ULTRA LOW DENSITY PULMONARY POWDERS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/724,781, filed on November 9, 2012; U.S. Provisional Application No. 61/884,319; U.S. Provisional Application No. 61/884,315; U.S. Provisional Application No. 61/884,436, all filed on September 30, 2013. This application is a continuation-in-part of Application No. 13/679,245, filed November 16, 2012, now U.S. Patent 8,545,878 and a continuation-in-part of U.S. Application No. 13/945,160, filed July 18, 2013. The entire teachings of the above applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Delivering large doses of drug through the pulmonary route is very difficult. Dry powder inhalers offer advantages in delivering high dose drugs. In a dry powder formulation, choosing a formulation with a high percentage of drug and a low percentage of excipient can help delivery high dose drugs, but it can often be difficult to manufacture and use such powders. Applicants have discovered an ultralow density pulmonary dry powder which allows for high doses of the powder to be packaged in a delivery compartment while being released from the inhaler as highly respirable particles.

SUMMARY OF THE INVENTION

The invention provides pharmaceutical compositions for pulmonary delivery comprising particles containing a pharmaceutical agent and having a geometric size of greater than about 5μm and a tap density of less than about 0.075 g/cm^3. The invention also provides methods for delivering the pharmaceutical compositions of the invention to the respiratory tract of a patient. In one embodiment, the pharmaceutical compositions include particles comprising levodopa for pulmonary delivery to the respiratory tract of a patient suffering from Parkinson's disease.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention is a pharmaceutical composition for pulmonary delivery comprising particles containing a pharmaceutical agent and having a median

geometric size of greater than about 5 microns (μm) and a tap density of less than about 0.075 g/cm^3. In one aspect of the invention, the tap density is from about 0.02 to 0.075 g/cm^3. In another aspect of the invention, the tap density is from about 0.02 to 0.05 g/cm^3. In a further aspect of the invention, the tap density is from about 0.03 to 0.06 g/cm^3. In one aspect of the invention, the tap density is from about 0.03 to 0.04 g/cm^3. In another aspect of the invention the median geometric size is about 5μm to 30μm, 5μm to 10μm, 7μm to 15 μm, or 7μm to 12μm.

In another embodiment, the invention is a method of delivering a pharmaceutical agent to the pulmonary system of a patient comprising the steps of:

providing a powder in a compartment and an inhaler to a patient wherein said powder comprises particles of a pharmaceutical agent;

dispersing the powder by breath actuation of the patient;

delivering the particles to the patient's respiratory system;

wherein upon dispersion of the powder, the particles delivered to the patient's respiratory system have a smaller median geometric diameter than the particles contained in said compartment.

In one aspect of the invention, the powder has a tap density of less than about 0.75 g/cm^3, from about 0.02 to 0.075 g/cm^3, or from about 0.025 to 0.055 g/cm^3.

In one aspect of this invention, an inhaler is a dry powder inhaler. A variety of inhalers can be used including the Aerolizer, Diskus, Flexhaler, Handihaler, Neohaler, Pressair, Rotahaler, Turbohaler, and Twisthaler. Other dry powder inhalers which can be used are described in US patent 6,766,799, US patent 7,278,425 and US patent 8,496,002 each of which are hereby incorporated in by reference for their disclosure relating to the inhalation devices described therein.

In one aspect of the invention, the compartment is a capsule or a blister pack. In one aspect of the invention, the inhaler has a resistance of about 0.05 to about 0.25, about 0.15 to about 0.25, 0.05 to about 0.15, 0.2 to about 0.25, or about 0.2. Resistance as referred herein is measured in: square root of cm H_2O/(Liters/minute).

In another aspect of the invention, the powder in said compartment has a median geometric diameter of greater than about 5 μm, of about 5 μm to about 30 μm, of about 5 μm to about 15 μm, or of about 7 μm to about 12 μm. In one specific embodiment, the

particles in said compartment have a median geometric diameter of 10-12 μm and the particles delivered to the patient's respiratory tract have a median geometric diameter of 8-9μm. In another embodiment, the particles delivered to the patient's respiratory tract have a 5% to 20% smaller, 5% to 10% smaller, or 8% to 15% smaller median geometric diameter than the particles in said compartment.

In one embodiment, the invention is a pharmaceutical composition for pulmonary deliver comprising particles of levodopa having a geometric size of greater than about 5μm and a tap density of less than about 0.075 g/cm^3. In one aspect of this invention, the particles comprise a phospholipid. In another aspect of this invention, the particles comprise a salt. In a further aspect of this invention, the particles comprise a surfactant or a polymer.

In one embodiment, particles of this invention have an external surface area of greater than 10m^2/g. In another embodiment, the external surface area is greater than 15m^2/g, greater than 20m^2/g or about 10 m^2/g to about 50 m^2/g.

In one specific embodiment, the invention is a pharmaceutical composition for pulmonary deliver comprising particles of levodopa having a geometric size of about 8 μm to about 12 μm and a tap density of about 0.025 g/cm^3 to about 0.050 g/cm^3. This specific invention, in some instances, may be characterized by particles having an aerodynamic diameter of between about 2.5μm and 5 μm, particles having an external surface area of about 10 m^2/g to about 50 m^2/g, or said particles further comprising a salt and a phospholipid. In one very specific embodiment, the invention is a pharmaceutical composition for pulmonary delivery comprising particles of levodopa, dipalmitoylphosphatidylcholine and sodium chloride, wherein said particles have a geometric size of about 8 μm to about 12 μm and a tap density of about 0.025 g/cm^3 to about 0.050 g/cm^3. In an even more specific embodiment, the invention is a pharmaceutical composition for pulmonary delivery comprising particles of levodopa, dipalmitoylphosphatidylcholine (DPPC) and sodium chloride, wherein said particles have a geometric size of about 8 μm to about 12μm, and a tap density of about 0.025 g/cm^3 to about 0.050 g/cm^3, an aerodynamic diameter of between about 2.5 μm and 5 μm, and an external surface area of about 10 to about 50 m^2/g.

The inhalation powder may contain additional excipients. Examples of excipients include salts such as sodium chloride (NaCl), sodium citrate, sodium lactate, and potassium chloride and phospholipids such as dipalmitoylphosphatidylcholine (DPPC) dilauroylphosphatidylcholine (DLPC), disaturated-phosphatidylcholine (DSPC). In one embodiment, the pharmaceutical composition contains a powder comprising 90% levodopa, 8% dipalmitoylphosphatidylcholine, and 2% sodium chloride as measured by % of dry solids in the powder. In one embodiment the pharmaceutical composition contains an inhalable powder having a dry weight ratio of 90:8:2 of levodopa:DPPC:NaCl. In another embodiment the capsule contains an inhalable powder having a dry weight ratio of 90:5:5 of levodopa:DPPC:NaCl.

Gravimetric analysis, using Cascade impactors, is a method of measuring the size distribution of airborne particles. The Andersen Cascade Impactor (ACI) is an eight-stage impactor that can separate aerosols into nine distinct fractions based on aerodynamic size. The size cutoffs of each stage are dependent upon the flow rate at which the ACI is operated. Preferably the ACI is calibrated at 60 L/min. In one embodiment, a two-stage collapsed ACI is used for particle optimization. The two-stage collapsed ACI consists of stages 0, 2 and F of the eight-stage ACI and allows for the collection of two separate powder fractions. At each stage an aerosol stream passes through the nozzles and impinges upon the surface. Particles in the aerosol stream with a large enough inertia will impact upon the plate. Smaller particles that do not have enough inertia to impact on the plate will remain in the aerosol stream and be carried to the next stage.

The ACI is calibrated so that the fraction of powder that is collected on a first stage is referred to herein as "fine particle fraction" or "FPF". The FPF corresponds to the percentage of particles that have an aerodynamic diameter of less than 5.6 μm. The fraction of powder that passed the first stage of the ACI and is deposited on the collection filter is referred to as "FPF(3.4)". This corresponds to the percentage of particles having an aerodynamic diameter of less than 3.4 μm.

The FPF fraction has been demonstrated to correlate to the fraction of the powder that is deposited in the lungs of the patient, while the FPF(3.4) has been demonstrated to correlate to the fraction of the powder that reaches the deep lung of a patient. In

accordance with the invention, the FPF of the inhalable powder of the nominal dose contained in the capsule (i.e., the percentage of particles in the powder contained in the capsule that have an aerodynamic diameter of less than 5.6 μm) is about 40% or more. In one embodiment the FPF of the nominal powder dose of the inhalable powder contained in the capsule is about 50%, 60%, or 70%, or 80%, or 90%. In one embodiment the FPF is about 50% to about 60% of the nominal powder dose of the inhalable powder contained in the inhaler. In one embodiment the FPF is about 55% to about 65% of the nominal powder dose of the inhalable powder contained in the inhaler. In one embodiment the FPF is about 50% to about 70% of the nominal powder dose of the inhalable powder contained in the inhaler. In one embodiment the FPF is about 57% to about 62% of the nominal powder dose of the inhalable powder contained in the inhaler. In one embodiment the FPF is about 50% to about 69% of the nominal powder dose of the inhalable powder contained in the inhaler. In one embodiment the FPF is about 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, or 65% of the nominal powder dose of the inhalable powder contained in the inhaler.

As used herein, the term "nominal powder dose" is the total amount of powder held in the capsule. As used herein, the term "nominal drug dose" is the total amount of drug (e.g. levodopa) contained in the nominal powder dose. The nominal powder dose is related to the nominal drug dose by the load percent of drug in the powder.

In one embodiment, the nominal powder dose is 25-50 mg by dry weight. In a further embodiment, the nominal powder dose is 25-40 mg by dry weight. In a still further embodiment, the nominal powder dose is 30-35 mg by dry weight or 32-38 mg by dry weight.

Another method for measuring the size distribution of airborne particles is the multi-stage liquid impinger (MSLI). The Multi-stage liquid Impinger (MSLI) operates on the same principles as the Anderson Cascade Impactor (ACI), but instead of eight stages there are five in the MSLI. Additionally, instead of each stage consisting of a solid plate, each MSLI stage consists of a methanol-wetted glass frit. The wetted stage is used to prevent bouncing and re-entrainment, which can occur using the ACI. The MSLI is used to provide an indication of the flow rate dependence of the powder. This can be

accomplished by operating the MSLI at 30, 60, and 90 L/min and measuring the fraction of the powder collected on stage 1 and the collection filter. If the fractions on each stage remain relatively constant across the different flow rates then the powder is considered to be approaching flow rate independence.

In one embodiment, the inhalable powders of the invention have a tap density of less than about 0.075 g/cm^3. For example, the particles have a tap density between 0.02 g/cm^3 and 0.075 g/cm^3, between 0.02 g/cm^3 and 0.05 g/cm^3, between 0.03 g/cm^3 and 0.06 g/cm^3, between 0.03 g/cm^3 and 0.04 g/cm^3, or less than about 0.05 g/cm^3, or a tap density less than about 0.04 g/cm^3, a tap density less than about 0.03 g/cm^3. Tap density can be measured by using instruments known to those skilled in the art such as the Dual Platform Microprocessor Controlled Tap Density Tester (Vankel, N.C.) or a GEOPYC ™ instrument (Micrometrics Instrument Corp., Norcross, GA, 30093). Tap density is a standard measure of the envelope mass density. Tap density can be determined using the method of USP Bulk Density and Tapped Density, United States Pharmacopia Convention, Rockville, Md., 10th Supplement, 4950-4951, 1999. Features which can contribute to low tap density include irregular surface texture and porous structure. The envelope mass density of an isotropic particle is defined as the mass of the particle divided by the minimum sphere envelope volume within which it can be enclosed. In one embodiment of the invention, the particles have an envelope mass density of less than about 0.4 g/cm^3.

The inhalable powder of the invention has a preferred particle size, e.g., a volume median geometric diameter (VMGD) of at least about 1 micron (μm). In one embodiment, the VMGD is greater than 5 μm. In other embodiments, the VMGD is between about 5 μm and 30 μm, between about 5 μm and 10 μm, between about 7 μm and 15 μm and between about 7 μm and 12 μm. The diameter of the spray-dried particles, for example, the VMGD, can be measured using a laser diffraction instrument (for example Helos, manufactured by Sympatec, Princeton, N.J.). Other instruments for measuring particle diameter are well known in the art. The diameter of particles in a sample will range depending upon factors such as particle composition and methods of synthesis. The distribution of size of particles in a sample can be selected to permit optimal deposition to targeted sites within the respiratory tract.

The particles of the inhalable powder of the invention preferably have a "mass median aerodynamic diameter" (MMAD), also referred to herein as "aerodynamic diameter", between about 1 μm and about 5 μm or any subrange encompassed between about 1 μm and about 5 μm. For example, the MMAD is between about 1 μm and about 3 μm, or the MMAD is between about 3 μm and about 5 μm. In one embodiment, the MMAD is between 1.5 μm and 2.5 μm. Experimentally, aerodynamic diameter can be determined by employing a gravitational settling method, whereby the time for an ensemble of powder particles to settle a certain distance is used to infer directly the aerodynamic diameter of the particles. An indirect method for measuring the mass median aerodynamic diameter (MMAD) is the multi-stage liquid impinger (MSLI). The aerodynamic diameter, d_{aer}, can be calculated from the equation:

$$d_{aer}=d_g\sqrt{\rho_{tap}}$$

where d_g is the geometric diameter, for example the MMGD, and ρ is the powder density.

Powders for use in capsules of this invention are typically produced by spray drying. In some cases, spray-drying can produce extremely dry particles which may have poor handling properties and may be difficult to compact into a capsule in a dense manner. A nitrogen source with a specified moisture level may be flown over, across, or through the dry powder to add specific moisture content to the dry powder. Such moisture can provide the desired working density of the powder. Spray drying methods in accordance with the invention are described in the Examples herein and in U.S. Patent Numbers: 6,848,197 and 8,197,845, incorporated herein by reference.

The inhalable powder comprising levodopa, for example, as described above is used to fill capsules suitable for use in an inhaler. The term "capsule material" as used herein refers to the material from which the shell of the capsule for inhalation is made. In one embodiment, the capsule material according to the invention is selected from among gelatin, cellulose derivatives, starch, starch derivatives, chitosan and synthetic plastics.

If gelatin is used as the capsule material, examples according to the invention may be selected from among polyethyleneglycol (PEG), PEG 3350, glycerol, sorbitol, propyleneglycol, PEO-PPO block copolymers and other polyalcohols and polyethers. If cellulose derivatives are used as the capsule material, examples according to the

invention may be selected from hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose and hydroxyethylcellulose. If synthetic plastics are used as the capsule material, examples according to the invention may be selected from polyethylene, polycarbonate, polyester, polypropylene and polyethylene terephthalate. In one embodiment, the capsule material further comprises titanium dioxide. In one preferred embodiment the capsule comprises HPMC and titanium dioxide. In one embodiment, the capsule comprises carrageenan. In a further embodiment, the capsule comprises potassium chloride. In a still further embodiment, the capsule comprises, HPMC, carrageenan, potassium chloride, and titanium dioxide. In one embodiment, the capsule size is selected from 000, 00, 0, 1, or 2. In a specific embodiment, the capsule size is 00.

In one specific embodiment, the capsule is a hydroxypropylmethylcellulose (HPMC) capsule. In another specific embodiment, the capsule is a hydroxypropylmethylcellulose size 00 capsule. In one specific embodiment the capsule material comprises HPMC and titanium dioxide and the capsule size is 00.

In one embodiment, a 00 capsule contains between 15 and 50 grams of levodopa by dry weight. In another embodiment, a 00 capsule contains between 20 and 40 grams of levodopa by dry weight. In another embodiment, a 00 capsule contains between 25 and 35 grams of levodopa by dry weight. In another embodiment, a 00 capsule contains about 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 grams of levodopa by dry weight.

In one aspect of the invention, the powders have low electrostatic charge to enable high dispersion from the capsule.

The capsules of the invention are particularly suitable for use in a dry powder inhaler for the delivery of a dry powder composition comprising levodopa to a patient afflicted with, for example, Parkinson's disease and in need of treatment with levodopa. The patient in need of treatment may require maintenance therapy for Parkinson's disease or rescue therapy for Parkinson's disease such as would be necessary in the case of an acute and/or freezing episode due to Parkinson's disease. In one embodiment, the capsules are used in a dry powder inhaler to deliver an effective amount of the dry powder composition to the patient in a single breath as is described in U.S. Patent Numbers, 6,858,199 and 7,556,798 incorporated herein by reference.

As used herein, the term "effective amount" means the amount needed to achieve the desired effect or efficacy. The actual effective amounts of drug can vary according to the specific drug or combination thereof being utilized, the particular composition formulated, the mode of administration, and the age, weight, condition of the patient, and severity of the episode being treated. In the case of a dopamine precursor, agonist or combination thereof it is an amount which reduces the Parkinson's symptoms which require therapy. Dosages for a particular patient are described herein and can be determined by one of ordinary skill in the art using conventional considerations, (e.g. by means of an appropriate, conventional pharmacological protocol). For example, effective amounts of oral levodopa range from about 50 milligrams (mg) to about 500 mg. In many instances, a common ongoing (oral) levodopa treatment schedule is 100 mg eight (8) times a day.

The administration of more than one dopamine precursor, agonist or combination thereof, in particular levodopa, carbidopa, apomorphine, and other drugs can be provided, either simultaneously or sequentially in time. Carbidopa or benserazide, for example, is often administered to ensure that peripheral carboxylase activity is completely shut down. Intramuscular, subcutaneous, oral and other administration routes can be employed. In one embodiment, these other agents are delivered to the pulmonary system. These compounds or compositions can be administered before, after or at the same time. In a preferred embodiment, particles that are administered to the respiratory tract include both Levodopa and carbidopa. The term "co-administration" is used herein to mean that the specific dopamine precursor, agonist or combination thereof and/or other compositions are administered at times to treat the episodes, as well as the underlying conditions described herein.

In one embodiment chronic levodopa therapy includes the use of the pharmaceutical compositions described herein in a dry powder inhaler for pulmonary delivery of levodopa combined with oral carbidopa. In another embodiment, pulmonary delivery of levodopa is provided during the episode, while chronic treatment can employ conventional oral administration of levodopa/carbidopa. In a further embodiment chronic levodopa therapy includes the use of the pharmaceutical compositions described herein in a dry powder inhaler for pulmonary delivery of

levodopa combined with oral benserazide. In another embodiment, pulmonary delivery of levodopa is provided during the episode, while chronic treatment can employ conventional oral administration of levodopa/ benserazide.

The present invention will be further understood by reference to the following non-limiting examples.

EXAMPLES

Example 1. Process one powder preparation

Levodopa and DPPC at room temperature for 30 minutes, after which the required amounts of water and ethanol are weighed and transferred to the jacketed aqueous and non-jacketed organic phase feed vessels respectively. The jacket on the aqueous phase vessel is set to 55 °C, and the weighed water is allowed to heat up to the 52.5 °C, following which the required amount of sodium chloride and L-dopa are added to the aqueous phase vessel and the required amount of DPPC is added to the organic phase vessel, and all of them are allowed to dissolve by stirring. The aqueous feed vessel headspace is purged with nitrogen maintained at 70 scfh.

Spray drying is initiated by starting the drying gas flow (set to 95 kg/hr) and the exhaust, and the heater for the drying gas is set to 125 °C. The product filter heater is turned on and set to 60 °C, and the liquid skid heater is turned on and set to 55 °C. After the spray dryer outlet temperature reaches 80 °C, the atomizing gas (set to 22 g/min) and the blank solvents (aqueous flow = 28 mL/min and organic flow = 42 mL/min) are initiated and allowed to stabilize, and the system is allowed to cool and stabilize to an outlet temperature of 52.5 °C. Product filter pulsing is initiated and product filter purge flow is set to 15 scfh. After the system stabilizes at 52.5 °C, the liquid skid inlets are switched to feed solvents. Table 1 summarizes the parameters maintained during the entire operation.

Process Parameters (OC)	Target value
Inlet Temperature (°C)	125.0
Outlet Temperature (°C)	52.5
Drying Gas Rate (kg/hr)	95.0
Chamber Pressure ("wc)	-2.0
Atomization Gas Flow Rate (g/min)	22.0
Aqueous Flow (mL/min)	28.0
Organic flow (mL/min)	42.0
Product filter purge rate (scfh)	15.0

Table 1: Process parameters for spray drying

Spray dried powder is collected every hour and transferred to a larger vessel under controlled conditions of 20 °C and 15% RH. After the feed solvents run out, the liquid skid inlets are switched to blank and allowed to run for about 10 minutes, during which the final powder is collected and combined. After 10 minutes on blank solvent, system shutdown is initiated by turning off the liquid lines, atomization gas, drying gas heater, drying gas inlet and finally the exhaust.

This process results in a powder containing about 3.4% water by weight.

Example 2. Process two powder preparation with special drying

Levodopa and DPPC at room temperature for 30 minutes, after which the required amounts of water and ethanol are weighed and transferred to the jacketed aqueous and non-jacketed organic phase feed vessels respectively. The jacket on the aqueous phase vessel is set to 55 °C, and the weighed water is allowed to heat up to the 52.5 °C, following which the required amount of sodium chloride and L-dopa are added to the aqueous phase vessel and the required amount of DPPC is added to the organic phase vessel, and all of them are allowed to dissolve by stirring. The aqueous feed vessel headspace is purged with nitrogen maintained at 70 scfh.

Spray drying is initiated by starting the drying gas flow (set to 95 kg/hr) and the exhaust, and the heater for the drying gas is set to 125 °C. The product filter and the optimized purge gas heaters are turned on and set to 60 °C, and the liquid skid heater is turned on and set to 55 °C. After the spray dryer outlet temperature reaches 80 °C, the atomizing gas (set to 22 g/min), the blank solvents (aqueous flow = 28 mL/min and

organic flow = 42 mL/min), and the optimized drying gas (set at 70 kg/hr) are initiated and allowed to stabilize, and the system is allowed to cool and stabilize to an outlet temperature of 52.5 °C. Product filter pulsing is initiated and product filter purge flow is set to 15 scfh. After the system stabilizes at 52.5 °C, the liquid skid inlets are switched to feed solvents. Table 2 summarizes the parameters maintained during the entire operation.

Process Parameters (OC)	Target value
Inlet Temperature (°C)	125.0
Outlet Temperature (°C)	52.5
Drying Gas Rate (kg/hr)	95.0
Chamber Pressure ("wc)	-2.0
Atomization Gas Flow Rate (g/min)	22.0
Aqueous Flow (mL/min)	28.0
Organic flow (mL/min)	42.0
Optimized drying purge rate (kg/hr)	70.0
Optimized drying purge temperature (°C)	52.5
Product filter purge rate (scfh)	15.0

Table 2: Process parameters for spray drying

Spray dried powder is collected every hour and transferred to a larger vessel under controlled conditions of 20 °C and 15% RH. After the feed solvents run out, the liquid skid inlets are switched to blank and allowed to run for about 10 minutes, during which the final powder is collected and combined. After 10 minutes on blank solvent, system shutdown is initiated by turning off the liquid lines, optimized drying gas, atomization gas, drying gas heater, drying gas inlet and finally the exhaust.

This process results in a powder containing about 2.2% water by weight. This reduction in water content by 1% results in a significant improvement in product stability.

Sample 1: Based on bulk powder (pre-filling):

VMGD = 10.2 μm; and

Tap density = 0.033 g/cm^3.

Sample 2: Same but using VMGD measured on filled lot (60031):

VMGD = 8.6 μm; and

Tap = 0.033 g/cm^3.

Sample 1. Emitted powder from a dry powder inhaler with a resistance of 0.2 (28.3 LPM):

VMGD = 9.4 μm; and
Tap density = 0.048 g/cm^3.

Sample 2. Emitted powder from a dry powder inhaler with a resistance of 0.2 ((60 LPM):

VMGD = 8.8 μm; and
Tap density = 0.042 g/cm^3.

The above particles are very low density for pulmonary products. These very low density particles are advantageous for packing into capsules. Because of the low density, these particles can be deaggregated or sheared prior to emission from an inhaler. These deaggregated/sheared particles have good flow properties and expected deposition into the lungs.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims. It should also be understood that the embodiments described herein are not mutually exclusive and that features from the various embodiments may be combined in whole or in part in accordance with the invention.

CLAIMS

What is claimed is:

1. A pharmaceutical composition for pulmonary delivery comprising particles containing a pharmaceutical agent wherein the particles have a geometric size of greater than about 5 μm and a tap density of less than about 0.075 g/cm^3.

2. The pharmaceutical composition of claim 1, wherein said tap density is from about 0.02 g/cm^3 to 0.075 g/cm^3.

3. The pharmaceutical composition of claim 1, wherein said tap density is from about 0.02 g/cm^3 to 0.05 g/cm^3.

4. The pharmaceutical composition of claim 1, wherein said tap density is from about 0.03 g/cm^3 to 0.06 g/cm^3.

5. The pharmaceutical composition of claim 1, wherein said tap density is from about 0.03 g/cm^3 to 0.04 g/cm^3.

6. The pharmaceutical composition of claim 1, wherein geometric size is about 5 μm to 30 μm.

7. The pharmaceutical composition of claim 1, wherein median geometric size is about 5 μm to 10 μm.

8. The pharmaceutical composition of claim 1, wherein median geometric size is about 7 μm to 15 μm.

9. The pharmaceutical composition of claim 1, wherein median geometric size is about 7 μm to 12 μm.

10. A method of delivering a pharmaceutical agent to the pulmonary system of a patient comprising the steps of:

providing a powder in a compartment and an inhaler to a patient wherein said powder comprises particles of a pharmaceutical agent;

dispersing the powder by breath actuation of the patient;

delivering the particles to the patient's respiratory system; and

wherein upon dispersion of the powder, the particles delivered to the patient's respiratory system have a smaller median geometric diameter than the particles contained in said compartment.

11. The method of claim 10, wherein said powder has a tap density of less than about 0.75 g/cm^3.

12. The method of claim 10, wherein said powder has a tap density is from about 0.02 g/cm^3 to 0.075 g/cm^3.

13. The method of claim 10, wherein said powder has a tap density is from about 0.025 g/cm^3 to 0.055 g/cm^3.

14. The method of claim 10, wherein said inhaler has a resistance of about 0.05 $\sqrt{cm}$ $H_2O/(L/min)$ to about 0.25 $\sqrt{cm}$ $H_2O/(L/min)$.

15. The method of claim 10, wherein said inhaler has a resistance of about 0.15 $\sqrt{cm}$ $H_2O/(L/min)$ to about 0.25 $\sqrt{cm}$ $H_2O/(L/min)$.

16. The method of claim 10, wherein said inhaler has a resistance of about 0.05 $\sqrt{cm}$ $H_2O/(L/min)$ to about 0.15 $\sqrt{cm}$ $H_2O/(L/min)$.

17. The method of claim 10, wherein said inhaler has a resistance of about 0.2 $\sqrt{cm}$ $H_2O/(L/min)$ to about 0.25 $\sqrt{cm}$ $H_2O/(L/min)$.

18. The method of claim 10, wherein said inhaler has a resistance of about 0.2 $\sqrt{cm}$ $H_2O/(L/min)$.

19. The method of claim 10, wherein the powder in said compartment has a median geometric diameter of greater than about 5 μm.

20. The method of claim 10, wherein the powder in said compartment has a median geometric diameter of about 5 μm to about 30 μm.

21. The method of claim 10, wherein the powder in said compartment has a median geometric diameter of about 5 μm to about 15 μm.

22. The method of claim 10, wherein the powder in said compartment has a median geometric diameter of about 7 μm to about 12 μm.

23. The method of claim 10, wherein the particles in said compartment have a median geometric diameter of 10-12 μm and the particles delivered to the patient's respiratory tract have a median geometric diameter of 8-9 μm.

24. The method of claim 10, wherein the particles delivered to the patient's respiratory tract have a 5% to 20% smaller median geometric diameter than the particles in said compartment.

25. The method of claim 10, wherein the particles delivered to the patient's respiratory tract have a 5% to 10% smaller median geometric diameter than the particles in said compartment.

26. The method of claim 10, wherein the particles delivered to the patient's respiratory tract have a 8% to 15% smaller median geometric diameter than the particles in said compartment.

27. A pharmaceutical composition for pulmonary delivery comprising particles of levodopa having a geometric size of greater than about 5 μm and a tap density of less than about 0.75 g/cm^3.

28. The pharmaceutical composition of claims 1 or 27, wherein said particles comprise a phospholipid.

29. The pharmaceutical composition of claims 1 or 27, wherein said particles comprise a salt.

30. The pharmaceutical composition of claims 1 or 27, wherein said particles comprise a surfactant.

31. The pharmaceutical composition of claims 1 or 27, wherein said particles comprise a polymer.

32. The pharmaceutical composition of claims 1 or 27, wherein said particles comprise a sugar.

33. The pharmaceutical composition of claims 1 or 27, wherein said particles have an external surface area of greater than about 10 m^2/g.

34. The pharmaceutical composition of claims 1 or 27, wherein said particles have an external surface area of greater than about 15 m^2/g.

35. The pharmaceutical composition of claims 1 or 27, wherein said particles have an external surface area of greater than about 20 m^2/g.

36. The pharmaceutical composition of claims 1 or 27, wherein said particles have an external surface area of about 10 m^2/g to about 50 m^2/g.

37. A pharmaceutical composition for pulmonary deliver comprising particles of levodopa having:

a geometric size of about 8 μm to about 12 μm; and

a tap density of about 0.025 g/cm^3 to about 0.050 g/cm^3.

38. The pharmaceutical composition of claim 37, wherein said particles have an aerodynamic diameter of between about 2.5 μm and 5 μm.

39. The pharmaceutical composition of claim 37, wherein said particles have an external surface area of about 10 m^2/g to about 50 m^2/g.

40. The pharmaceutical composition of claim 37, wherein said particles further comprise a salt and a phospholipid.

41. A pharmaceutical composition for pulmonary delivery comprising particles of levodopa having:

a geometric size of about 8 μm to about 12 μm;

a tap density of about 0.025 g/cm^3 to about 0.050 g/cm^3;

a water content between 1.90 and 2.90 weight percent.