**CONFIRMATION NO:**	**9049**
Title:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		

FILED ELECTRONICALLY ON: January 11, 2017

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

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

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

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

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

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

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

-- OR --

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

-- OR --

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

-- OR --

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

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

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

-- OR --

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

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

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

-- AND --

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

D. ☐ *37 CFR §1.97 (e).* Statement.

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

-- AND/OR --

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

-- AND/OR --

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

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

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

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

-- OR --

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

-- AND/OR --

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

-- AND/OR --

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

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

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

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

-- OR --

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

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

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

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

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

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

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

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: January 11, 2017

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

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

UNITED STATES PATENT AND TRADEMARK OFFICE

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

21971 7590 03/30/2017

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

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/30/2017	ELECTRONIC

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

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

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

patentdocket@wsgr.com

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

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *1/10/2017*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *20,22-24,27-36,40-45 and 48-54* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *20,22-24,27-36,40-45 and 48-54* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

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

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/10/2017 has been entered.

Applicants' arguments, filed 1/10/2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

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

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

Claims 20, 22-24, 27-36, 40-45 and 48-54 are rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, "treating seizure, protecting against seizure, reducing or ameliorating the intensity of seizure, reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure" is considered to be unclear based on the recitation of "and/or". It is unclear whether the method must meet all the recited functions as implied by "and" or if meeting any of the recited functions is sufficient to meet the recited method as implied by "or" language. Further, based on the current claim language of "A method of intranasal administration of a benzodiazepine drug for treating seizure…", it is unclear whether it is the benzodiazepine drug which is required to be responsible for the treatment or the method as a whole. Clarification is requested.

Claim Rejections – 35 U.S.C. § 103

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

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

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

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

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20, 22-24, 27-36, 40-45 and 48-54 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lehat (Intranasal midazolam for childhood seizures,

The Lancet, vol.352, August 22, 1998 – See IDS dated 10/29/2013) in view of Sonne (U.S. 6,193,985- See IDS dated 9/16/2009) and Meezan (U.S. 2006/0046962).

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

Lehat does not teach suitable excipients for the formulation.

Sonne teaches tocopherol compositions for the delivery of biologically active agents which are only sparingly soluble in water (col. 1, lines 7-13), such as diazepam (col. 1, lines 7-14). One particular nasal formulation contains 5g of diazepam, 44 g Tenox GT2 (70% tocopherol), 5 g Vitamin E TPGS (glycol), 1.45 g Pluronic and 0.1g benzalkonium chloride (example 1 at col. 7, lines 32-45). In preparing the formulation, the ingredients are heated slowly until a homogeneous phase is achieved (Sonne also teaches that co-solvent such as ethanol, benzyl alcohol, sesame oil or propylene glycol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, it may be used in an amount of about 11% by weight of the formulation (See example 3 at col.8, lines 28-43). When sesame oil is used, it may be used in an amount of about 44% (example18, col12, lines 37-51) or about 60% (example 16 at col.12, lines 10-17). α-tocopherol may be used in amounts of 20 to 99.9% (col.5, lines 56-61). The active ingredient should be present in an amount of 0.001% to 40% (col.5, lines 55-61). Diazepam may be present at about 5% by weight (example 11 at col. 11, lines 1-13). Preservative as well as odor masking compounds may be included in the (col.7, lines 4-12). The composition may be

in the form of a spray formulation (col. 6, lines 28-35). In general, about 100µL can be administered to the nose at a time (col.7, lines 25-30). Sonne teaches that the "compositions of the invention may be used directly as a solution of bioactive agents in the tocopherol solvent" (col.3, lines 60-61) and that the "[v]iscosity can be reduced by the addition of co-solvents such as ethanol (col.3, lines 65-66). Sonne teaches that "transmucosal delivery is preferred" (col.3, line 54) and "[n]asal...administrations are particularly preferred" (col.3, lines 58-59). The compositions of the invention may contain from 1-99.99% tocopherol (col.5, lines 55-57). Sonne also teaches that a co-solvent such as ethanol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53).

Sonne does not teach the surfactant is an alkyl glycoside.

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

Meezan does not teach using a benzodiazapine active ingredient.

It would have been obvious to one of ordinary skill in the art treating seizures as taught by Lehat to administer the benzodiazepine in the composition taught by Sonne to improve benzodiazepine solubility. Further, it would have been obvious to one of skill in

the art administering the nasal spray formulation of Sonne to use the surfactant taught by Meezan to improve the bioavailability of drug administered via a nasal spray.

Applicants present the following arguments against the rejection.

Applicants argue that Sonne does not suggest that surfactants could be used to increase absorption or bioavailability of a drug. Because Sonne suggests tocopherols may serve to increase absorption or bioavailability of a drug, “Sonne teaches away from combining tocopherol and alkyl glycosides, presumably because tocopherol already serves to increase bioavailability of a drug” (Argument at p.8, lines 2-4).

Examiner disagrees. Sonne explicitly teaches “[t]o optimize the stability of the emulsions, it may be appropriate to add surfactants such as Vitamin E TPGS poloxamers (eg. Pluronic.RTM.), cetearyl glucoside, polysorbates or sorbitan esters of fatty acids, or any of the other surfactants well known in the art” (col.6, lines 54-58). Given an explicit teaching to include a surfactant, there is no reason for one of skill in the art to be taught away from including a surfactant. Accordingly, the rejection is maintained.

Applicants previously argued that Sonne teaches away from the instantly claimed method by stating that bioactive agents dissolved in tocopherol solvents create viscous solutions such that "the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application." Sonne does teach that the viscosity can be reduced by the addition of co-solvents such as ethanol...but this is less

desired since solutions of this type tend to be irritating to certain mucosal tissues". Though Sonne does not teach which types of tissue may be irritated by alcohol, Sonne presents ethanol containing formulations only for oral and rectal administration, not for intranasal administration. Thus, Applicants request the rejection be withdrawn.

Examiner disagreed. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including non-preferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Here, while ethanol addition is not listed as a most preferred method for viscosity reduction, it is taught as a suitable method for such. A prior art reference must be considered for all that it teaches or suggests to one of ordinary skill in the art. It should not be limited to the exemplary formulations. It is further noted that nasal formulations are not limited to sprays, which may require higher amounts of ethanol, but can be in the form of drops, which can be more viscous.

Applicants previously argues that no exemplary formulations of Sonne teach the presence of ethanol and nasal administration. Examiner previously cited to a rectal formulation for providing an amount of ethanol, but has not given a reason why a solution suitable for rectal administration would also be suitable for nasal administration. Thus, the rejection should be withdrawn.

Examiner disagreed. Sonne teaches that the compositions may be administered to mucosal membranes, for example in the nose or rectum (col.3, lines 54-59). In fact, nasal and rectal administrations are particularly preferred (Id.).

Applicants previously argued that the “consisting of" language excludes other components, such as those required to form separate phases, such as in an emulsion. Thus, the combination of Sonne and Meezan would not have suggested the instantly claimed subject matter.

Examiner disagreed. Sonne teaches that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues (col.2, lines 54-58). The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent (col.3, lines 60-61). However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application (col.3, lines 62-64). To increase viscosity, co-solvents such as ethanol can be added (col.3, lines 65-67). Since ethanol can be irritating to certain mucosal tissue, Sonne alternatively teaches emulsification as a means to lower viscosity (col.4, lines 1-2). Thus, Sonne teaches three formulating alternatives, (1) high viscosity, (2) co-solvent (i.e. ethanol) addition and (3) emulsification. The high viscosity teaching and the co-solvent teaching render obvious the instantly recited claims.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20, 22-24, 27-36, 40-45 and 48-54 stand provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 23, 25-30, 33-56 and 60-65 of copending Application No. 14/527,613 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to choose from the components recited in the copending application.

Applicants state they will consider filing a terminal disclaimer over the copending application when present claims are found otherwise allowable.

Accordingly, the rejection is maintained.

Conclusion

No claims are allowed.

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

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

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

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	JP-2011516425-A	05-26-2011	HALE BIOPHARMA VENTURES LLC [US], et al.	See WO-2009121039-A2 For English	☒
	002	WO-2009121039-A2	10-01-2009	HALE BIOPHARMA VENTURES LLC [US], et al.		☐
	003	CN-1303674A	12-02-1999	INST. OF MEDICAL INDUSTRY SHAND [CN]	English abstract provided	☒

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	03/20/2017

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

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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	Chinese Patent Application No. 201280039077.9 Office Action dated November 21, 2016.	☒
	002	Chinese Patent Application No. 201280039077.9 Third Office Action dated March 17, 2016.	☒
	003	European Patent Application No. 12801372.9 Communication dated July 5, 2016.	☐
	004	Japanese Patent Application No. 2014-515967 Office Action dated March 30, 2016.	☒
	005	Japanese Patent Application No. 2014-515967 Office Action dated November 28, 2016.	☒
	006	U.S. Patent Application No. 14/527,613 Office Action dated July 14, 2016.	☐
	007	U.S. Patent Application No. 14/948,081 Office Action dated October 31, 2016.	☐
	008	Canadian Patent Application No. 2756690 Examiner's Report dated October 20, 2015	☐
	009	Chinese Patent Application No. 2012800390779 Second Office Action dated August 11, 2015	☒

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	03/20/2017

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventor(s): Steve Cartt, *et al.* Serial No.: 12/413,439 Filed: March 27, 2009 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Examiner: Adam C. Milligan Confirmation No.: 9049 Customer No.: 21971

FILED ELECTRONICALLY ON JUNE 28, 2017

RESPONSE TO OFFICE ACTION

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

Commissioner:

This Amendment is submitted in response to the Office Action dated March 30, 2017. The Commissioner is authorized to charge any additional fees which may be required to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

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

Remarks begin on page **7**.

CLAIMS

Amendments to the Claims

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

Listing of Claims:

1-19. (Canceled).

20. (Currently Amended) A method of ~~intranasal administration of a benzodiazepine drug for~~ treating seizure, ~~protecting against seizure,~~ reducing the intensity of seizure, or ameliorating the intensity of seizure, ~~reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure~~ in a human patient with a seizure disorder, said method consisting of:

administering to one or more nasal mucosal membranes of said patient a pharmaceutical nasal spray solution, said pharmaceutical nasal spray solution consisting of:

(a) 1 to 20 mg of a benzodiazepine drug,

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

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

(d) ~~about~~ 0.01 % (w/v) to ~~about~~ 1 % (w/v) of one or more alkyl glycosides.

21. (Canceled).

22. (Canceled).

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

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

25. (Canceled)

26. (Canceled)

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

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

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

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

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

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

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

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

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

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

37. (Canceled)

38. (Canceled)

39. (Canceled).

40. (Currently Amended) The method of claim [[38]] 20, wherein said pharmaceutical~~ly acceptable spray formulation~~ solution has a volume of from ~~about~~ 10 μL to ~~about~~ 200 μL.

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

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

43. (Previously Presented) The method of claim 40, wherein said administration of said pharmaceutical solution consists of spraying a first quantity of said pharmaceutical solution into a first nostril, spraying a second quantity of said pharmaceutical solution into a second nostril, and optionally after a pre-selected time delay, spraying a third quantity of said pharmaceutical solution into said first nostril.

44. (Previously Presented) The method of claim 40, wherein said administration of said pharmaceutical solution consists of spraying a first quantity of said pharmaceutical solution into a first nostril, spraying a second quantity of said pharmaceutical solution into a second nostril, after a pre-selected time delay, spraying a third quantity of said pharmaceutical solution into said first nostril, and optionally after a pre-selected time delay, spraying at least a fourth quantity of said pharmaceutical solution into the second nostril.

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

46. (Canceled).

47. (Canceled).

48. (Currently Amended) The method of claim 20, wherein said pharmaceutical solution consists of diazepam, vitamin E, ethanol, and said alkyl glycoside.

49. (Previously Presented) The method of claim 48, wherein said alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, or a combination of two or more thereof.

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

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

52. (Previously Presented) The method of claim 51, wherein said alkyl glycoside is dodecyl maltoside, tetradecyl maltoside, sucrose dodecanoate, sucrose monostearate, sucrose distearate, or a combination of two or more thereof.

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

54. (Currently Amended) The method of claim 35, wherein said one or more alcohols or glycols, or any combinations thereof, are present in said pharmaceutical solution in an amount from ~~about~~ 25% to ~~about~~ 55% (w/w).

55. (New) A method of treating seizure, reducing the intensity of seizure, or ameliorating the intensity of seizure, in a human patient with a seizure disorder, said method consisting of:

administering to one or more nasal mucosal membranes of said patient a pharmaceutical nasal spray solution, said pharmaceutical nasal spray solution consisting of:

(a) 1 to 20 mg of a diazepam,

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

(c) one or more alcohols in an amount from 10% to 70% (w/w), and

(d) 0.01 % (w/v) to 1 % (w/v) of one or more alkyl glycosides.

56. (New) The method of claim 55, wherein said one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, are present in said pharmaceutical solution in an amount from 45% to 85% (w/w).

57. (New) The method claim 55, wherein said one or more natural or synthetic tocopherols or tocotrienols, or any combinations thereof, are present in said pharmaceutical solution in an amount from 60% to 75% (w/w).

58. (New) The method of claim 55, wherein said one or more alcohols are selected from the group consisting of: ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, any isomers thereof, and any combinations thereof.

59. (New) The method of claim 58, wherein said one or more alcohols are present in said pharmaceutical solution in an amount from 15% to 55% (w/w).

60. (New) The method of claim 58, wherein said one or more alcohols are present in said pharmaceutical solution in an amount from 25% to 40% (w/w).

61. (New) The method of claim 58, wherein said alkyl glycoside is dodecyl maltoside.

62. (New) The method of claim 61, wherein said one or more alcohols are present in said pharmaceutical solution in an amount from 15% to 55% (w/w).

63. (New) The method of claim 61, wherein said one or more alcohols are present in said pharmaceutical solution in an amount from 25% to 40% (w/w).

REMARKS

Claims 20, 23, 24, 27-36, 40-45, and 48-63 are currently pending ("Pending Claims"). Claims 1-19, 21, 22, 25, 26, 37-39, 46, and 47 are cancelled. Claims 20, 30-36, 40, 48, and 54 are currently amended. Claims 55-63 are newly presented. Applicants respectfully request that the present amendment be entered, and request prompt examination of the present application. No new matter is presented by any amendment made herein.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Office Action rejected claims 20, 22-24, 27-36, 40-45, and 48-54 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants traverse this rejection for at least the reasons stated herein.

As Applicants understand the Office Action, the rejection is based on the alleged ambiguity of the phrase "treating seizure, . . . reducing or ameliorating the frequency of seizure, and/or preventing occurrence or re-occurrence of seizure." Applicants have amended claim 20 to change "and/or" to "or," and to further clarify the claim. As amended, the pertinent part of the claims read "treating seizure, reducing the intensity of seizure, or ameliorating the intensity of seizure . . . ." Applicants submit that one of ordinary skill in the art would be able to determine the meaning of this phrase with reasonable certainty. For at least these reasons, Applicants request withdrawal of the rejection under § 112, Second Paragraph.

Rejection under 35 U.S.C. § 103 (a)

The Office Action rejected claims 20, 22-24, 27-36, 40-45, and 48-54 under 35 U.S.C. § 103(a) as allegedly unpatentable over Lahat (Intranasal midazolam for childhood seizures, The Lancet, vol. 352, August 22, 1998), in view of Sonne (U.S. 6,193,985) and Meezan (U.S. 2006/0046962). Applicant traverses this rejection, at least for the reasons set forth herein.

Claims 20 and 55, which are illustrative of the Pending Claims, read as follows[1]:

> 20. A method of treating seizure, reducing the intensity of seizure, or ameliorating the intensity of seizure, in a human patient with a seizure disorder, said method consisting of:

[1] Markings to show changes have been removed.

administering to one or more nasal mucosal membranes of said patient a pharmaceutical nasal spray solution, said pharmaceutical nasal spray solution consisting of:

(a) 1 to 20 mg of a benzodiazepine drug,

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

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

(d) 0.01 % (w/v) to 1 % (w/v) of one or more alkyl glycosides.

55. A method of treating seizure, reducing the intensity of seizure, or ameliorating the intensity of seizure, in a human patient with a seizure disorder, said method consisting of: administering to one or more nasal mucosal membranes of said patient a pharmaceutical nasal spray solution, said pharmaceutical nasal spray solution consisting of:

(a) 1 to 20 mg of a diazepam,

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

(c) one or more alcohols in an amount from 10% to 70% (w/w), and

(d) 0.01 % (w/v) to 1 % (w/v) of one or more alkyl glycosides.

As can be seen in representative claims 20 and 55, all the Pending Claims require administration of a pharmaceutical nasal spray solution to the nasal mucosal membranes, wherein the solution consists of only the ingredients recited in the claims, and specifically contains from 10% to 70% (w/w) of one or more alcohols or glycols (claims 20 et seq.) or one or more alcohols (claims 55-63). The combination of Lahat, Somme, and Meehan et al. ("the References") fails to teach the claimed method, at least because:

1. None of the References teach intranasal administration of a pharmaceutical solution containing alcohol at any concentration.

2. None of the References teach administration to any tissue of a pharmaceutical solution containing alcohol at a concentration of 10% to 70% (w/w).

3. The combination of references suggests that administration of a pharmaceutical solution containing alcohol would irritate the nasal mucosa. Thus, the combination of references teaches away from intranasal administration of a solution containing 10% to 70% alcohol (w/w).

The Office Action does not allege, and Applicant submits that it is not the case, that either Lahat or Meezan et al. teach administration to the nasal mucosa of a pharmaceutical solution containing any benzodiazepine in combination with any concentration of alcohol. Thus, two of the three cited references teach nothing regarding administration, let alone intranasal

administration, of pharmaceutical compositions containing alcohol. Further, neither reference suggests that intranasal administration of 10% to 70% alcohol would be tolerated.

Sonne also fails to teach intranasal administration of a solution containing alcohol at any concentration, let alone at a concentration of 10-70% (w/w) alcohol. While Sonne does teach that ethanol may be used as a co-solvent to reduce viscosity, Sonne also teaches that ethanol is irritating to "certain mucosal tissues," without specifying which mucosal tissues are irritated by ethanol. *See* Sonne, 3:65-68. Thus, Sonne fails to teach which mucosal tissues would tolerate ethanol, or at what concentrations. Importantly, Sonne provides no general teaching of which ethanol concentrations or ranges of ethanol concentrations may be administered to any mucosal tissue. Without such general teaching, one of ordinary skill in the art would have to rely on the examples to determine: (1) which mucosal tissues tolerate ethanol; and (2) what concentrations of ethanol are tolerated by those tissues.

Sonne provides no example in which any formulation containing any concentration of ethanol greater than 7.5% is administered to any tissue. Thus, Sonne fails to provide a teaching, suggestion, or motivation to administer a formulation containing 10% to 70% (w/w) ethanol to any tissue. One of ordinary skill in the art would not have had a reasonable expectation that administration of such a formulation to the nasal mucosa would yield a successful therapy, because Sonne 3:65-68 suggests that ethanol is irritating to certain mucosa, never teaches intranasal administration of any concentration of ethanol, and fails to teach administration of 10% to 70% (w/w) ethanol solutions to any mucosal tissues.

Sonne further fails to teach a single example of administration of alcohol, at any concentration, to the nasal mucosa. Examples 1, 2, 8, 9, 10, 11, 15, 16, 17, 18, and 19 teach formulations for intranasal administration. None of the intranasal formulations contains any ethanol. Again, it is noted that these examples are the only guidance one of ordinary skill in the art would find in Sonne regarding intranasal formulations. Given the general admonition of Sonne 3:65-68 that ethanol is irritating to some mucosal tissues, and the lack of even a single example of an intranasal solution containing any ethanol, one of ordinary skill in the art would have reasonably concluded that the nasal mucosa is a tissue that is irritated by ethanol, and would have thus concluded that intranasal administration of the recited formulations, which contain alcohol of 10% to 70% (w/w), would not succeed as a therapeutic method.

Furthermore, Examples 1, 2, 8, 9, 10, 15, 17, and 19 are emulsions (contain water); Example 11 contains triacetin; and Examples 16 and 18 require 59.9% and 44.5% sesame oil, respectively, whereas the formulations recited in the instant claims exclude such additional ingredients. Thus, Sonne fails to teach intranasal administration of a pharmaceutical formulation "consisting of" the ingredients recited in the claims. One of ordinary skill in the art would have understood Sonne to teach in the direction of intranasal formulations containing water, triacetin or sesame oil, and away from intranasal formulations containing 10% to 70% (w/w) alcohol.

While Sonne does teach administration of ethanol-containing formulations to other mucosal tissues, namely the rectum (Example 3), and the mouth (Examples 5, 12, and 14), in each case the formulation applied to the mucosal tissue is less than 10% (w/w) ethanol. Specifically, in each of Examples 3, and 5, the described emulsion contains only 5% (w/w) ethanol; and in Examples 12 and 14 the described solutions contain only 5% and 7.5% (w/w) ethanol, respectively. Thus, Sonne provides absolutely no teaching of administration of a formulation containing 10% to 70% (w/w) alcohol to any mucosal tissue, let alone the nasal mucosa. Given the general teaching of Sonne 3:65-68 regarding the irritant effect of ethanol, and the absence of any teaching that higher concentrations would be tolerated, one of ordinary skill in the art would have avoided ethanol concentrations higher than those exemplified, out of concern that such higher concentrations would be irritating.

As the combination of Lahat, Sonne, and Meezan fails to teach or suggest intranasal administration of a solution containing 10% to 70% (w/w) alcohol, and in fact suggests that such administration would not be tolerated, one of ordinary skill in the art would not have found the Pending Claims obvious in light of these references.

Furthermore, Applicants note that claims 35, 51, 59, and 62 require 15% to 55% (w/w) alcohol; and claims 36, 54, 60, and 63 require 25% to 40% (w/w) alcohol. None of the references applied in the Office Action teaches 15% to 55% (w/w) or 25% to 40% (w/w) alcohol. Thus, the reasoning set forth above applies especially strongly to these claims, as Sonne generally teaches that ethanol is irritating to mucosal tissues, and fails to teach any formulation having an ethanol concentration within these recited ranges. Applicants submit that claims 35, 36, 51, 54, 59, and 60-63 are patentable over the combination of Lahat, Sonne, and Meezan for at least the reasons stated above, with respect to claims 20 and 55, and for at least the additional

reasons that Sonne's admonition at 3:65-68 regarding ethanol's irritating effects in some mucosal tissues would have discouraged those skilled in the art from administering formulations containing such high concentrations of alcohol as high as 15% or 25% (w/w) to the nasal mucosa.

Provisional Nonstatutory Double Patenting Rejection

The Examiner provisionally rejected claims 20-24, 27-36, 38 and 40-53 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 23, 25-30, 33-56 and 60-65 of co-pending U.S. Patent Application No. 14/527,613.

Applicant requests that the rejection be held in abeyance until allowable subject matter is indicated. Applicant will consider filing a terminal disclaimer at that time. In view of the remarks and amendments submitted herein, Applicant believes that the application is in condition for allowance and such action is earnestly solicited.

CONCLUSION

Applicants believe that the application is in condition for allowance and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, or should there be any remaining issues of a minor or purely formal nature that may be readily disposed of through a supplemental amendment, or Examiner's amendment, Applicants encourage the Examiner to telephone the undersigned at 858-350-2367.

Applicants hereby authorize the Commissioner to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: June 28, 2017

By: /Raj J. Advani/

Raj J. Advani
Reg. No. 52,543

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2367
Customer No. 021971

Electronic Acknowledgement Receipt

EFS ID:	29640348
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Raj J. Advani/Lori Ford
Filer Authorized By:	Raj J. Advani
Attorney Docket Number:	35401-716.201
Receipt Date:	28-JUN-2017
Filing Date:	27-MAR-2009
Time Stamp:	17:40:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		34550_716_201_Response.pdf	81175 34788e6ae523be82e529e440b47595d02e29e50d	yes	13

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	7
	Applicant Arguments/Remarks Made in an Amendment	8	13
Warnings:			
Information:			
	Total Files Size (in bytes):	81175	

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.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		None			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
		None				

Continued on next page

Examiner Signature		Date Considered	

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

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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	Japanese Patent Application No. 2014-515967 Office Action dated April 24, 2017.	☒
	002	U.S. Patent Application No. 13/371,274 Office Action dated April 10, 2013.	☐
	003	U.S. Patent Application No. 13/371,274 Office Action dated September 26, 2012.	☐
	004	U.S. Patent Application No. 14/152,686 Office Action dated August 25, 2015.	☐
	005	U.S. Patent Application No. 14/152,686 Office Action dated December 31, 2014.	☐
	006	U.S. Patent Application No. 14/152,686 Office Action dated July 5, 2016.	☐
	007	U.S. Patent Application No. 14/527,613 Office Action dated April 21, 2017.	☐
	008	U.S. Patent Application No. 14/948,041 Office Action dated June 20, 2017.	☐

Examiner Signature		Date Considered	

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

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

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Raj J. Advani/diane garcia
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	29641195
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Raj J. Advani/diane garcia
Filer Authorized By:	Raj J. Advani
Attorney Docket Number:	35401-716.201
Receipt Date:	28-JUN-2017
Filing Date:	27-MAR-2009
Time Stamp:	18:36:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$90
RAM confirmation Number	062917INTEFSW00005865232415
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	US13371274_OA_10APR2013.pdf	633331 98e6147aa1685bf131e7f97868f4dc21129a95bd	no	16
Warnings:					
Information:					
2	Non Patent Literature	US13371274_OA_26SEPT2012.pdf	697011 badcf75161ed8ee3f0d0ac0cd7566f9992ceb3cd	no	18
Warnings:					
Information:					
3	Non Patent Literature	US14152686_OA_25AUG2015.pdf	508367 fabf2acac53156435716ff5f242c71fab41732f2	no	14
Warnings:					
Information:					
4	Non Patent Literature	US14152686_OA_31DEC2014.pdf	1189514 28ad3c347ff0eb72049ac1998c8e6e595b59c1d4	no	30
Warnings:					
Information:					
5	Non Patent Literature	US14152686_OA_05JUL2016.pdf	277334 ed94eee6dc94a00c4d7de346e4a848a6afbe4f11	no	7
Warnings:					
Information:					
6	Non Patent Literature	US14527613_OA_21APR2017.pdf	407325 b2e1258f67878a0022f37d5eab96d7743b1c62f0	no	7
Warnings:					
Information:					

7	Non Patent Literature	US14948081_OA_20JUN2017.pdf	2681702 7723c67bb6ac5230c39e937fa69a94e3da092d41	no	42
Warnings:					
Information:					
8	Non Patent Literature	JP2014515967_OA_ENG_24APR2017.pdf	129360 d41b3737caf16920c197111b30a6835a3506a87c	no	2
Warnings:					
Information:					
9		35401-716-201.pdf	260514 ee79cd83303a8843484c9e18316d0754d7519e6e	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	4
	Information Disclosure Statement (IDS) Form (SB08)	5	6

Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	30354 0ae128a5a0de6e2559bd4c8d073dbeed3ff62d21	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	6814812	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	CARTT; Steve et al.	Group Art Unit:	1612
Serial Number:	12/413,439	Examiner:	Milligan, Adam
Filing or 371 (c) Date:	2009-03-27	**CONFIRMATION NO:**	**9049**
Title:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		

FILED ELECTRONICALLY ON: June 28, 2017

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

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

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

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

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

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

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

-- OR --

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

-- OR --

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

-- OR --

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

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

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

-- OR --

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

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

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

-- AND --

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

D. ☐ *37 CFR §1.97 (e).* Statement.

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

-- AND/OR --

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

-- AND/OR --

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

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

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

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

-- OR --

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

-- AND/OR --

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

-- AND/OR --

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

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

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

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

-- OR --

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

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

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

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

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

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

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

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: June 28, 2017

By: /Raj Advani/
Raj Advani, Reg. No. 52543

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

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

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

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT **06/28/2017**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 35	Minus	** 62	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

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

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

LIE
SHEILA D. CHAPMAN

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventor(s): Steve Cartt, *et al.* Serial No.: 12/413,439 Filed: March 27, 2009 Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	Group Art Unit: 1612 Examiner: Adam C. Milligan Confirmation No.: 9049 Customer No.: 21971

FILED ELECTRONICALLY ON AUGUST 17, 2017

REQUEST FOR CORRECTION OF INVENTORSHIP IN A PATENT APPLICATION UNDER 37 CFR §1.48
AND REQUEST FOR CORRECTED FILING RECEIPT

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

Commissioner:

Applicant hereby requests that the inventorship be amended in the above-referenced patent application pursuant to 37 C.F.R. §1.48(a).

☒ The Office is requested to amend the inventorship to **ADD** the following inventor:

Edward T. MAGGIO

In support of this Request, Applicant provides:

☒ (1) A Corrected Application Data Sheet in accordance with § 1.76 that identifies each inventor by his or her legal name;

(2) ☒ (3) The processing fee set forth in 37 C.F.R. § 1.17(i).

☒ (3) The processing fee set forth in 37 C.F.R. § 1.17(d).

☒ *Fee Authorization.* The Commissioner is hereby authorized to charge the above-referenced fees totaling **$440.00** and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Applicant requests that a corrected Filing Receipt be issued.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: August 17, 2017

By: /Raj J. Advani/

Raj J. Advani
Reg. No. 52,543

650 Page Mill Road
Palo Alto, CA 94304
(858) 350-2300
Customer No. 021971

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	12/413,439
Filing Date	March 27, 2009
First Named Inventor	Steve Cartt
Title	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
Art Unit	1612
Examiner Name	Adam C. Milligan
Attorney Docket Number	35401-716.201

SIGNATURE of Applicant or Patent Practitioner

Signature	/Raj J. Advani/	Date (Optional)	2017-08-17
Name	Raj J. Advani	Registration Number	52543
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82B(07-12)

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in the attached transmittal letter.

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

21971

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A or equivalent):

Name	Registration Number		Name	Registration Number

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☐ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant:

☐ Inventor or Joint Inventor

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (*e.g.*, a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document)

SIGNATURE of Applicant for Patent

Signature		Date	4/12/13
Name	David F. Hale	Telephone	858-756-2480
Title and Company	Chairman and CEO, Hale Biopharma Ventures, LLC		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below *.

☒ *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Hale Biopharma Ventures, LLC

Application No./Patent No.: 12/413,439 Filed/Issue Date: March 27, 2009

Titled: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Hale Biopharma Ventures, LLC, a limited liability company

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Steve Cartt et al. To: Hale Biopharma Ventures

   The document was recorded in the United States Patent and Trademark Office at
   Reel 022897, Frame 0583, or for which a copy thereof is attached.

2. From: Steve Cartt et al. To: Hale Biopharma Ventures, LLC

   The document was recorded in the United States Patent and Trademark Office at
   Reel 042775, Frame 0799, or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Edward T. Maggio To: Hale Biopharma Ventures, LLC

The document was recorded in the United States Patent and Trademark Office at
Reel 027957, Frame 0603, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Raj J. Advani/	August 17, 2017
Signature	Date
Raj J. Advani	52543
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

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

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

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

CORRECTED ADS

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	12/413,439
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Steve		Cartt	

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

City	~~Union City~~ Hillsborough	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	~~3260 Whipple Road~~ 1055 Black Mountain Road		
Address 2			
City	~~Union City~~ Hillsborough	State/Province	CA
Postal Code	~~94567~~ 94010	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David		Medeiros	

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

City	~~South San Francisco~~ Sparks	State/Province	~~CA~~ NV	Country of Residence	US

Mailing Address of Inventor:

Address 1	~~212 Crown Circle~~ 1702 A Street, #C		
Address 2			
City	~~South San Francisco~~ Sparks	State/Province	~~CA~~ NV
Postal Code	~~94080~~ 89431	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Garry	Thomas	Gwozdz	

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

City	Jim Thorpe	State/Province	PA	Country of Residence	US

Mailing Address of Inventor:

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

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Andrew		Loxley	

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

City	~~Philadelphia~~ Brussels	State/Province	~~PA~~	Country of Residence	~~US~~ BELGIUM

Mailing Address of Inventor:

Address 1	~~126 Market Street, #5~~ Rue Emile Claus 42		
Address 2			
City	~~Philadelphia~~ Brussels	State/Province	~~PA~~
Postal Code	~~19106~~ 1050	Country	~~US~~ BELGIUM

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mark		Mitchnick	

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

City	East Hampton	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

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

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David	F.	Hale	

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

City	San Diego	State/Province	CA	Country of Residence	US

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Mailing Address of Inventor:

Address 1	~~9232 Bernardo Lakes Drive~~ 12340 El Camino Real		
Address 2	Suite 425		
City	San Diego	**State/Province**	CA
Postal Code	~~92127~~ 92130	**Country**	US

Inventor 7 — Remove

Legal Name

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

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

City	San Diego	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	11770 Bernardo Plaza Court		
Address 2	Suite 353		
City	San Diego	**State/Province**	CA
Postal Code	92128	**Country**	US

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

Correspondence Information:

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

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

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

Application Information:

Title of the Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		
Attorney Docket Number	35401-716.201	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

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

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	61040558	2008-03-28

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Foreign Priority Information:

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

Remove

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

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

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Applicant Information:

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

Applicant 1

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:	

If the Applicant is an Organization check here. ☒

Organization Name	Hale Biopharma Ventures, LLC

Mailing Address Information For Applicant:

Address 1	1042-B N. El Camino Real, Suite 430		
Address 2			
City	Encinitas	**State/Province**	CA
Country	US	Postal Code	92024
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

Assignee 1

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

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

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

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Raj J. Advani/			Date (YYYY-MM-DD)	2017-08-17
First Name	Raj J.	Last Name	Advani	Registration Number	52543

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	35401-716.201
	Application Number	
Title of Invention	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Raj J. Advani/Lori Ford
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION FEE-37CFR 1.17(H) (GROUP II)	2464	1	70	70
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
CORRECTION OF INVENTORSHIP ON MERITS	2819	1	300	300
		Total in USD ($)		**370**

Electronic Acknowledgement Receipt

EFS ID:	30113555
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Raj J. Advani/Lori Ford
Filer Authorized By:	Raj J. Advani
Attorney Docket Number:	35401-716.201
Receipt Date:	17-AUG-2017
Filing Date:	27-MAR-2009
Time Stamp:	17:43:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$370
RAM confirmation Number	081817INTEFSW00004614232415
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request under Rule 48 correcting inventorship	35401_716_201_148_Request_and_Request_Corrected_FR.pdf	23507 7e94e13adecc72f806edfa7ae516044e51ff195b	no	2
Warnings:					
Information:					
2	Power of Attorney	35401_716_201_POA_82.PDF	2093986 ed732b82769737bafb842d214d10bc4f2745365b	no	2
Warnings:					
Information:					
3	Assignee showing of ownership per 37 CFR 3.73	35401_716_201_373c_Statement.PDF	122586 bb5019cb2f270b661a3e283b654fb5bcfda88558	no	3
Warnings:					
Information:					
4	Application Data Sheet	35401_716_201_Supp_ADS.pdf	597336 45aebf1da88a117e3574b3a713d94d352797abde	no	10
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
5	Fee Worksheet (SB06)	fee-info.pdf	32040 1669390a4990ad76b20483be2d658479039ee16d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2869455		

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.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 08/22/2017

ABALINAN SALE #00000020 Mailroom Dt: 08/17/2017 232415 12413439
01 FC : 2830 70.00 DA

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 08/22/2017

ABALINAN ADJ #00000004 Mailroom Dt: 08/17/2017
Seq No: 4614 Sales Acctg Dt: 08/18/2017 232415 12413439
01 FC : 2464 70.00 CR

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/413,439	03/27/2009	1612	1814	35401-716.201	47	2

CONFIRMATION NO. 9049

UPDATED FILING RECEIPT

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

OC000000093859228

Date Mailed: 08/24/2017

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

Inventor(s)

Steve Cartt, Hillsborough, CA;
David Medeiros, Sparks, NV;
Gary Thomas Gwozdz, Nazareth, PA;
Andrew Loxley, Brussels, BELGIUM;
Mark Mitchnick, East Hampton, NY;
David F. Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

Applicant(s)

Steve Cartt, Hillsborough, CA;
David Medeiros, Sparks, NV;
Gary Thomas Gwozdz, Nazareth, PA;
Andrew Loxley, Brussels, BELGIUM;
Mark Mitchnick, East Hampton, NY;
David F. Hale, San Diego, CA;
Edward T. Maggio, San Diego, CA;

Assignment For Published Patent Application

HALE BIOPHARMA VENTURES, LLC, Encinitas, CA

Power of Attorney: The patent practitioners associated with Customer Number 021971

Domestic Priority data as claimed by applicant

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

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Preliminary Class

424

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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

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

NOT GRANTED

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

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

CONFIRMATION NO. 9049

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

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000093659229

Date Mailed: 08/24/2017

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 08/17/2017.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

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

/rmohamed/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

CONFIRMATION NO. 9049

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

37 CFR 1.48(f)
ACKNOWLEDGEMENT LETTER

OC000000093659230

Date Mailed: 08/24/2017

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(f)

This is in response to the applicant's request under 37 CFR 1.48(f) submitted on 08/17/2017.

The request under 37 CFR 1.48(f) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

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

/rmohamed/

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-20170196884	07-13-2017	CARTT; Steve et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	WO-2012174158-A2	12-20-2012	HALE BIOPHARMA VENTURES LLC [US], et al.		☐

Examiner Signature		Date Considered	

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

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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	Chinese Patent Application No. 201280039077.9 Reexamination Notification issued June 29, 2017.	☒

Examiner Signature		Date Considered	

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(71) Applicant *(for all designated States except US)*: **HALE BIOPHARMA VENTURES, LLC** [US/US]; 1042-B North El Camino Real, Suite 430, Encinitas, CA 92024 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CARTT, Steve** [US/US]; 3260 Whipple Road, Union City, CA 94587 (US). **MEDEIROS, David** [US/US]; 212 Crown Circle, South San Francisco, CA 94080 (US). **GWOZDZ, Garry, Thomas** [US/US]; 432 Pine Street, Jim Thorpe, PA 18229 (US). **LOXLEY, Andrew** [US/US]; 126 Market Street, #5, Philadelphia, PA 19106 (US). **MITCHNICK, Mark** [US/US]; 80 Three Mile Harbor Drive, East Hampton, NY 11937 (US). **HALE, David** [US/US]; 9232 Bernardo Lakes Drive, San Diego, CA 92127 (US). **MAGGIO, Edward, T.** [US/US]; 16870 W. Bernardo Drive, Suite 390, San Diego, CA 92127 (US).

(74) Agent: **GRUMBLING, Matthew, V.**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94304 (US).

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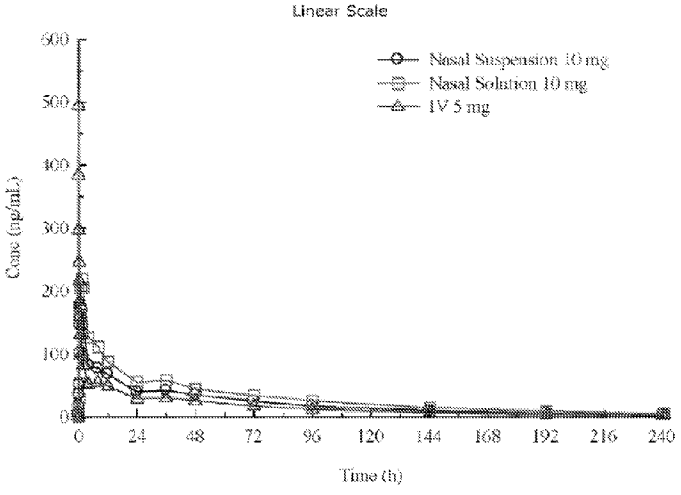
(54) Title: ADMINISTRATION OF BENZODIAZEPINE

(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



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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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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 gama-aminobutyric acid (GABA).

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INCORPORATION BY REFERENCE

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Definitions

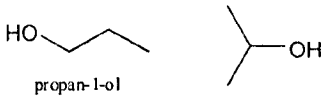
[068] As used herein the phrase "therapeutically effective amount" (or more simply "effective amount") includes an amount sufficient to provide a specific therapeutic response for which the drug is administered to

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

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

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

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



propan-1-ol propan-2-ol

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

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

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

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

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

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

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

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

Benzodiazepine Drugs

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

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

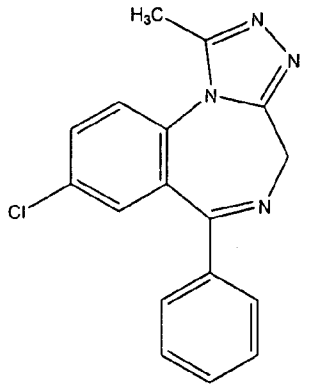
[081] For example, most benzodiazepines are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. By use of the present carrier system, which in some embodiments, provides an improved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

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

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

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

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



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

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

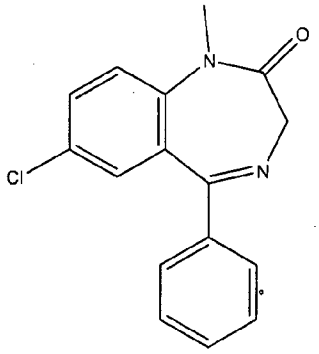
[088] In some embodiments, alprazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Alprazolam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

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

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

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

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



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

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

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

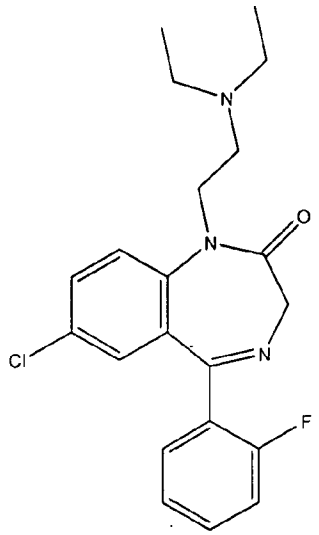
[094] In some embodiments, diazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Diazepam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

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

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

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

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



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

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

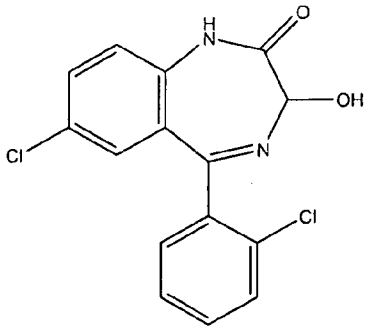
[0100] In some embodiments, flurazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Flurazepam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

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

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

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

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



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

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

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

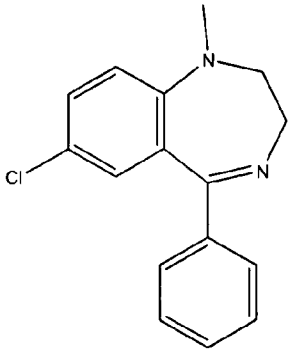
[0106] In some embodiments, lorazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Lorazepam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

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

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

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

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



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

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

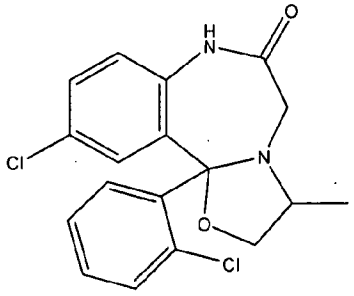
[0112] In some embodiments, medazepam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Medazepam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

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

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

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

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



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

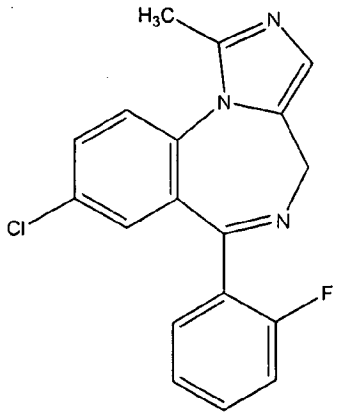
[0117] In some embodiments, mexazolam is used alone or in combination with other drugs to provide an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations of the foregoing effects.

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

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

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

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



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

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

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

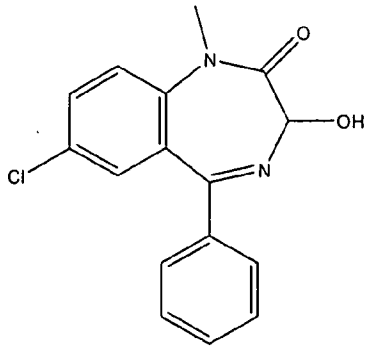
[0125] In some embodiments, midazolam is used alone or in combination with another anticonvulsant drug to treat seizure, protect against seizure, reduce or ameliorate the intensity of seizure, reduce or ameliorate the frequency of seizure, and/or prevent occurrence or re-occurrence of seizure. Midazolam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

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

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

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

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



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

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

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

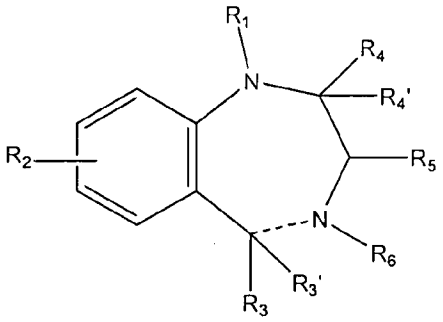
[0132] Temazepam may also be administered by another person (*e.g.* an acquaintance or associate, a family member or a health care professional) to the patient while the patient is in a state of seizure. Thus, one of the advantages of the formulations according to the present invention is the ability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

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

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

Pharmaceutically Acceptable Salts

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



Formula I

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

[0135] Pharmaceutically acceptable mineral acids include HCl, H_2SO_4, H_2SO_3, H_3PO_4, H_3PO_3, and others that will be recognized by those of skill in the art. Pharmaceutically acceptable organic acids include acetic acid, benzoic acid, tartaric acid, citric acid, oxalic acid, maleic acid, malonic acid, etc. Thus, in some embodiments, the pharmaceutically acceptable acid may be selected from the group consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acidascorbic acid (L), aspartic acid (L), benzenesulfonic acid, benzoic acid, camphoric acid (+), camphor-10-sulfonic acid (+), capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acidfumaric acid, galactaric acid, gentisic acid, glucoheptonic acid (D), gluconic acid (D), glucuronic acid (D), glutamic acid,

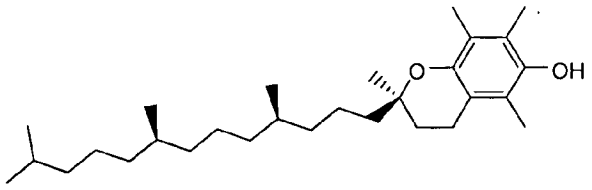
glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid (DL), lactobionic acid, lauric acid, maleic acid, malic acid (- L), malonic acid, mandelic acid (DL), methanesulfonic acid, benzenesulfonic acid (besylic acid), naphthalene-1,5-disulfonic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

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

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

Carrier System

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



α-tocopherol

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

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

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

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

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

Additional Excipients

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

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

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

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

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

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

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

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

Mucosal Membrane Preparations

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

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

Alprazolam

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

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

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

Diazepam

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

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

Flurazepam

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

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

Lorazepam

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

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

Medazepam

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

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

Mexazolam

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

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

Midazolam

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

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

Temazepam

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

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

Formulation

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

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

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

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

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

Formulation Process

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

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

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

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

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

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

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

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

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

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

Additional Active and Inactive Ingredients

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

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

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

[0182] Additionally, some embodiments of the compositions and methods of using the compositions comprise an additional ingredient in the composition selected from other anticonvulsants. By way of non-limiting example, such active ingredients include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, gentamicin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and ethacridine; enzymes such as lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, active vitamin D and vitamin C; sex hormones; hypotensives; sedatives; anti-tumor agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen, diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride or pharmaceutically acceptable salts or combinations thereof.

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

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

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

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

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

Administration

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

Alprazolam

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

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

Diazepam

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

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

Flurazepam

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

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

Lorazepam

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

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

Medazepam

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

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

Mexazolam

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

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

Midazolam

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

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

Temazepam

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

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

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

Examples

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

Example 1

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

Table 1-1

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

Example 2

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

Table 2-1

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

Example 3 – Formulation of Diazepam Solutions

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

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

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

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

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

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

Example 4 -- Formulation of Diazepam Suspensions

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

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

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

Table 4-1: Diazepam Suspension Formulations

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

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

Example 5 -- Stability of Diazepam Solutions and Suspensions

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

Table 5-1: Summary of PSI sample control numbers

Formulation #	25°C/60% RH	30°C/65% RH	40°C/75% RH
Solution 00 – 70 mg/ml solution, 65% Vitamin E	083101.01	083101.02	083101.02
Solution 02 – 70 mg/ml solution, 80%	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 month 25°C/60 %RH	1 month 30°C/65 %RH	1 month 40°C/75 %RH	3 month 25°C/60 %RH	3 month 30°C/65 %RH	3 month 40°C/75 %RH	6 month 25°C/60 %RH	6 month 30°C/65 %RH	6 month 40°C/75 %RH

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

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

Table 5-5: Summary of Solution 02 results

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

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

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

Table 5-6: Summary of Suspension 01 results

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

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

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

Table 5-7: Summary of Suspension 03 results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Example 6

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

Example 7

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

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

Example 8

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

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

Example 9

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

Example 10

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

Example 11

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

Table 11-1

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

*Vitamin E, **Dodecyl maltoside

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 11-3

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

	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
Parameter [a]	n	Mean (SD) [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-t} (h×ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h×ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λz (h^{-1})	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
t½ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

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

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

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

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

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical solution for nasal administration consisting of:

(a) a benzodiazepine drug;

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

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

(d) an alkyl glycoside,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

FIG. 1

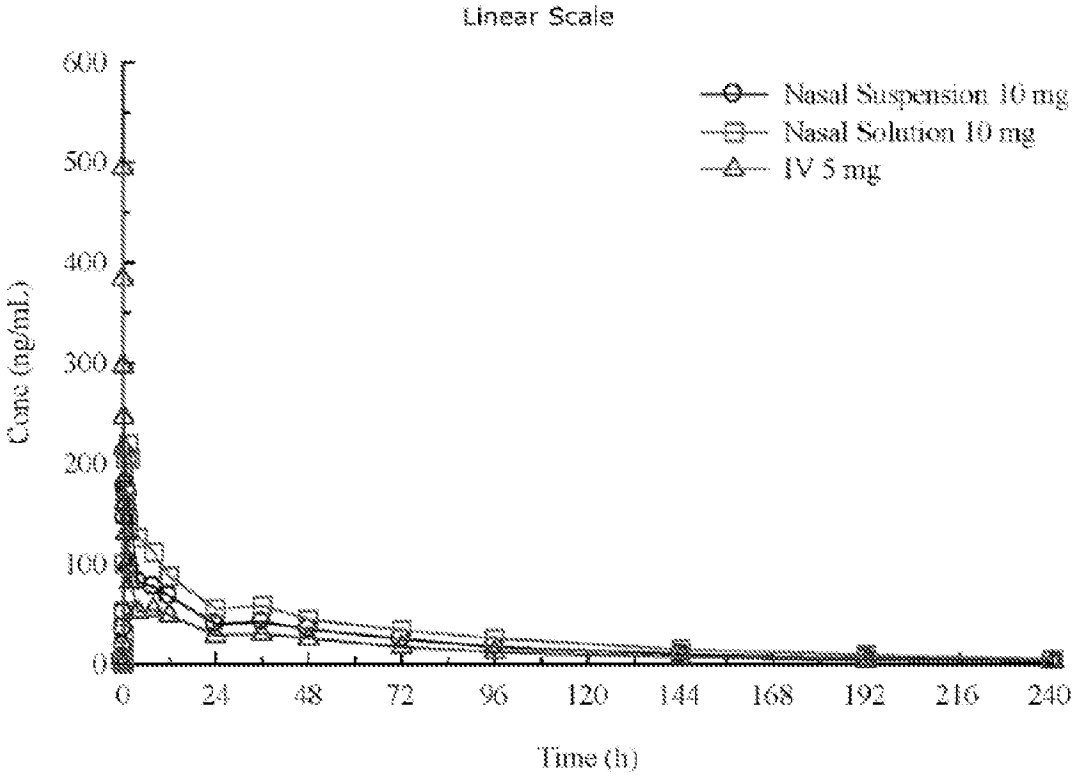

Linear Scale
Nasal Suspension 10 mg
Nasal Solution 10 mg
IV 5 mg
Conc (ng/mL)
600
500
400
300
200
100
0
0
24
48
72
96
120
144
168
192
216
240
Time (h)

FIG. 2

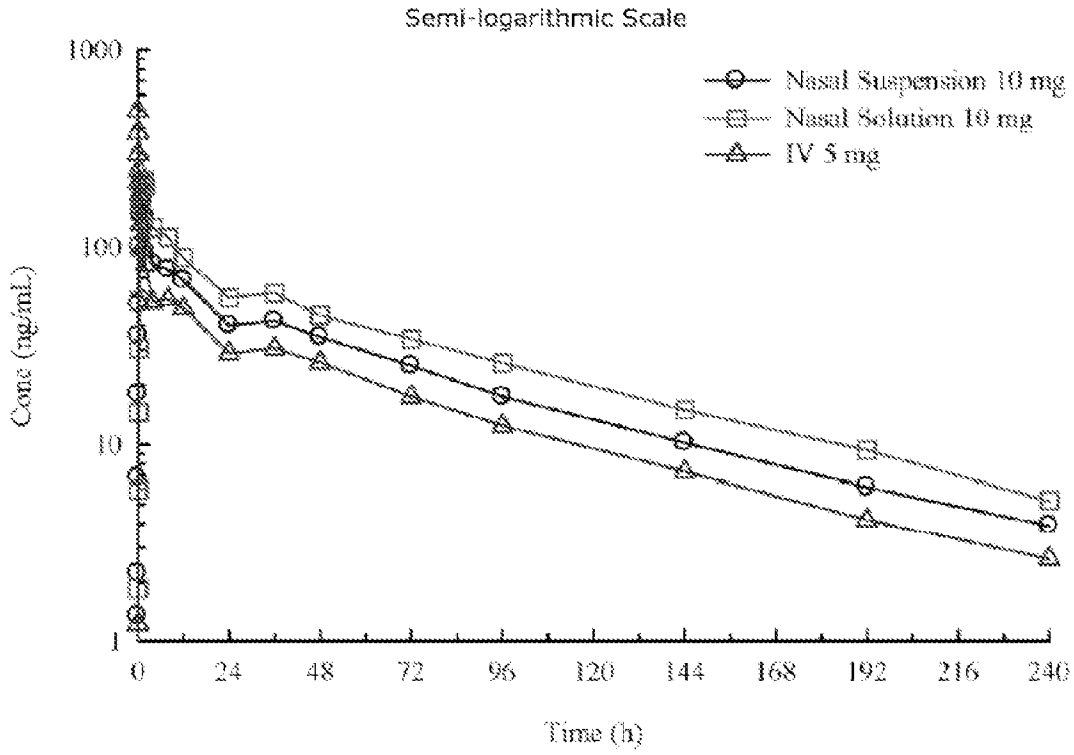

Semi-logarithmic Scale
Nasal Suspension 10 mg
Nasal Solution 10 mg
IV 5 mg
Conc (ng/mL)
1000
100
10
1
0
24
48
72
96
120
144
168
192
216
240
Time (h)

FIG. 3

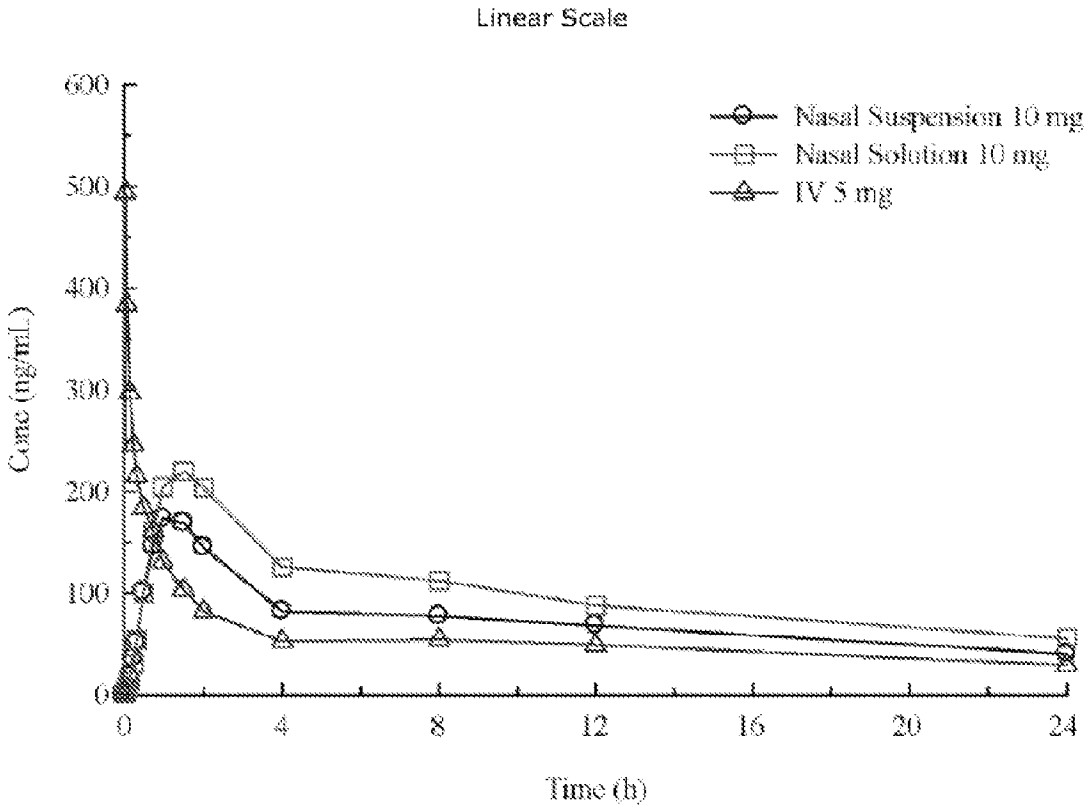

Linear Scale
Nasal Suspension 10 mg
Nasal Solution 10 mg
IV 5 mg
Cone (ng/mL)
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (h)

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

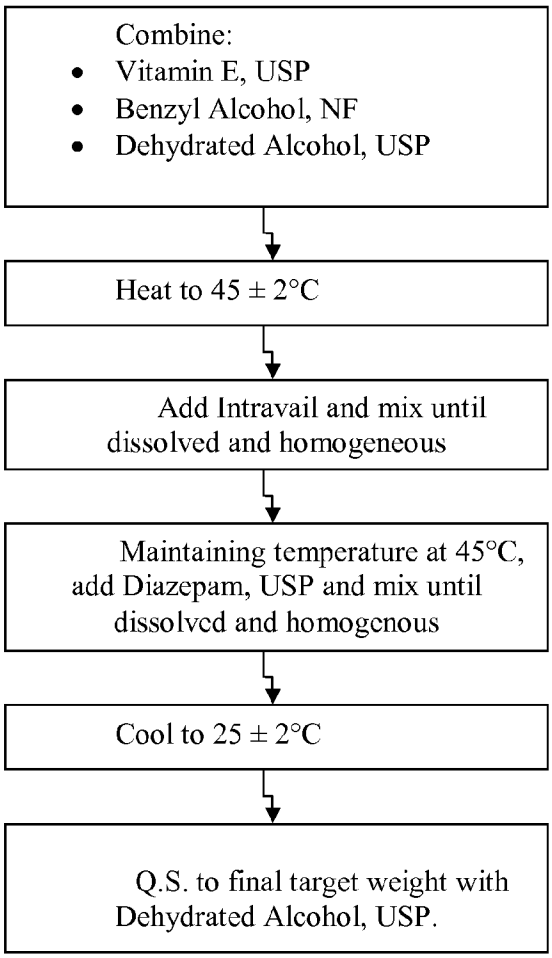
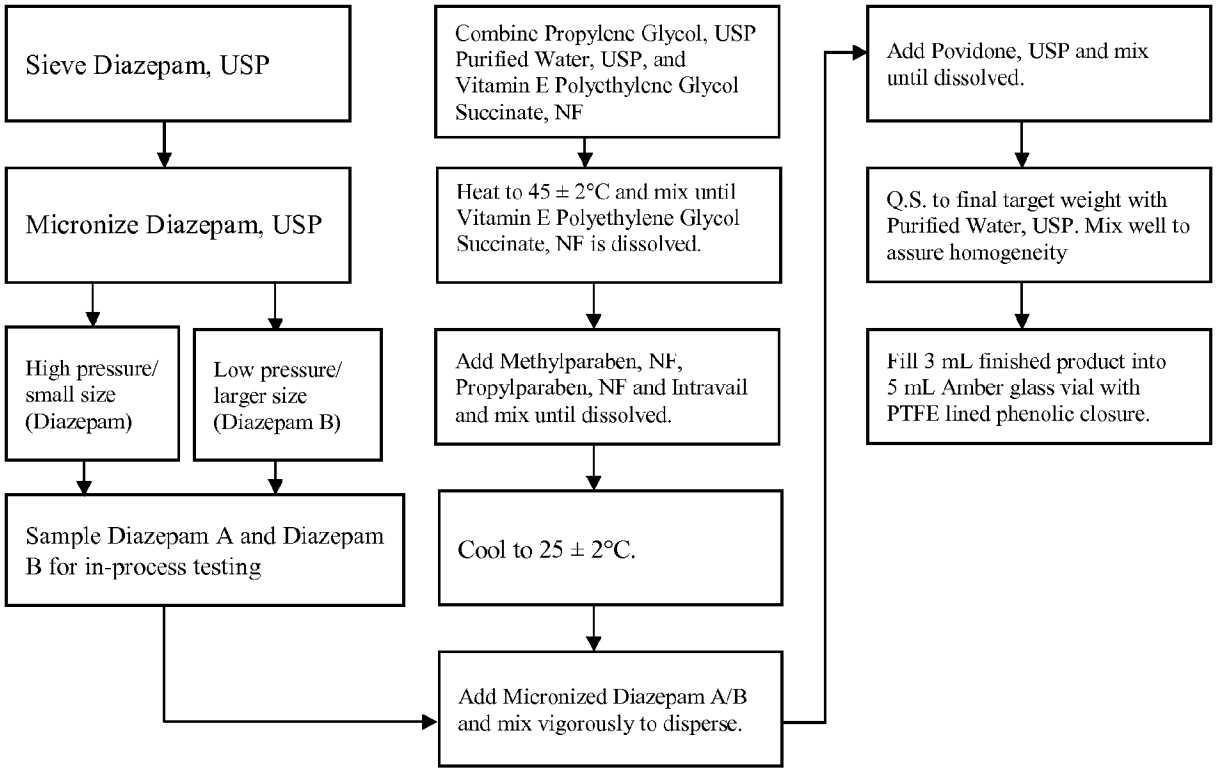


FIG. 5: Flow Diagram for Preparation of Diazepam Suspension

Flow Diagram for the Manufacture of NRL-1A



Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Raj J. Advani/diane garcia
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	30357220
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Raj J. Advani/diane garcia
Filer Authorized By:	Raj J. Advani
Attorney Docket Number:	35401-716.201
Receipt Date:	13-SEP-2017
Filing Date:	27-MAR-2009
Time Stamp:	18:47:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$90
RAM confirmation Number	091417INTEFSW00005983232415
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		35401-716-201.pdf	258731 6644de084ecf276dd4a3f96ace18076237bf8eba	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	6	
Warnings:					
Information:					
2	Foreign Reference	WO12174158.pdf	4185956 b89452ea292b347302dae49d17e1c43f80d2b1e4	no	78
Warnings:					
Information:					
3	Non Patent Literature	CN2012800390779_OA_Eng_29JUN2017.pdf	160229 125983c787ec77620fdd1d6dfa473801d5718a9a	no	5
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30354 e38141c5eb1a42303b2ab30c1ee6e676f10fdf3a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4635270		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	CARTT; Steve et al.	Group Art Unit:	1612
Serial Number:	12/413,439	Examiner:	Milligan, Adam
Filing or 371 (c) Date:	2009-03-27	**CONFIRMATION NO:**	**9049**
Title:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS		

FILED ELECTRONICALLY ON: 09-13-2017

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

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

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

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

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

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

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

-- OR --

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

-- OR --

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

-- OR --

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

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

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $90.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $90.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No.35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: September 13, 2017

By: /Raj Advani/
Raj Advani, Reg. No. 52543

650 Page Mill Road
Palo Alto, CA 94304-1050
(650) 493-9300
Customer No. 21971

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/413,439	03/27/2009	Steve Cartt	35401-716.201	9049

21971 7590 10/19/2017

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/19/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Office Action Summary	Application No. 12/413,439	Applicant(s) CARTT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/28/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *20,23,24,27-36,40-45 and 48-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *20,23,24,27-36,40-45 and 48-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Applicants' arguments, filed 6/28/2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20, 23, 24, 27-36, 40-45 and 48-63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lehat (Intranasal midazolam for childhood seizures, The Lancet, vol.352, August 22, 1998 – See IDS dated 10/29/2013) in view of Sonne (U.S. 6,193,985- See IDS dated 9/16/2009) and Meezan (U.S. 2006/0046962).

Lehat teaches diazepam is widely used to treat acute seizures in adults and children and that intranasal administration of benzodiazepine compounds has been demonstrated as an effective way to manage acute childhood seizures (Abstract).

Lehat does not teach suitable excipients for the formulation.

Sonne teaches tocopherol compositions for the delivery of biologically active agents which are only sparingly soluble in water (col. 1, lines 7-13), such as diazepam

(col. 1, lines 7-14). One particular nasal formulation contains 5g of diazepam, 44 g Tenox GT2 (70% tocopherol), 5 g Vitamin E TPGS (glycol), 1.45 g Pluronic and 0.1g benzalkonium chloride (example 1 at col. 7, lines 32-45). In preparing the formulation, the ingredients are heated slowly until a homogeneous phase is achieved (Sonne also teaches that co-solvent such as ethanol, benzyl alcohol, sesame oil or propylene glycol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53). When ethanol is used in the formulations, it may be used in an amount of about 11% by weight of the formulation (See example 3 at col.8, lines 28-43). When sesame oil is used, it may be used in an amount of about 44% (example18, col12, lines 37-51) or about 60% (example 16 at col.12, lines 10-17). α-tocopherol may be used in amounts of 20 to 99.9% (col.5, lines 56-61). The active ingredient should be present in an amount of 0.001% to 40% (col.5, lines 55-61). Diazepam may be present at about 5% by weight (example 11 at col. 11, lines 1-13). Preservative as well as odor masking compounds may be included in the (col.7, lines 4-12). The composition may be in the form of a spray formulation (col. 6, lines 28-35). In general, about 100µL can be administered to the nose at a time (col.7, lines 25-30). Sonne teaches that the “compositions of the invention may be used directly as a solution of bioactive agents in the tocopherol solvent” (col.3, lines 60-61) and that the "[v]iscosity can be reduced by the addition of co-solvents such as ethanol (col.3, lines 65-66). Sonne teaches that “transmucosal delivery is preferred" (col.3, line 54) and "[n]asal...administrations are particularly preferred" (col.3, lines 58-59). The compositions of the invention may contain from 1-99.99% tocopherol (col.5, lines 55-57). Sonne also teaches that a co-

solvent such as ethanol can be used in order to optimize the formulations bioadhesion, sprayability and viscosity (col. 6, lines 47-53).

Sonne does not teach the surfactant is an alkyl glycoside.

Meezan teaches that alkyl glycosidase is an absorption enhancing surfactant for drug administration (¶150). Specifically, Meezan demonstrates that the addition of 0.25% of alkyl glycoside can increase drug absorption from about 3% bioavailabilty to about 90% bioavailability when the drug is administered via a nasal spray. Meezan further teaches that the active ingredient for the nasal spray may be in the form of nanoparticles (¶63).

Meezan does not teach using a benzodiazapine active ingredient.

It would have been obvious to one of ordinary skill in the art treating seizures as taught by Lehat to administer the benzodiazepine in the composition taught by Sonne to improve benzodiazepine solubility. Further, it would have been obvious to one of skill in the art administering the nasal spray formulation of Sonne to use the surfactant taught by Meezan to improve the bioavailability of drug administered via a nasal spray.

Applicants present the following arguments against the rejection.

Applicants argue that none of the references teach intranasal administration of a pharmaceutical solution containing alcohol at any concentration or teach administration to any tissue of a pharmaceutical solution containing alcohol at a concentration of 10% to 70% w/w.

Examiner disagrees. As discussed above, Sonne teaches the inclusion of ethanol, benzyl alcohol or propylene glycol in an amount sufficient to provide the desired formulation bioadhesion, sprayability and viscosity. Sonne teaches that the compositions may be administered to mucosal membranes, for example in the nose or rectum (col.3, lines 54-59). In fact, nasal and rectal administrations are particularly preferred (Id.).

Applicants argue that the combination of references suggests that administration of a pharmaceutical solution containing alcohol would irritate the nasal mucosa. Sonne teaches that the viscosity can be reduced by the addition of co-solvents such as ethanol...but this is less desired since solutions of this type tend to be irritating to certain mucosal tissues". Though Sonne does not teach which types of tissue may be irritated by alcohol, Sonne presents exemplary ethanol containing formulations only for oral and rectal administration, not for intranasal administration. Thus, Applicants request the rejection be withdrawn.

Examiner disagrees. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including non-preferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Here, while ethanol addition is not listed as a most preferred method for viscosity reduction, it is taught as a suitable method for such. A prior art reference must be considered for all that it teaches or suggests to one of ordinary skill in the art. It should not be limited to the exemplary formulations. It is

further noted that nasal formulations are not limited to sprays, which may require higher amounts of ethanol, but can be in the form of drops, which can be more viscous.

Applicants argue that the “consisting of" language excludes other components, such as those required to form separate phases, such as in an emulsion. Thus, the combination of Sonne and Meezan would not have suggested the instantly claimed subject matter.

Examiner disagrees. Sonne teaches that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues (col.2, lines 54-58). The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent (col.3, lines 60-61). However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application (col.3, lines 62-64). To increase viscosity, co-solvents such as ethanol can be added (col.3, lines 65-67). Since ethanol can be irritating to certain mucosal tissue, Sonne alternatively teaches emulsification as a means to lower viscosity (col.4, lines 1-2). Thus, Sonne teaches three formulating alternatives, (1) high viscosity, (2) co-solvent (i.e. ethanol) addition and (3) emulsification. The high viscosity teaching and the co-solvent teaching render obvious the instantly recited claims.

Applicants argue that Sonne fails to provide examples of formulations containing alcohol greater than 7.5% administered to any tissue and fails to provide an example of alcohol at any concentration administered to the nasal mucosa, so the rejection should be withdrawn.

Examiner disagrees. Anticipation may require such a specific embodiment, but the standard for obviousness does not require that a reference provide an exemplary formulation. Since the rejection was made under obviousness and not anticipation, Applicants argument is not found persuasive.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20, 23, 24, 27-36, 40-45 and 48-63 stand rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 9,763,876 (formerly Application No. 14/527,613) Although the claims at issue are not identical, they are not patentably distinct from each other because it would have

been obvious to one of ordinary skill in the art to choose from the components recited in the '613 patent and arrive at the present claims.

Applicants state they will consider filing a terminal disclaimer over the copending application when present claims are found otherwise allowable.

Based on Applicants request, the rejection is maintained. Examiner notes that the rejection is no longer provisional.

Examiner further notes that if the restriction requirement were to be withdrawn, a double patenting rejection would also exist over U.S. Patent 8,895,546.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/A.C.M/	001	US-20170196884	07-13-2017	CARTT; Steve et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
/A.C.M/	001	WO-2012174158-A2	12-20-2012	HALE BIOPHARMA VENTURES LLC [US], et al.		☐

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	10/14/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	12413439
Filing Date	03-27-2009
First Named Inventor	CARTT; Steve
Art Unit	1612
Examiner Name	Milligan, Adam C.
Attorney Docket Number	35401-716.201

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
/A.C.M/	001	Chinese Patent Application No. 201280039077.9 Reexamination Notification issued June 29, 2017.	☒

Examiner Signature	/ADAM C MILLIGAN/	Date Considered	10/14/2017

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PTO/SB/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 35401-716.201

Application Number: 12/413,439 - Conf. #9049

Filed: March 27, 2009

For: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

Art Unit: 1612

Examiner: Adam C. Milligan

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☑	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 700
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23-2415.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration number 68911.

☐ attorney or agent acting under 37 CFR 1.34. Registration number .

/Nathaniel T. Leachman/ — Signature

April 17, 2018 — Date

Nathaniel T. Leachman — Typed or printed name

858-350-2227 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	12413439
Filing Date:	27-Mar-2009
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Filer:	Nathaniel Thaddeus Leachman/Jenniffer Huddleston
Attorney Docket Number:	35401-716.201

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
			Total in USD ($)	**700**

Electronic Acknowledgement Receipt

EFS ID:	32365316
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Nathaniel Thaddeus Leachman/Jenniffer Huddleston
Filer Authorized By:	Nathaniel Thaddeus Leachman
Attorney Docket Number:	35401-716.201
Receipt Date:	17-APR-2018
Filing Date:	27-MAR-2009
Time Stamp:	17:14:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$700
RAM confirmation Number	041818INTEFSW00003834232415
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	35401716201_EOT_Transmittal.pdf	113289 3bad87c3d96e199cab88ae1d6a0e8d4202fed9c7	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30653 e4b728aa4b2932f5d68261092c720991124c5205	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	143942		

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/413,439	03/27/2009	Steve Cartt	35401-716.201	9049

21971 7590 06/01/2018

WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CALIFORNIA 94304-1050
UNITED STATES OF AMERICA

EXAMINER	
MILLIGAN, ADAM C	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/01/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@wsgr.com

Notice of Abandonment	Application No.	Applicant(s)
	12/413,439	Cartt et al.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☑ Applicant's failure to timely file a proper reply to the Office letter mailed on 19 October 2017.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of:(1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☑ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $ _____ is insufficient. A balance of $ _____ is due.
   The issue fee required by 37CFR 1.18 is $ _____ . The publication fee, if required by 37 CFR 1.18(d), is $ _____ .
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33 (b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

_____

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.