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PROVISIONAL PATENT APPLICATION

ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

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ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

[007] Intravenous administration perhaps provides a faster route of administration. However intravenous administration is generally limited to trained health care professionals in tightly controlled clinical settings. Additionally, sterility must be maintained. Furthermore, administering any drug intravenously can be painful and is likely impractical for patients suffering from a phobia of needles.

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

SUMMARY OF THE INVENTION

[009] In some embodiments, 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.

[010] 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.

[011] 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.

[012] 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.

[013] 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.

[014] 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).

[015] 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).

[016] 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.

[017] 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). 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). In some embodiments, the benzodiazepine drug is dissolved in a carrier system.

[018] 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.

[019] 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.

[020] 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.

[021] 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.

[022] 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).

[023] 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).

[024] 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.

[025] 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.

[026] 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

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