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(54) Title: NASAL ADMINISTRATION OF BENZODIAZEPINES

(57) Abstract: Particulate formulations of benzodiazepines, such as diazepam, are used for nasal administration of diazepine drugs to patients. Multimodal particulate formulations of benzodiazepines and methods for their use, e.g. by nasal administration for the treatment of seizure, are also provided.

NASAL ADMINISTRATION OF BENZODIAZEPINES

[0001] This application claims benefit of priority of provisional application United States serial number 60/916,550, filed on May 7, 2007, the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This application relates to the administration of benzodiazepine drugs, and in particular to the nasal administration of benzodiazepine drugs.

BACKGROUND OF THE INVENTION

[0003] Benzodiazepines, such as diazepam, lorazepam and medazepam, make up a class of psychoactive drugs. Most benzodiazepines are classified as anxiolytic, sedative and/or hypnotic. The class of benzodiazepines are minor tranquilizers possessing varying hypnotic, sedative, anxiolytic, anticonvulsant, muscle relaxant and amnesic properties. Various benzodiazepines are useful in treating anxiety, insomnia, agitation, seizures, and muscle spasms, as well as alcohol withdrawal. They can also be used before certain medical procedures such as endoscopies, dental work, or other medical procedures where tension and anxiety are present, and prior to some medical procedures in order to induce amnesia.

[0004] As anti-convulsants, benzodiazepines may be used separately or in adjunctive therapy. Various formulations for treatment of seizure with benzodiazepines have been developed. Generally speaking, the oral route of administration is considered sub-optimal for acute treatment of seizures, as the amount of time require for the drug to reach therapeutically relevant concentrations in the blood plasma is rather long – as much as an hour. Moreover, some benzodiazepines, such as diazepam, have poor oral bioavailability and/or suffer from significant first-pass liver effects. Alternatives to oral dosing of benzodiazepines, including diazepam, have been developed.

[0005] These alternatives include intravenous, suppository and intranasal formulations. The intravenous route provides perhaps the fastest route of administration to date; however intravenous administration is generally limited to trained health care professionals (e.g. nurses). Thus, the intravenous administration of benzodiazepines for acute treatment of seizure is limited to tightly controlled clinical settings, such as emergency rooms and in-patient hospital and/or hospice care.

[0006] Suppository formulations of benzodiazepines have a rapid onset of action and require little professional expertise for their administration. 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. Thus, while suppository formulations have found some success in the treatment of children by their parents or guardians, they are unlikely to gain widespread acceptance as a means for acute treatment of seizure in adults outside controlled clinical environments.

[0007] Nasal formulations of benzodiazepines have been suggested for the acute treatment of seizure. Benzodiazepines are quickly absorbed and transported across the mucosa of the nasal sinuses, which results in fast achievement of pharmaceutically effective plasma levels. However, the utility of the existing nasal benzodiazepine formulations has been limited to a degree by the poor solubility of such benzodiazepines as diazepam. Nasal 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, since administration of larger volumes usually exceeds the capacity of the nasal sinuses and results in volumes in excess of about 250 µl bypassing the sinuses and flowing down the back of the throat where it is swallowed. As smaller dose volumes are preferred for nasal administration, poor water solubility of benzodiazepines limits the effective dose that may be administered to a patient at any given time. This in turn limits the clinical effectiveness of nasally-administered benzodiazepines for the acute treatment of seizure.

[0008] There is a need for benzodiazepine formulations that are capable of providing to the nasal mucosa sufficient quantity of benzodiazepine in a small enough volume to provide therapeutically effective blood plasma concentration of benzodiazepine within a short period after administration of the formulation to the nasal mucosa. There is also a need for methods of treating a variety of disorders, including anxiety and seizure, by administering a therapeutically effective amount of a benzodiazepine drug to the nasal mucosa. In particular, there is a need for an intranasal formulation of diazepam that is capable of producing anticonvulsant effective blood plasma levels within a short period after having been administered to a patient. There is also a need for a method of providing acute relief from seizure to a patient within a short period after administering a benzodiazepine, such as diazepam, to the patient. These and other objects and advantages are provided by the invention described herein.

SUMMARY OF THE INVENTION

[0009] The foregoing and further needs are met by embodiments of the present invention, which provide a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second effective mean particle diameter, wherein the first effective mean particle diameter is at least 1.5 times, at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 2.5 times or at least 3 times that of the second effective mean particle diameter.

[0010] The foregoing and further needs are met by embodiments of the present invention, which provide a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second effective mean particle diameter, wherein the first effective mean particle diameter is at least twice that of the second effective mean particle diameter.

[0011] The foregoing and further needs are met by embodiments of the present invention, which provide a method of using a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second effective mean particle diameter, wherein the first effective mean particle diameter is at least 1.5 times, at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 2.5 times or at least 3 times that of the second effective mean particle diameter. The method comprises administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0012] The foregoing and further needs are met by embodiments of the present invention, which provide a method of using a composition for nasal administration of a medicament, comprising a first population of particles having a first effective mean particle diameter and a second population of particles having a second

effective mean particle diameter, wherein the first effective mean particle diameter is at least twice that of the second effective mean particle diameter. The method comprises administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0013] The foregoing and further needs are met by embodiments of the present invention, which provide a pharmaceutical particulate composition for nasal delivery of a medicament comprising particulates having a multimodal particle size distribution.

[0014] The foregoing and further needs are met by embodiments of the present invention, which provide a method of using a pharmaceutical particulate composition for nasal delivery of a medicament comprising particulates having a multimodal particle size distribution, comprising administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0015] The foregoing and further needs are further met by embodiments of the present invention, which provide an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 μm and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm.

[0016] The foregoing and further needs are further met by embodiments of the present invention, which provide a method of using an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 μm and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm, the method comprising administering an effective amount of the composition to the nose by spraying a therapeutically effective amount of the composition into at least one nostril.

[0017] The foregoing and further needs are met by embodiments of the present invention, which provide a method of administering a benzodiazepine drug to a patient, comprising administering to the nose or nasal cavity an effective amount of an aerosol composition of an aqueous suspension or dispersion of nanoparticulate benzodiazepine particles, wherein: the droplets of the aerosol have a mass median aerodynamic diameter (MMAD) less than or equal to about 1000 μm and the nanoparticulate benzodiazepine particles have an effective average particle size of less than about 5000 nm.

[0018] The foregoing and further needs are additionally met by embodiments of the present invention, which provide a pharmaceutical composition for nasal administration of benzodiazepine comprising benzodiazepine particles and one or more non-cationic surface active agents adsorbed to a surface thereof.

[0019] The foregoing and further needs are further met by embodiments of the invention, which provides a method of administering a pharmaceutical composition for nasal administration of benzodiazepine comprising benzodiazepine particles and one or more non-cationic surface active agents adsorbed to a surface thereof, the method comprising administering an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0020] The foregoing and further needs are met by embodiments of the present invention, which provide a method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or

nasal cavity a pharmaceutical composition comprising particles of a benzodiazepine drug having a surface active agent adsorbed to a surface thereof.

[0021] The foregoing and further needs are met by embodiments of the present invention, which provide a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles.

[0022] The foregoing and additional needs are further met by embodiments of the present invention, which provide a method of administering a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles, the method comprising administering an effective amount of the dispersion or suspension to the nose by administering a therapeutically effective amount of the composition to at least one nostril.

[0023] The foregoing and further needs are additionally met by embodiments of the present invention, which provide, a method of administering a benzodiazepine drug to a patient, comprising administering to the patient's nose or nasal cavity a pharmaceutical composition comprising a non-aqueous dispersion or suspension of nanoparticulate benzodiazepine particles.

[0024] The foregoing and additional needs are further met by embodiments of the invention, which provide a nanoparticulate composition comprising: (a) a benzodiazepine having an effective average particle size of less than about 2000 nm, wherein the benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, pharmaceutically acceptable salts and esters thereof, and mixtures thereof; and (b) at least one surface stabilizer. In some embodiments, the surface stabilizer is selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant.

[0025] The foregoing and additional needs are further met by a method of treating a subject in need comprising administering to the subject a nanoparticulate benzodiazepine composition comprising: (a) a benzodiazepine having an effective average particle size of less than about 2000 nm, wherein the benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, pharmaceutically acceptable salts and esters thereof, and mixtures thereof; and (b) at least one surface stabilizer. In some embodiments, the surface stabilizer is selected from the group consisting of a nonionic surfactant, an ionic surfactant, a cationic surfactant, an anionic surfactant, and a zwitterionic surfactant.

[0026] These and further advantages and characteristics of the present invention will become apparent to the person skilled in the art upon consideration of the description and claims.

INCORPORATION BY REFERENCE

[0027] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

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