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(54) Title: DELIVERY OF DIAZEPAM THROUGH AN INHALATION ROUTE

(57) Abstract: The present invention relates to the delivery of diazepam through an inhalation route. Specifically, it relates to aerosols containing diazepam that are used in inhalation therapy. In a composition aspect of the present invention, the aerosol comprises particles comprising at least 5 percent by weight of diazepam. In a method aspect of the present invention, diazepam is delivered to a mammal through an inhalation route. The method comprises: a) heating a composition, wherein the composition comprises at least 5 percent by weight of diazepam, to form a vapor; and, b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. In a kit aspect of the present invention, a kit for delivering diazepam through an inhalation route to a mammal is provided which comprises: a) a composition comprising at least 5 percent by weight of diazepam; and, b) a device that forms a diazepam containing aerosol from the composition, for inhalation by the mammal.

DELIVERY OF DIAZEPAM THROUGH AN INHALATION ROUTE

[0001] This application claims priority to U.S. provisional application Ser. No. 60/345,882 entitled "Delivery of Diazepam Through an Inhalation Route," filed November 9, 2001, Rabinowitz, the entire disclosure of which is hereby incorporated by reference.

Field of the Invention

[0002] The present invention relates to the delivery of diazepam through an inhalation route. Specifically, it relates to aerosols containing diazepam that are used in inhalation therapy.

Background of the Invention

[0003] VALIUM® is a composition currently marketed for the management of anxiety disorders and the relief of anxiety symptoms. It is administered both orally and by injection. The active ingredient in VALIUM® is diazepam, which is typically provided in doses of 2 mg to 20 mg.

[0004] The delivery methods for diazepam have a number of limitations. Oral administration typically provides for a relatively long onset of action (e.g. $\geq$ 1 h). Intravenous injection, while rapidly delivering a drug, involves the discomfort and risk of infection associated with catheterization or injection. It is desirable to provide a new route of administration for diazepam that allows for a rapid onset of action without the disadvantages of catheterization or injection. The provision of such a route is an object of the present invention.

Summary of the Invention

[0005] The present invention relates to the delivery of diazepam through an inhalation route. Specifically, it relates to aerosols containing diazepam that are used in inhalation therapy.

[0006] In a composition aspect of the present invention, the aerosol comprises particles comprising at least 5 percent by weight of diazepam. Preferably, the particles comprise at least 10 percent by weight of diazepam. More preferably, the particles comprise at least 20

percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent or 99.97 percent by weight of diazepam.

[0007] Typically, the aerosol has a mass of at least 10 μg. Preferably, the aerosol has a mass of at least 100 μg. More preferably, the aerosol has a mass of at least 200 μ.

[0008] Typically, the aerosol particles comprise less than 10 percent by weight of diazepam degradation products. Preferably, the particles comprise less than 5 percent by weight of diazepam degradation products. More preferably, the particles comprise less than 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of diazepam degradation products.

[0009] Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0010] Typically, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 15 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 8 mg/L.

[0011] Typically, the aerosol has an inhalable aerosol particle density greater than 10^6 particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than 10^7 particles/mL. More preferably, the aerosol has an inhalable aerosol particle density greater than 10^8 particles/mL.

[0012] Typically, the aerosol particles have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0013] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.1.

[0014] Typically, the aerosol is formed by heating a composition containing diazepam to form a vapor and subsequently allowing the vapor to condense into an aerosol.

[0015] In a method aspect of the present invention, diazepam is delivered to a mammal through an inhalation route. The method comprises: a) heating a composition, wherein the composition comprises at least 5 percent by weight of diazepam; and, b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. Preferably, the composition that is heated comprises at least 10 percent by weight of diazepam. More preferably, the composition comprises 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of diazepam.

[0016] Typically, the delivered aerosol particles comprise at least 5 percent by weight of diazepam. Preferably, the particles comprise at least 10 percent by weight of diazepam. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of diazepam.

[0017] Typically, the condensation aerosol has a mass of at least 10 μg. Preferably, the aerosol has a mass of at least 100 μg. More preferably, the aerosol has a mass of at least 200 μ.

[0018] Typically, the delivered aerosol particles comprise less than 10 percent by weight of diazepam degradation products. Preferably, the particles comprise less than 5 percent by weight of diazepam degradation products. More preferably, the particles comprise less than 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of diazepam degradation products.

[0019] Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0020] Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0021] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric

standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.1.

[0022] Typically, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 15 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 8 mg/L.

[0023] Typically, the delivered aerosol has an inhalable aerosol particle density greater than 10^6 particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than 10^7 particles/mL. More preferably, the aerosol has an inhalable aerosol particle density greater than 10^8 particles/mL.

[0024] Typically, the rate of inhalable aerosol particle formation of the delivered condensation aerosol is greater than 10^8 particles per second. Preferably, the aerosol is formed at a rate greater than 10^9 inhalable particles per second. More preferably, the aerosol is formed at a rate greater than 10^{10} inhalable particles per second.

[0025] Typically, the delivered aerosol is formed at a rate greater than 0.25 mg/second. Preferably, the aerosol is formed at a rate greater than 0.5 mg/second. More preferably, the aerosol is formed at a rate greater than 1 or 2 mg/second.

[0026] Typically, the condensation aerosol delivers between 0.2 mg and 20 mg of diazepam to the mammal in a single inspiration. Preferably, between 0.35 mg and 10 mg of diazepam are delivered to the mammal in a single inspiration. More preferably, between 0.5 mg and 8 mg of diazepam are delivered to the mammal in a single inspiration.

[0027] Typically, the delivered condensation aerosol results in a peak plasma concentration of diazepam in the mammal in less than 1 h. Preferably, the peak plasma concentration is reached in less than 0.5 h. More preferably, the peak plasma concentration is reached in less than 0.2, 0.1, 0.05, 0.02 , 0.01, or 0.005 h (arterial measurement).

[0028] Typically, the delivered condensation aerosol is used to treat anxiety.

[0029] In a kit aspect of the present invention, a kit for delivering diazepam through an inhalation route to a mammal is provided which comprises: a) a composition comprising at least 5 percent by weight of diazepam; and, b) a device that forms a diazepam containing aerosol from the composition, for inhalation by the mammal. Preferably, the composition comprises at least 10 percent by weight of diazepam. More preferably, the composition

comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of diazepam.

[0030] Typically, the device contained in the kit comprises: a) an element for heating the diazepam composition to form a vapor; b) an element allowing the vapor to cool to form an aerosol; and, c) an element permitting the mammal to inhale the aerosol.

Brief Description of the Figures

[0031] Fig. 1 shows a device used to deliver diazepam containing aerosols to a mammal through an inhalation route.

Detailed Description of the Invention

Definitions

[0032] "Aerodynamic diameter" of a given particle refers to the diameter of a spherical droplet with a density of 1 g/mL (the density of water) that has the same settling velocity as the given particle.

[0033] "Aerosol" refers to a suspension of solid or liquid particles in a gas.

[0034] "Aerosol drug mass density" refers to the mass of diazepam per unit volume of aerosol.

[0035] "Aerosol mass density" refers to the mass of particulate matter per unit volume of aerosol.

[0036] "Aerosol particle density" refers to the number of particles per unit volume of aerosol.

[0037] "Condensation aerosol" refers to an aerosol formed by vaporization of a substance followed by condensation of the substance into an aerosol.

[0038] "Diazepam" refers to 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

[0039] "Diazepam" degradation product refers to a compound resulting from a chemical modification of diazepam. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis. Examples of products from such reactions include $C_{16}H_{15}N_2O_2Cl$ (imine hydrolysis) and $C_{14}H_{12}NOCl$ (imine hydrolysis followed by amide hydrolysis).

[0040] "Inhalable aerosol drug mass density" refers to the aerosol drug mass density produced by an inhalation device and delivered into a typical patient tidal volume.

[0041] "Inhalable aerosol mass density" refers to the aerosol mass density produced by an inhalation device and delivered into a typical patient tidal volume.

[0042] "Inhalable aerosol particle density" refers to the aerosol particle density of particles of size between 100 nm and 5 microns produced by an inhalation device and delivered into a typical patient tidal volume.

[0043] "Mass median aerodynamic diameter" or "MMAD" of an aerosol refers to the aerodynamic diameter for which half the particulate mass of the aerosol is contributed by particles with an aerodynamic diameter larger than the MMAD and half by particles with an aerodynamic diameter smaller than the MMAD.

[0044] "Rate of aerosol formation" refers to the mass of aerosolized particulate matter produced by an inhalation device per unit time.

[0045] "Rate of inhalable aerosol particle formation" refers to the number of particles of size between 100 nm and 5 microns produced by an inhalation device per unit time.

[0046] "Rate of drug aerosol formation" refers to the mass of aerosolized diazepam produced by an inhalation device per unit time.

[0047] "Settling velocity" refers to the terminal velocity of an aerosol particle undergoing gravitational settling in air.

[0048] "Typical patient tidal volume" refers to 1 L for an adult patient and 15 mL/kg for a pediatric patient.

[0049] "Vapor" refers to a gas, and "vapor phase" refers to a gas phase. The term "thermal vapor" refers to a vapor phase, aerosol, or mixture of aerosol-vapor phases, formed preferably by heating.

Formation of Diazepam Containing Aerosols

[0050] Any suitable method is used to form the aerosols of the present invention. A preferred method, however, involves heating a composition comprising diazepam to produce a vapor, followed by cooling of the vapor such that it condenses to provide a diazepam comprising aerosol (condensation aerosol). The composition is heated in one of two forms: as pure active compound (*i.e.*, pure diazepam); or, as a mixture of active

compound and a pharmaceutically acceptable excipient. Typically, the composition is heated on a solid support.

[0051] Pharmaceutically acceptable excipients are either volatile or nonvolatile. Volatile excipients, when heated, are concurrently volatilized, aerosolized and inhaled with diazepam. Classes of such excipients are known in the art and include, without limitation, gaseous, supercritical fluid, liquid and solid solvents. The following is a list of exemplary carriers within the classes: water; terpenes, such as menthol; alcohols, such as ethanol, propylene glycol, glycerol and other similar alcohols; dimethylformamide; dimethylacetamide; wax; supercritical carbon dioxide; dry ice; and mixtures thereof.

[0052] Solid supports on which the composition is heated are of a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (*e.g.*, less than 1.0 mm-sized) pores. Preferably, solid supports provide a large surface to volume ratio (*e.g.*, greater than 100 per meter) and a large surface to mass ratio (*e.g.*, greater than 1 cm^2 per gram).

[0053] A solid support of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

[0054] A number of different materials are used to construct the solid supports. Classes of such materials include, without limitation, metals, inorganic materials, carbonaceous materials and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite, porous carbons, carbon yarns and carbon felts; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

[0055] Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amphorous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 m^2/g from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Carbon yarns and felts are available from American Kynol, Inc., New York, NY.

Chromatography resins such as octadecycl silane chemically bonded to porous silica are exemplary coated variants of silica.

[0056] The heating of the diazepam compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following: passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as exothermic solvation, hydration of pyrophoric materials and oxidation of combustible materials.

Delivery of Diazepam Containing Aerosols

[0057] Diazepam containing aerosols of the present invention are delivered to a mammal using an inhalation device. Where the aerosol is a condensation aerosol, the device has at least three elements: an element for heating a diazepam containing composition to form a vapor; an element allowing the vapor to cool, thereby providing a condensation aerosol; and, an element permitting the mammal to inhale the aerosol. Various suitable heating methods are described above. The element that allows cooling is, in it simplest form, an inert passageway linking the heating means to the inhalation means. The element permitting inhalation is an aerosol exit portal that forms a connection between the cooling element and the mammal's respiratory system.

[0058] One device used to deliver diazepam containing aerosol is described in reference to Fig. 1. Delivery device 100 has a proximal end 102 and a distal end 104, a heating module 106, a power source 108, and a mouthpiece 110. A diazepam composition is deposited on a surface 112 of heating module 106. Upon activation of a user activated switch 114, power source 108 initiates heating of heating module 106 (*e.g*, through ignition of combustible fuel or passage of current through a resistive heating element). The diazepam composition volatilizes due to the heating of heating module 106 and condenses to form a condensation aerosol prior to reaching the mouthpiece 110 at the proximal end of the device 102. Air flow traveling from the device distal end 104 to the mouthpiece 110 carries the condensation aerosol to the mouthpiece 110, where it is inhaled by the mammal.

[0059] Devices, if desired, contain a variety of components to facilitate the delivery of diazepam containing aerosols. For instance, the device may include any component known in the art to control the timing of drug aerosolization relative to inhalation (*e.g.*, breath-

actuation), to provide feedback to patients on the rate and/or volume of inhalation, to prevent excessive use (*i.e.*, "lock-out" feature), to prevent use by unauthorized individuals, and/or to record dosing histories.

Dosage of Diazepam Containing Aerosols

[0060] For the management of anxiety disorders and relief of anxiety symptoms, diazepam is given orally at strengths of 2 mg to 10 mg, 2 to 4 times daily. As an aerosol, 0.2 mg to 20 mg of diazepam is generally provided per inspiration for the same indication. A typical dosage of a diazepam aerosol is either administered as a single inhalation or as a series of inhalations taken within an hour or less. Where the drug is administered as a series of inhalations, a different amount may be delivered in each inhalation.

[0061] One can determine the appropriate dose of a diazepam containing aerosol to treat a particular condition using methods such as animal experiments and a dose-finding (Phase I/II) clinical trial. One animal experiment involves measuring plasma concentrations of drug in an animal after its exposure to the aerosol. Mammals such as dogs or primates are typically used in such studies, since their respiratory systems are similar to that of a human. Initial dose levels for testing in humans are generally less than or equal to the dose in the mammal model that resulted in plasma drug levels associated with a therapeutic effect in humans. Dose escalation in humans is then performed, until either an optimal therapeutic response is obtained or a dose-limiting toxicity is encountered.

Analysis of Diazepam Containing Aerosols

[0062] Purity of a diazepam containing aerosol is determined using a number of methods, examples of which are described in Sekine *et al.*, *Journal of Forensic Science* 32:1271-1280 (1987) and *Martin et al.*, *Journal of Analytic Toxicology* 13:158-162 (1989). One method involves forming the aerosol in a device through which a gas flow (*e.g.*, air flow) is maintained, generally at a rate between 0.4 and 60 L/min. The gas flow carries the aerosol into one or more traps. After isolation from the trap, the aerosol is subjected to an analytical technique, such as gas or liquid chromatography, that permits a determination of composition purity.

[0063] A variety of different traps are used for aerosol collection. The following list contains examples of such traps: filters; glass wool; impingers; solvent traps, such as dry

ice-cooled ethanol, methanol, acetone and dichloromethane traps at various pH values; syringes that sample the aerosol; empty, low-pressure (*e.g.*, vacuum) containers into which the aerosol is drawn; and, empty containers that fully surround and enclose the aerosol generating device. Where a solid such as glass wool is used, it is typically extracted with a solvent such as ethanol. The solvent extract is subjected to analysis rather than the solid (*i.e.*, glass wool) itself. Where a syringe or container is used, the container is similarly extracted with a solvent.

[0064] The gas or liquid chromatograph discussed above contains a detection system (*i.e.*, detector). Such detection systems are well known in the art and include, for example, flame ionization, photon absorption and mass spectrometry detectors. An advantage of a mass spectrometry detector is that it can be used to determine the structure of diazepam degradation products.

[0065] Particle size distribution of a diazepam containing aerosol is determined using any suitable method in the art (*e.g.*, cascade impaction). An Andersen Eight Stage Non-viable Cascade Impactor (Andersen Instruments, Smyrna, GA) linked to a furnace tube by a mock throat (USP throat, Andersen Instruments, Smyrna, GA) is one system used for cascade impaction studies.

[0066] Inhalable aerosol mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring the mass collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient.

[0067] Inhalable aerosol drug mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring the amount of active drug compound collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient. The amount of active drug compound collected in the chamber is determined by extracting the chamber, conducting

chromatographic analysis of the extract and comparing the results of the chromatographic analysis to those of a standard containing known amounts of drug.

[0068] Inhalable aerosol particle density is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device and measuring the number of particles of given size collected in the chamber. The number of particles of a given size may be directly measured based on the light-scattering properties of the particles. Alternatively, the number of particles of a given size may be determined by measuring the mass of particles within the given size range and calculating the number of particles based on the mass as follows: Total number of particles = Sum (from size range 1 to size range N) of number of particles in each size range. Number of particles in a given size range = Mass in the size range/Mass of a typical particle in the size range. Mass of a typical particle in a given size range = $\pi*D^3*\varphi/6$, where D is a typical particle diameter in the size range (generally, the mean of the boundary MMADs defining the size range) in microns, φ is the particle density (in g/mL) and mass is given in units of picograms (g^{-12}).

[0069] Rate of inhalable aerosol particle formation is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device. The delivery is for a set period of time (*e.g.*, 3 s), and the number of particles of a given size collected in the chamber is determined as outlined above. The rate of particle formation is equal to the number of 100 nm to 5 micron particles collected divided by the duration of the collection time.

[0070] Rate of aerosol formation is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device. The delivery is for a set period of time (*e.g.*, 3 s), and the mass of particulate matter collected is determined by weighing the confined chamber before and after the delivery of the particulate matter. The rate of aerosol formation is equal to the increase in mass in the chamber divided by the duration of the collection time. Alternatively, where a change in mass of the delivery device or component thereof can only occur through release of the aerosol phase particulate matter, the mass of particulate matter may be equated with the mass lost from the device or component during the delivery of the aerosol. In this case, the rate of aerosol formation is equal to the decrease in mass of the device or component during the delivery event divided by the duration of the delivery event.

[0071] Rate of drug aerosol formation is determined, for example, by delivering a diazepam containing aerosol into a confined chamber via an inhalation device over a set period of time (*e.g.*, 3 s). Where the aerosol is pure diazepam, the amount of drug collected in the chamber is measured as described above. The rate of drug aerosol formation is equal to the amount of diazepam collected in the chamber divided by the duration of the collection time. Where the diazepam containing aerosol comprises a pharmaceutically acceptable excipient, multiplying the rate of aerosol formation by the percentage of diazepam in the aerosol provides the rate of drug aerosol formation.

Utility of Diazepam Containing Aerosols

[0072] The following are, without limitation, typical indications for diazepam aerosols: moderate and severe anxiety disorders and symptoms of anxiety; panic attacks and situational anxiety; acute alcohol withdrawal; muscle spasm; insomnia; and, nausea.

[0073] The following examples are meant to illustrate, rather than limit, the present invention.

[0074] Diazepam was purchased from Sigma (www.sigma-aldrich.com).

EXAMPLE 1

Volatilization of Diazepam

Diazepam (10.0 mg) in 120 μL dichloromethane was coated onto a circular piece of aluminum foil (10 cm in diameter). The dichloromethane was allowed to evaporate. The aluminum foil was secured onto a 100 mm x 50 mm petridish using parafilm. After cooling the glass bottom of the petridish with dry ice, the aluminum side of the apparatus was placed on a hot plate at 240 °C for 10 s. The apparatus was removed from the hot plate and allowed to cool. Acetonitrile was injected through the aluminum foil onto the inside of the glass surface using a 3 mL syringe. The acetonitrile solution was concentrated and analyzed by high performance liquid chromatography with UV absorbance detection at 225 nm light, which indicated that the volatilized material was at least 99.9% pure.

EXAMPLE 2

Volatilization of Diazepam Using a Halogen Bulb Heat Source

[0075] A solution of 5.3 mg diazepam in 120 μL dichloromethane was coated on a 3 cm x 8 cm piece of aluminum foil. The dichloromethane was allowed to evaporate. The

coated foil was wrapped around a 300 watt halogen tube (Feit Electric Company, Pico Rivera, CA), which was inserted into a glass tube sealed at one end with a rubber stopper. Running 40 V of alternating current (driven by line power controlled by a variac) through the bulb for 17 s afforded diazepam thermal vapor (including diazepam aerosol), which collected on the glass tube walls. Reverse-phase HPLC analysis with detection by absorption of 225 nm light showed the collected material to be at least 99.9% pure diazepam.

EXAMPLE 3

Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Diazepam Aerosol

[0076] A solution of 18.2 mg diazepam in 200 μL dichloromethane was spread out in a thin layer on the central portion of a 4 cm x 9 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. One of the openings of the tube was sealed with a rubber stopper, another was loosely covered with the end of the halogen tube, and the third was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 1.74 microns with a geometric standard deviation of 2.02. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm^3). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of 5.87×10^{10} particles/L (5.87×10^7 particles/mL). The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the

formation time of 6 s, giving a rate of inhalable aerosol particle formation of 9.8×10^9 particles/second.

[0077] Table 1: Determination of the characteristics of a diazepam condensation aerosol by cascade impaction using an Andersen 8-stage non-viable cascade impactor run at 1 cubic foot per minute air flow.

Stage	Particle size range (microns)	Average particle size (microns)	Mass collected (mg)	Number of particles
0	9.0-10.0	9.5	0.2	4.46×10^5
1	5.8-9.0	7.4	0	0
2	4.7-5.8	5.25	0.3	3.96×10^6
3	3.3-4.7	4.0	0.8	2.39×10^7
4	2.1-3.3	2.7	1.4	1.36×10^8
5	1.1-2.1	1.6	2.8	1.31×10^9
6	0.7-1.1	0.9	1.3	3.41×10^9
7	0.4-0.7	0.55	0.4	6.11×10^9
8	0-0.4	0.2	0.2	4.77×10^{10}

EXAMPLE 4

Drug Mass Density and Rate of Drug Aerosol Formation of Diazepam Aerosol

[0078] A solution of 5.1 mg diazepam in 200 µL dichloromethane was spread out in a thin layer on the central portion of a 4 cm x 9 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. One of the openings of the tube was sealed with a rubber stopper, another was loosely covered with the end of the halogen tube, and the third was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 6 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with dichloromethane and the extract analyzed by

HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of diazepam revealed that 3.8 mg of > 99% pure diazepam had been collected in the flask, resulting in an aerosol drug mass density of 3.8 mg/L. The aluminum foil upon which the diazepam had previously been coated was weighed following the experiment. Of the 5.1 mg originally coated on the aluminum, all of the material was found to have aerosolized in the 6 s time period, implying a rate of drug aerosol formation of 0.85 mg/s.

Claims

1. An aerosol for inhalation therapy, wherein the aerosol comprises particles comprising at least 10 percent by weight of diazepam.

2. The aerosol according to Claim 1, wherein the mass of the aerosol is at least 0.10 mg.

3. The aerosol according to Claim 1, wherein the aerosol particles have a mass median aerodynamic diameter of less than 3 microns.

4. The aerosol according to Claim 1, wherein the particles comprise less than 2.5 percent by weight of diazepam degradation products.

5. The aerosol according to Claim 3, wherein the aerosol comprises particles comprising at least 90 percent by weight of diazepam.

6. The aerosol according to Claim 5, wherein the aerosol particles have a mass median aerodynamic diameter less than 2 microns.

7. The aerosol according to Claim 6, wherein the aerosol comprises particles comprising at least 97 percent by weight of diazepam.

8. A method of delivering diazepam to a mammal through an inhalation route, wherein the route comprises:

a) heating a composition, wherein the composition comprises at least 5 percent by weight of diazepam, to form a vapor; and,

b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles,

which is inhaled by the mammal.

9. The method according to Claim 8, wherein the particles comprise at least 10 percent by weight of diazepam.

10. The method according to Claim 8, wherein the mass of the aerosol is at least 0.10 mg.

11. The method according to Claim 8, wherein the aerosol particles have a mass median aerodynamic diameter of less than 3 microns.

12. The method according to Claim 8, wherein the particles comprise less than 2.5 percent by weight of diazepam degradation products.

13. The method according to Claim 11, wherein the aerosol comprises particles comprising at least 90 percent by weight of diazepam.

14. The method according to Claim 13, wherein the aerosol particles have a mass median aerodynamic diameter less than 2 microns.

15. The method according to Claim 14, wherein the aerosol comprises particles comprising at least 97 percent by weight of diazepam.

16. A kit for delivering diazepam through an inhalation route to a mammal, wherein the kit comprises:

a) a composition comprising at least 5 percent by weight of diazepam; and,

b) a device that forms a diazepam aerosol from the composition, for inhalation by the mammal

and wherein the device comprises:

a) an element for heating the diazepam composition to form a vapor;

b) an element allowing the vapor to cool to form an aerosol; and,

c) an element permitting the mammal to inhale the aerosol.

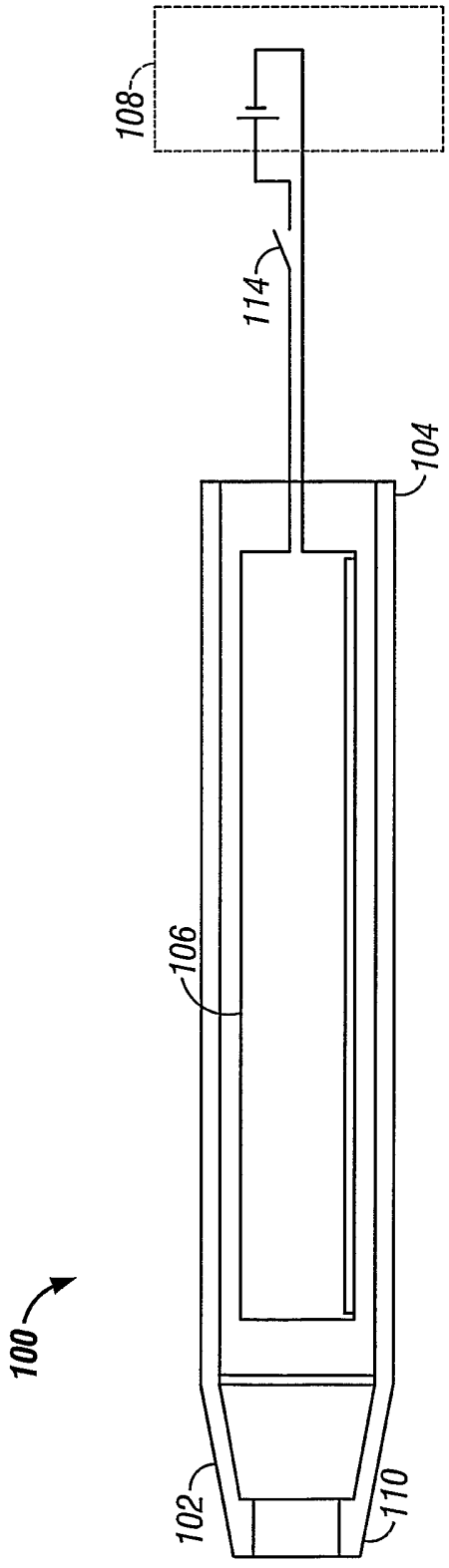

FIG. 1

INTERNATIONAL SEARCH REPORT

Internat ... pplication No
PCT/US 02/15820

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/72 A61K31/5513

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 388 574 A (INGEBRETHSEN BRADLEY J) 14 February 1995 (1995-02-14) column 2, line 65 -column 6, line 39 column 6, line 54 column 10, line 34 - line 55 column 11, line 25 - line 47 claim 12 figure 1	1-16
X	US 5 985 309 A (VANBEVER RITA ET AL) 16 November 1999 (1999-11-16) column 4, line 66 -column 5, line 47 column 10, line 5 - line 16 column 12, line 41	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2002	09/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Giménez Miralles, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatic pplication No
PCT/US 02/15820

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 72827 A (ACUSPHERE INC) 7 December 2000 (2000-12-07) page 6, line 27 - line 31 page 9, line 10 - line 13 page 23, line 18 -----	1-7

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/15820

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-15
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 8-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 8-15

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic pplication No
PCT/US 02/15820

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NO 20015753 A	28-01-2002
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