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(54) **AEROSOL AND INJECTABLE
FORMULATIONS OF NANOPARTICULATE
BENZODIAZEPINE**

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(57) **ABSTRACT**

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Described are nanoparticulate formulations of a benzodiazepine, such as lorazepam, that does not require the presence of polyethylene glycol and propylene glycol as stabilizers, and methods of making and using such formulations. The formulations are particularly useful in aerosol and injectable dosage forms, and comprise nanoparticulate benzodiazepine, such as lorazepam, and at least one surface stabilizer. The formulations are useful in the treatment of status epilepticus, treatment of irritable bowel syndrome, sleep induction, acute psychosis, and as a pre-anesthesia medication.

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AEROSOL AND INJECTABLE FORMULATIONS OF NANOPARTICULATE BENZODIAZEPINE

FIELD OF THE INVENTION

[0001] The present invention is directed to aerosol and injectable formulations of nanoparticulate benzodiazepine, and preferably, nanoparticulate lorazepam. The compositions of the invention are useful in treating status epilepticus, sleep induction, acute psychosis, irritable bowel syndrome, and for pre-anesthesia medication. Also encompassed by the invention are methods of making and using such compositions.

BACKGROUND OF THE INVENTION

I. Administration Routes for Drugs

[0002] The route of administration of a drug substance can be critical to its pharmacological effectiveness. Various routes of administration exist, and all have their own advantages and disadvantages. Oral drug delivery of tablets, capsules, liquids, and the like is the most convenient approach to drug delivery, but many drug compounds are not amenable to oral administration. For example, modern protein drugs which are unstable in the acidic gastric environment or which are rapidly degraded by proteolytic enzymes in the digestive tract are poor candidates for oral administration. Similarly, poorly water soluble compounds which do not dissolve rapidly enough to be orally absorbed are likely to be ineffective when given as oral dosage forms. Oral administration can also be undesirable because drugs which are administered orally are generally distributed to all tissues in the body, and not just to the intended site of pharmacological activity. Alternative types of systemic administration are subcutaneous or intravenous injection. This approach avoids the gastrointestinal tract and therefore can be an effective route for delivery of proteins and peptides. However, these routes of administration have a low rate of patient compliance, especially for drugs such as insulin which must be administered one or more times daily. Additional alternative methods of drug delivery have been developed including transdermal, rectal, vaginal, intranasal, and pulmonary delivery.

[0003] Nasal drug delivery relies on inhalation of an aerosol through the nose so that active drug substance can reach the nasal mucosa. Drugs intended for systemic activity can be absorbed into the bloodstream because the nasal mucosa is highly vascularized. Alternatively, if the drug is intended to act topically, it is delivered directly to the site of activity and does not have to distribute throughout the body; hence, relatively low doses may be used. Examples of such drugs are decongestants, antihistamines, and anti-inflammatory steroids for seasonal allergic rhinitis.

[0004] Pulmonary drug delivery relies on inhalation of an aerosol through the mouth and throat so that the drug substance can reach the lung. For systemically active drugs, it is desirable for the drug particles to reach the alveolar region of the lung, whereas drugs which act on the smooth muscle of the conducting airways should preferentially

[0005] A. Droplet/Particle Size Determines Deposition Site

[0006] In developing a therapeutic aerosol, the aerodynamic size distribution of the inhaled particles is the single most important variable in defining the site of droplet or particle deposition in the patient; in short, it will determine whether drug targeting succeeds or fails. See P. Byron, "Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems," *Respiratory Drug Delivery*, 144-151, 144 (CRC Press, 1989). Thus, a prerequisite in developing a therapeutic aerosol is a preferential particle size. The deposition of inhaled aerosols involves different mechanisms for different size particles. D. Swift (1980); Parodi et al., "Airborne Particles and Their Pulmonary Deposition," in *Scientific Foundations of Respiratory Medicine*, Scaddings et al. (eds.), pp. 545-557 (W. B. Saunders, Philadelphia, 1981); J. Heyder, "Mechanism of Aerosol Particle Deposition," *Chest*, 80:820-823 (1981).

[0007] Generally, inhaled particles are subject to deposition by one of two mechanisms: impaction, which usually predominates for larger particles, and sedimentation, which is prevalent for smaller particles. Impaction occurs when the momentum of an inhaled particle is large enough that the particle does not follow the air stream and encounters a physiological surface. In contrast, sedimentation occurs primarily in the deep lung when very small particles which have traveled with the inhaled air stream encounter physiological surfaces as a result of random diffusion within the air stream. For intranasally administered drug compounds which are inhaled through the nose, it is desirable for the drug to impact directly on the nasal mucosa; thus, large (ca. 5 to 100 μm) particles or droplets are generally preferred for targeting of nasal delivery.

[0008] Pulmonary drug delivery is accomplished by inhalation of an aerosol through the mouth and throat. Particles having aerodynamic diameters of greater than about 5 microns generally do not reach the lung; instead, they tend to impact the back of the throat and are swallowed and possibly orally absorbed. Particles having diameters of about 2 to about 5 microns are small enough to reach the upper- to mid-pulmonary region (conducting airways), but are too large to reach the alveoli. Even smaller particles, i.e., about 0.5 to about 2 microns, are capable of reaching the alveolar region. Particles having diameters smaller than about 0.5 microns can also be deposited in the alveolar region by sedimentation, although very small particles may be exhaled.

[0009] B. Devices Used For Nasal And Pulmonary Drug Delivery

[0010] Drugs intended for intranasal delivery (systemic and local) can be administered as aqueous solutions or suspensions, as solutions or suspensions in halogenated hydrocarbon propellants (pressurized metered-dose inhalers), or as dry powders. Metered-dose spray pumps for aqueous formulations, pMDIs, and DPIs for nasal delivery are available from, for example, Valois of America or Pfeiffer of America.

[0011] Drugs intended for pulmonary delivery can also be administered as aqueous formulations, as suspensions or

liquid nebulizers employing either hydraulic or ultrasonic atomization, propellant-based systems require suitable pressurized metered-dose inhalers (pMDIs), and dry powders require dry powder inhaler devices (DPIs) which are capable of dispersing the drug substance effectively. For aqueous and other non-pressurized liquid systems, a variety of nebulizers (including small volume nebulizers) are available to aerosolize the formulations. Compressor-driven nebulizers incorporate jet technology and use compressed air to generate the liquid aerosol. Such devices are commercially available from, for example, Healthdyne Technologies, Inc.; Invacare, Inc.; Mountain Medical Equipment, Inc.; Pari Respiratory, Inc.; Mada Medical, Inc.; Puritan-Bennet; Schuco, Inc., DeVilbiss Health Care, Inc.; and Hospitak, Inc. Ultrasonic nebulizers rely on mechanical energy in the form of vibration of a piezoelectric crystal to generate inhalable liquid droplets and are commercially available from, for example, Omron Healthcare, Inc. and DeVilbiss Health Care, Inc.

[0012] A propellant driven inhaler (pMDI) releases a metered dose of medicine upon each actuation. The medicine is formulated as a suspension or solution of a drug substance in a suitable propellant such as a halogenated hydrocarbon. pMDIs are described in, for example, Newman, S. P., *Aerosols and the Lung*, Clarke et al., eds., pp. 197-224 (Butterworths, London, England, 1984).

[0013] Dry powder inhalers (DPIs), which involve deaggregation and aerosolization of dry powders, normally rely upon a burst of inspired air that is drawn through the unit to deliver a drug dosage. Such devices are described in, for example, U.S. Pat. No. 4,807,814 to Douche et al., which is directed to a pneumatic powder ejector having a suction stage and an injection stage; SU 628930 (Abstract), describing a hand-held powder disperser having an axial air flow tube; Fox et al., *Powder and Bulk Engineering*, pages 33-36 (March 1988), describing a venturi eductor having an axial air inlet tube upstream of a venturi restriction; EP 347 779, describing a hand-held powder disperser having a collapsible expansion chamber, and U.S. Pat. No. 5,785,049 to Smith et al., directed to dry powder delivery devices for drugs.

[0014] C. Problems with Conventional Aerosol and Injectable Compositions and Methods

[0015] Conventional techniques are extremely inefficient in delivering agents to the lung for a variety of reasons. Prior to the present invention, attempts to develop inhalable aqueous suspensions of poorly water soluble drugs have been largely unsuccessful. For example, it has been reported that ultrasonic nebulization of a suspension containing fluorescein and latex drug spheres, representing insoluble drug particles, resulted in only 1% aerosolization of the particles, while air-jet nebulization resulted in only a fraction of particles being aerosolized (Susan L. Tian, "Functionality Testing Used to Rationally Assess Performance of a Model Respiratory Solution or Suspension in a Nebulizer," Dissertation Abstracts International, 56/12-B, pp. 6578 (1995)). Another problem encountered with nebulization of liquid formulations prior to the present invention was the long (4-20 min) period of time required for administration of a therapeutic dose. Long administration times are required

substance. Prolonged administration times are undesirable because they lessen patient compliance and make it difficult to control the dose administered. Lastly, aerosol formulations of micronized drug are not feasible for deep lung delivery of insoluble compounds because the droplets needed to reach the alveolar region (0.5 to 2 microns) are too small to accommodate micronized drug crystals, which are typically 2-3 microns or more in diameter.

[0016] Conventional pMDIs are also inefficient in delivering drug substance to the lung. In most cases, pMDIs consist of suspensions of micronized drug substance in halogenated hydrocarbons such as chlorofluorocarbons (CFCs) or hydrofluoroalkanes (HFAs). Actuation of the pMDI results in delivery of a metered dose of drug and propellant, both of which exit the device at high velocities because of the propellant pressures. The high velocity and momentum of the drug particles results in a high degree of oropharyngeal impaction as well as loss to the device used to deliver the agent. These losses lead to variability in therapeutic agent levels and poor therapeutic control. In addition, oropharyngeal deposition of drugs intended for topical administration to the conducting airways (such as corticosteroids) can lead to systemic absorption with resultant undesirable side effects. Additionally, conventional micronization (air-jet milling) of pure drug substance can reduce the drug particle size to no less than about 2-3 microns. Thus, the micronized material typically used in pMDIs is inherently unsuitable for delivery to the alveolar region and is not expected to deposit below the central bronchiole region of the lung.

[0017] Prior to the present invention, delivery of dry powders to the lung typically used micronized drug substance. In the dry powder form, micronized substances tend to have substantial interparticle electrostatic attractive forces which prevent the powders from flowing smoothly and generally make them difficult to disperse. Thus, two key challenges to pulmonary delivery of dry powders are the ability of the device to accurately meter the intended dose and the ability of the device to fully disperse the micronized particles. For many devices and formulations, the extent of dispersion is dependent upon the patient's inspiration rate, which itself may be variable and can lead to a variability in the delivered dose.

[0018] Delivery of drugs to the nasal mucosa can also be accomplished with aqueous, propellant-based, or dry powder formulations. However, absorption of poorly soluble drugs can be problematic because of mucociliary clearance which transports deposited particles from the nasal mucosa to the throat where they are swallowed. Complete clearance generally occurs within about 15-20 minutes. Thus, poorly soluble drugs which do not dissolve within this time frame are unavailable for either local or systemic activity.

[0019] As described below in the Background of Nanoparticulate Active Agent Compositions, several published U.S. patents and patent applications describe aerosols of nanoparticulate drugs. However, none of these documents describe aerosols of a nanoparticulate benzodiazepine, such as lorazepam.

II. Background Regarding Lorazepam

4-benzodiazepin-2-one. Its molecular formula is $C_{15}H_{10}Cl_2N_2O_2$, and it has a molecular weight of 321.16. Lorazepam has only slight solubility in water, i.e., 0.08 mg/mL. U.S. Pat. No. 6,699,849 to Loftsson et al., which is specifically incorporated by reference, refers to lorazepam and benzodiazepine. Lorazepam is a controlled substance. *Merck Index*, Thirteenth Ed., p. 999 (Merck & Co., Whitehouse Station, N.J. 2001). As pharmaceutically acceptable salts including organic salts or esters of lorazepam can be employed as a substitute for lorazepam, the references below to lorazepam are also intended to include lorazepam salts and esters and mixtures thereof.

[0021] Because of lorazepam's low water solubility, it is generally formulated for oral administration. However, oral administration of lorazepam has disadvantages. For example, lorazepam is susceptible to enzymatic degradation by glucuronyl transferase enzyme in the intestine or in the intestinal mucosa, as disclosed in U.S. Pat. No. 6,692,766 to Rubinstein et al., which is incorporated by reference. Sterile lorazepam typically includes a preservative such as benzyl alcohol and requires refrigeration. Lorazepam delivered orally may have a slow absorption and onset of action.

[0022] Injectable formulations of lorazepam are preferable over oral administration doses because intravenous (IV) or intramuscular (IM) administration of a drug results in a significantly shorter response time as compared to oral administration. Moreover, injectable formulations of pain medication are also preferable for post-operative health care, where oral administration may not be feasible. Injectable formulations of lorazepam are particularly preferred, as lorazepam is not addictive, in contrast to other injectable formulations of drugs, such as morphine and ketorolac (Toradol®).

[0023] However, injectable lorazepam formulations are difficult to formulate due to the low water-solubility of lorazepam. Moreover, current injectable formulations of lorazepam are undesirable because the formulations must include polyethylene glycol and propylene glycol as solubilizers, which can result in pain at the injection site.

III. Background Regarding Nanoparticulate Active Agent Compositions

[0024] Nanoparticulate compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent also describes methods of making such nanoparticulate compositions but does not describe compositions comprising a benzodiazepine, such as lorazepam, in nanoparticulate form. Methods of making nanoparticulate compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0025] Nanoparticulate compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation Dur-

Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly-(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for

U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form;" U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" U.S. Pat. No. 6,582,285 for "Apparatus for Sanitary Wet Milling;" and U.S. Pat. No. 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" U.S. Pat. No. 6,742,734 for "System and Method for Milling Materials;" U.S. Pat. No. 6,745,962 for "Small Scale Mill and Method Thereof;" U.S. Pat. No. 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" and U.S. Pat. No. 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" all of which are specifically incorporated by reference. In addition, U.S. patent application Ser. No. 20020012675 A1, published on Jan. 31, 2002, for "Compositions of Nanoparticulate Drugs and Methods of Formulating and Administering Same," is specifically incorporated by reference.

rials," describe nanoparticulate compositions, and are specifically incorporated by reference.

[0026] In particular, documents referring to aerosols of nanoparticulate drugs include U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions" and U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions," and documents referring to injectable compositions of nanoparticulate drugs include U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen," and U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles." None of these documents describe injectable or aerosol compositions of a nanoparticulate benzodiazepine, such as lorazepam.

[0027] Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter" all of which are specifically incorporated herein by reference.

[0028] There remains a need in the art for improved dosage forms of benzodiazepines, such as lorazepam. The present invention satisfies this need.

SUMMARY OF THE INVENTION

[0029] The present invention is directed to the surprising and unexpected discovery of new aerosol and injectable dosage forms of a nanoparticulate benzodiazepine, such as lorazepam. The formulations comprises a nanoparticulate benzodiazepine, such as nanoparticulate lorazepam, having an effective average particle size of less than about 2000 nm. The nanoparticulate benzodiazepine, such as lorazepam, preferably has at least one surface stabilizer either adsorbed onto or associated with the surface of the benzodiazepine. In one embodiment of the invention, the surface stabilizer is a povidone polymer. Because lorazepam is practically insoluble in water, significant bioavailability can be problematic.

[0030] In one embodiment there is provided an aerosol that delivers an optimal dosage of a benzodiazepine, such as lorazepam. The aerosols of the invention do not require a preservative such as benzyl alcohol, which affects lorazepam stability.

[0031] In another embodiment, a safe and effective injectable formulation of a benzodiazepine, such as lorazepam, is provided. The injectable formulation eliminates the need for propylene glycol and polyethylene glycol, such as polyoxyl 60 hydrogenated castor oil (HCO-60), as solubilizers for injectable lorazepam compositions, and solves the problem of the insolubility of lorazepam in water. This is beneficial, as in convention non-nanoparticulate injectable benzodiazepine formulations comprising polyoxyl 60 hydrogenated

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