US 20080279784A1

(19) **United States**

(12) **Patent Application Publication**

Cartt et al.

(10) **Pub. No.: US 2008/0279784 A1**

(43) **Pub. Date: Nov. 13, 2008**

(54) **NASAL ADMINISTRATION OF BENZODIAZEPINES**

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(21) Appl. No.: **12/116,842**

(22) Filed: **May 7, 2008**

Related U.S. Application Data

(60) Provisional application No. 60/916,550, filed on May 7, 2007.

Publication Classification

(51) **Int. Cl.**

A61K 9/12	(2006.01)
A61K 31/5513	(2006.01)
A61P 25/00	(2006.01)
A61K 31/5517	(2006.01)

(52) **U.S. Cl.** **424/43**; 514/221; 514/220; 514/219

(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 U.S. Ser. No. 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 [illegible] 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 [illegible]

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

[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,

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.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The present invention provides nasal formulations for administering benzodiazepine drugs, such as diazepam, lorazepam or midazolam, to a patient in need of therapeutic treatment with a benzodiazepine drug. In some embodiments, the invention further provides methods of administering a benzodiazepine to a patient, comprising nasally administering an effective amount of the benzodiazepine to the patient, wherein the effective amount of the composition is effective 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. In some embodiments, the invention further provides methods of administering a benzodiazepine to a patient, comprising nasally administering an effective amount of the benzodiazepine to the patient, wherein the effective amount of the composition is effective to provide a therapeutic effect selected from an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations thereof.

[0029] As used herein, the terms "average" and "mean" are synonymous, unless otherwise stated. As used herein, the terms "particle size" and "particle diameter" are synonymous, unless otherwise stated. As used herein, the phrase "effective mean particle diameter" is intended to by synonymous with "effective average particle size" as used in United States pre-grant publication number 2006-0198896, which is incorporated herein by reference in its entirety. Effective mean particle diameter (effective average particle size) may be measured by an art-recognized method, such as by light-scattering methods, microscopy, or other appropriate methods. Redispersibility can be tested e.g. as set forth in the examples of U.S. Pat. No. 6,375,986, which is incorporated herein by reference.

[0030] In some embodiments, the invention provides 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. In some embodiments, the invention provides 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. In some embodiments, the first population of particles comprises a first active ingredient. In some embodiments, the first population of particles and the second population of particles both comprise the first active ingredient. In some embodiments, the second population of particles comprises a second active ingredient. In some embodiments, the first population of particles, the second population of particles or both the first and second populations of particles comprise a first active ingredient and a second active ingredient. In some embodiments, the medicament comprises a benzodiazepine. In some embodiments, the medicament comprises a benzodiazepine selected from the group consisting of: alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, medazepam, lorazepam, prazepam, quazepam, triazolam, temazepam, loprazolam, and pharmaceutically acceptable salts and combinations thereof. In some embodiments, the benzodiazepine comprises at least one member of the group consisting of alprazolam, diazepam, flurazepam, lorazepam, medazepam, mexazolam, midazolam, temazepam and pharmaceutically acceptable salts and combinations thereof. In some embodiments, the benzodiazepine comprises one or more members of the group consisting of: diazepam, lorazepam, midazolam and pharmaceutically acceptable salts thereof. In some embodiments, the particles in the medicament have a mean diameter of greater than about 500 nm, greater than about 1000 nm, greater than about 2000 nm, greater than about 4000 nm or greater than about 5000 nm. In some embodiments, the second population of particles or both are coated with at least one surface acting agent. In some embodiments, at least one surface acting agent is a cationic surfactant, a non-ionic surfactant, an anionic surfactant, a surface active biological modifier or a zwitterionic surfactant. In some embodiments, at least one surface acting agent is a cationic surfactant selected from the group consisting of natural phospholipids, synthetic phospholipids, quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans, lauryldimethylbenzylammonium chloride, acyl carnitine hydrochlorides, dimethyldioctadecylammomium bromide (DDAB), dioleyoltrimethylammonium propane (DOTAP), dimyristoyltrimethylammonium propane (DMTAP), dimethylaminoethanecarbamoyl cholesterol (DC-Chol), 1,2-diacylglycero-3-(O-alkyl)phosphocholine, O-alkylphosphatidylcholine, alkyl pyridinium halides, and long-chain alkyl amines such as, for example, n-octylamine and oleylamine. In some embodiments, at least one surface acting agent is an anionic surface active agent selected from the group consisting of natural anionic phospholipids, synthetic anionic phospholipids and anionic polymers. In some embodiments, the natural anionic phospholipids, synthetic anionic phospholipids and anionic polymers are selected from the group consisting of polyacrylic acid, carrageenan k type II, carbopol 980, carbopol 974 P, carbopol 971 P, polycarbophil, sodium carboxymethylcellulose, sodium hyaluronate or combinations thereof. In some embodiments, at least one surface acting agent is selected from the group consisting of thiolated polymers. In some embodiments, the thiolated polymer is selected from the group consisting of cysteine

lose, chitosan modified with 2-iminothiolate (e.g. chitosan-4-thiobutylamidine conjugates, chitosan-thioglycolic acid conjugates, chitosan-cysteine conjugates). In some embodiments, at least one surface acting agent is selected from the group consisting of polymeric mucilaginous polysaccharides. In some embodiments, the polymeric mucilaginous polysaccharide is from the aloe vera plant. In some embodiments, at least one surface acting agent is methylcellulose, ethylcellulose, hydroxypropylmethylcellulose (HPMC) or a mixture of two or more thereof. In some embodiments, the composition comprises a third population of benzodiazepine particles having a third mean particle size distribution different from the first and second populations of particles. In some embodiments, the composition further comprises one or more additional ingredient selected from active pharmaceutical ingredients and enhancers. In some embodiments, the first population of particles has a mean diameter in the range of about 25 to about 4000 nm and the second population of particles has a mean diameter in the range of about 500 to about 10,000 nm. In some embodiments, the first population of particles has a mean diameter in the range of about 50 to about 2000 nm and the second population of particles has a mean diameter in the range of about 1000 nm to about 10,000 nm. In some embodiments, the first population of particles has a mean diameter in the range of about 50 to about 1000 nm and the second population of particles has a mean diameter in the range of about 1000 nm to about 10,000 nm. In some embodiments, the mean particle diameter of the first population of particles is smaller than the mean particle diameter of the second population of particles. In some embodiments, the first population of particles has a mean diameter in the range of about 50 to about 500 nm and the second population of particles has a mean diameter in the range of about 2000 to about 10,000 nm. In some embodiments, the difference between the mean particle size of the first and second populations is greater than about 100 nm, greater than about 200 nm, greater than about 500 nm, greater than about 1000 nm, greater than about 2000 nm, greater than about 3000 nm, greater than about 4000 nm, greater than about 5000 nm, greater than about 6000 nm, greater than about 7000 nm, greater than about 8000 nm, greater than about 9000 nm or greater than about 10,000 nm. In some embodiments, the difference between the mean particle size of the first and second particle populations is greater than about 10%, greater than about 20% or greater than about 30% of the mean particle diameter of the second population of particles. In some embodiments, the benzodiazepine particles do not contain solvent residues resulting from solvent extraction or solvent precipitation.

[0031] In some embodiments, the invention provides a method of using a composition for nasal administration of a medicament, the composition 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. In some embodiments, 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, 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. In some embodiments, the first effective

an effective amount of the composition to the nose by administering a therapeutically effective amount of the composition to at least one nostril. In some embodiments, at least a portion of the therapeutically effective amount of the composition to each nostril. In some embodiments, the method comprises administering a first quantity of the composition to a first nostril, administering a second quantity of the composition to a second nostril, and optionally after a pre-selected time delay, administering a third quantity of the composition to 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 composition to the second nostril. In some embodiments, the effective amount of the composition is effective 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. In some embodiments, the effective amount of the composition is effective to provide a therapeutic effect selected from an anxiolytic effect, an anticonvulsant effect, a sedative effect, a skeletal muscle relaxant effect, an amnesic effect or combinations thereof. In some embodiments, a therapeutically effective plasma level of benzodiazepine drug is obtained within about 1 hours of administration to the patient. In some embodiments, the therapeutically effective plasma level of the benzodiazepine drug is obtained within about 30 minutes of administration of the composition to the patient. In some embodiments, the therapeutically effective plasma level of the benzodiazepine is obtained within about 15 minutes of administration of the composition to the patient. In some embodiments, the therapeutically effective plasma level of benzodiazepine drug is obtained within about 10 minutes of administration of the composition to the patient. In some embodiments, the therapeutically effective plasma level of benzodiazepine drug is obtained within about 5 minutes of administration of the composition to the patient. In some embodiments, a maximum (peak) plasma concentration (C_{max}) is obtained for the benzodiazepine drug at a time (T_{max}) less than about 1 hour after administration of the composition to a patient. In some embodiments, T_{max} is less than about 30 minutes after administration of the composition to the patient. In some embodiments, T_{max} is less than about 15 minutes after administration of the composition to the patient. In some embodiments, T_{max} is less than about 12 minutes after administration of the composition to the patient. In some embodiments, a benzodiazepine plasma concentration curve having a first benzodiazepine plasma concentration maximum (Cmax1) and a second benzodiazepine plasma concentration maximum (Cmax2) is obtained. In some embodiments, the first benzodiazepine plasma concentration maximum (Cmax1) is obtained from 1 to 30 minutes after administration of the composition and the second benzodiazepine plasma concentration maximum (Cmax2) is obtained from 5 to 360 minutes after administration of the composition. In some embodiments, Cmax1 is obtained from 5 to 20 minutes after administration of the composition and Cmax2 is obtained from 10 to 60 minutes after administration. In some embodiments, Cmax1 and Cmax2 are obtained at times Tmax1 and Tmax2 that are at least about 5 minutes, at least about 10 minutes, at least about 20 minutes or at least about 30 minutes apart. In some embodiments, Cmax1 is obtained at time Tmax1 and Cmax2 is obtained at time Tmax2, wherein a difference between

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