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(54) **Title**: ULTRA LOW DENSITY PULMONARY POWDERS

(57) **Abstract**: The invention provides pharmaceutical compositions for pulmonary delivery comprising particles containing a pharmaceutical agent and having a geometric size of greater than about 5 μm 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.

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/69107

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/16, 39/00; A61P 11/06 (2014.01)
USPC - 424/46, 469, 489
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(8) - A61K 31/58, 38/28, 39/00, 9/14, 9/16, 9/26; A61P 11/06 (2014.01)
USPC - 424/43, 46, 184.1, 400, 428, 469, 489, 499; 514/174

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 practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Scholar; Pubmed; IP.com; powder, particle, inhaler, levodopa, l-dopa, resistance, pulmonary, delivery, geometric, diameter, tap density, polymer, sugar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,652,837 B1 (EDWARDS, DA et al.) November 25, 2003; column 4, lines 4-41; column 7, lines 40-42; column 24, lines 33-37; column 26, lines 1-9	1-9, 28/1, 29/1, 30/1, 31/1, 32/1
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Y		12-13, 33/1, 34/1, 35/1, 36/1, 37-40
X	US 7,879,358 B2 (JACKSON, B et al.) February 1, 2011; column 2, lines 5-7, lines 14-19, lines 39-43; column 5, lines 30-33, lines 49-55; column 6, lines 11-21; column 7, lines 25-31; column 8, lines 1-4; column 11, lines 40-44; column 12, lines 44-53; column 16, lines 63-67	10-11, 19-22, 27, 28/27, 29/27, 30/27, 31/27, 32/27
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Y		12-18, 33/27, 34/27, 35/27, 36/27, 37-40
Y	WO 1997/040819 A1 (SCHULTZ, R et al.) November 6, 1997; page 7, lines 10-14	14-18
Y	US 7,384,649 B2 (BATYCKY, RP et al.) June 10, 2008; column 2, lines 23-28	33/1, 33/27, 36/1, 36/27
Y	US 2010/0197565 A1 (SMUTNEY, CC et al.) August 5, 2010; paragraphs [0133], [0185]	34/1, 34/27, 35/1, 35/27, 39
A	US 2012/0064126 A1 (SUNG, JC et al.) March 15, 2012; paragraphs [0011], [0163]	23-26
A	US 2011/0123574 A1 (BASU, SK et al.) May 26, 2011; paragraph [0248]	23-26

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
04 February 2014 (04.02.2014)	05 MAR 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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权利要求书2页 说明书8页

(54)发明名称

超低密度的肺部粉末

(57)摘要

本发明提供用于肺部递送的包含颗粒的药物组合物，所述颗粒含有药剂，并且具有大于约5μm的几何尺寸和小于约0.075g/cm^{3}的振实密度。本发明还提供用于递送本发明的药物组合物至患者呼吸道的方法。

CN 105120843 A

1. 一种用于肺部递送的药物组合物，其包含含有药剂的颗粒，其中所述颗粒具有大于约 5 μm 的几何尺寸和小于约 0.075g/cm^{3}的振实密度。

2. 如权利要求 1 所述的药物组合物，其中所述振实密度为约 0.02g/cm^{3}至 0.075g/cm^3。

3. 如权利要求 1 所述的药物组合物，其中所述振实密度为约 0.02g/cm^{3}至 0.05g/cm^3。

4. 如权利要求 1 所述的药物组合物，其中所述振实密度为约 0.03g/cm^{3}至 0.06g/cm^3。

5. 如权利要求 1 所述的药物组合物，其中所述振实密度为约 0.03g/cm^{3}至 0.04g/cm^3。

6. 如权利要求 1 所述的药物组合物，其中几何尺寸为约 5 μm 至 30 μm。

7. 如权利要求 1 所述的药物组合物，其中中值几何尺寸为约 5 μm 至 10 μm。

8. 如权利要求 1 所述的药物组合物，其中中值几何尺寸为约 7 μm 至 15 μm。

9. 如权利要求 1 所述的药物组合物，其中中值几何尺寸为约 7 μm 至 12 μm。

10. 一种递送药剂至患者的肺部系统的方法，其包括如下的步骤：

向患者提供在隔室和吸入器中的粉末，其中所述粉末包含药剂的颗粒；

通过所述患者的呼吸致动来分散所述粉末；

递送所述颗粒至所述患者的呼吸系统；并且

其中通过所述粉末的分散，递送至所述患者呼吸系统的所述颗粒具有小于所述隔室中含有的颗粒的中值几何直径。

11. 如权利要求 10 所述的方法，其中所述粉末具有小于约 0.75g/cm^{3}的振实密度。

12. 如权利要求 10 所述的方法，其中所述粉末具有约 0.02g/cm^{3}至 0.075g/cm^{3}的振实密度。

13. 如权利要求 10 所述的方法，其中所述粉末具有约 0.025g/cm^{3}至 0.055g/cm^{3}的振实密度。

14. 如权利要求 10 所述的方法，其中所述吸入器具有约 0.05 √ cm H_2O/(L/min) 至约 0.25 √ cm H_2O/(L/min) 的阻抗。

15. 如权利要求 10 所述的方法，其中所述吸入器具有约 0.15 √ cm H_2O/(L/min) 至约 0.25 √ cm H_2O/(L/min) 的阻抗。

16. 如权利要求 10 所述的方法，其中所述吸入器具有约 0.05 √ cm H_2O/(L/min) 至约 0.15 √ cm H_2O/(L/min) 的阻抗。

17. 如权利要求 10 所述的方法，其中所述吸入器具有约 0.2 √ cm H_2O/(L/min) 至约 0.25 √ cm H_2O/(L/min) 的阻抗。

18. 如权利要求 10 所述的方法，其中所述吸入器具有约 0.2 √ cm H_2O/(L/min) 的阻抗。

19. 如权利要求 10 所述的方法，其中在所述隔室中的所述粉末具有大于约 5 μm 的中值几何直径。

20. 如权利要求 10 所述的方法，其中在所述隔室中的所述粉末具有约 5 μm 至约 30 μm 的中值几何直径。

21. 如权利要求 10 所述的方法，其中在所述隔室中的所述粉末具有约 5 μm 至约 15 μm 的中值几何直径。

22. 如权利要求 10 所述的方法，其中在所述隔室中的所述粉末具有约 7 μm 至约 12 μm 的中值几何直径。

23. 如权利要求 10 所述的方法，其中在所述隔室中的所述颗粒具有 10-12 μm 的中值几

何直径，而递送至所述患者呼吸道的所述颗粒具有 8-9 μm 的中值几何直径。

24. 如权利要求 10 所述的方法，其中递送至所述患者呼吸道的所述颗粒具有比在所述隔室中的所述颗粒小 5％至 20％的中值几何直径。

25. 如权利要求 10 所述的方法，其中递送至所述患者呼吸道的所述颗粒具有比在所述隔室中的所述颗粒小 5％至 10％的中值几何直径。

26. 如权利要求 10 所述的方法，其中递送至所述患者呼吸道的所述颗粒具有比在所述隔室中的所述颗粒小 8％至 15％的中值几何直径。

27. 一种用于肺部递送的药物组合物，其包含左旋多巴颗粒，所述左旋多巴颗粒具有大于约 5 μm 的几何尺寸和小于约 0.75g/cm^3的振实密度。

28. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒包含磷脂。

29. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒包含盐。

30. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒包含表面活性剂。

31. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒包含聚合物。

32. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒包含糖。

33. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒具有大于约 10m^2/g 的外表面积。

34. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒具有大于约 15m^2/g 的外表面积。

35. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒具有大于约 20m^2/g 的外表面积。

36. 如权利要求 1 或 27 所述的药物组合物，其中所述颗粒具有约 10m^2/g 至约 50m^2/g 的外表面积。

37. 一种用于肺部递送的药物组合物，其包含左旋多巴颗粒，所述左旋多巴颗粒具有：

约 8 μm 至约 12 μm 的几何尺寸；以及

约 0.025g/cm^3至约 0.050g/cm^3的振实密度。

38. 如权利要求 37 所述的药物组合物，其中所述颗粒具有在约 2.5 μm 和 5 μm 之间的空气动力学直径。

39. 如权利要求 37 所述的药物组合物，其中所述颗粒具有约 10m^2/g 至约 50m^2/g 的外表面积。

40. 如权利要求 37 所述的药物组合物，其中所述颗粒还包含盐和磷脂。

41. 一种用于肺部递送的药物组合物，其包含左旋多巴颗粒，所述左旋多巴颗粒具有：

约 8 μm 至约 12 μm 的几何尺寸；

约 0.025g/cm^3至约 0.050g/cm^3的振实密度；

在 1.90 重量％和 2.90 重量％之间的水含量。

超低密度的肺部粉末

[0001] 相关申请

[0002] 本申请要求于2012年11月9日提交的美国临时申请号61/724,781；均于2013年9月30日提交的美国临时申请号61/884,319、美国临时申请号61/884,315、美国临时申请号61/884,436的权益。本申请是2012年11月16日提交的申请号13/679,245，现在的美国专利8,545,878的部分继续申请，并且是2013年7月18日提交的美国申请号13/945,160的部分继续申请。以上申请的全部教义以引用的方式并入本文。

[0003] 发明背景

[0004] 通过肺部途径递送大剂量的药物是非常困难的。干粉吸入器在递送高剂量药物时提供优点。在干粉制剂中，选择具有高百分率药物和低百分率赋形剂的制剂可以帮助递送高剂量药物，但通常难以制造和使用此类粉末。申请人已经发现一种超低密度的肺部干粉，所述干粉允许高剂量的粉末被包装在递送隔室中，同时作为高度可吸入的颗粒从吸入器中释放。

[0005] 发明概述

[0006] 本发明提供用于肺部递送的包含颗粒的药物组合物，所述颗粒含有药剂，并且具有大于约5μm的几何尺寸和小于约0.075g/cm^{3}的振实密度。本发明还提供用于递送本发明的药物组合物至患者呼吸道的方法。在一个实施方案中，所述药物组合物包含用于肺部递送至患有帕金森病的患者的呼吸道的含有左旋多巴的颗粒。

[0007] 发明详述

[0008] 在一个实施方案中，本发明为用于肺部递送的包含颗粒的药物组合物，所述颗粒含有药剂，并且具有大于约5微米（μm）的中值几何尺寸和小于约0.075g/cm^{3}的振实密度。在本发明的一个方面，振实密度为约0.02至0.075g/cm^3。在本发明的另一个方面，振实密度为约0.02至0.05g/cm^3。在本发明的又一个方面，振实密度为约0.03至0.06g/cm^3。在本发明的一个方面，振实密度为约0.03至0.04g/cm^3。在本发明的另一个方面，中值几何尺寸为约5μm至30μm、5μm至10μm、7μm至15μm，或7μm至12μm。

[0009] 在另一个实施方案中，本发明为一种递送药剂至患者的肺部系统的方法，所述方法包括如下的步骤：

[0010] 向患者提供在隔室和吸入器中的粉末，其中所述粉末包含药剂的颗粒；

[0011] 通过患者的呼吸致动分散粉末；

[0012] 递送颗粒至患者的呼吸系统；

[0013] 其中通过粉末的分散，递送至患者呼吸系统的颗粒具有小于所述隔室中含有的颗粒的中值几何直径。

[0014] 在本发明的一个方面，粉末具有小于约0.75g/cm^3、约0.02至0.075g/cm^3，或约0.025至0.055g/cm^{3}的振实密度。

[0015] 在本发明的一个方面，吸入器为干粉吸入器。可以使用多种吸入器，包括Aerolizer、Diskus、Flexhaler、Handihaler、Neohaler、Pressair、Rotahaler、Turbohaler和Twisthaler。可以使用的其它干粉吸入器描述于美国专利6,766,799、美国专利

7,278,425 和美国专利 8,496,002 中，所述专利中的每个以其涉及本文所述吸入装置的公开内容以引用的方式在此并入。

[0016] 在本发明的一个方面，隔室为胶囊或泡罩包装。在本发明的一个方面，吸入器具有约 0.05 至约 0.25、约 0.15 至约 0.25、0.05 至约 0.15、0.2 至约 0.25，或约 0.2 的阻抗。本文所指的阻抗以厘米 H_2O 的平方根 /（升 / 分钟）计。

[0017] 在本发明的另一个方面，所述隔室中的粉末具有大于约 5μm、约 5μm 至约 30μm、约 5μm 至约 15μm，或约 7μm 至约 12μm 的中值几何直径。在一个具体实施方案中，所述隔室中的颗粒具有 10-12μm 的中值几何直径，而递送至患者呼吸道的颗粒具有 8-9μm 的中值几何直径。在另一个实施方案中，递送至患者呼吸道的颗粒具有比所述隔室中的颗粒小 5％至 20％、小 5％至 10％，或小 8％至 15％的中值几何直径。

[0018] 在一个实施方案中，本发明为用于肺部递送的药物组合物，所述药物组合物包含左旋多巴颗粒，所述左旋多巴颗粒具有大于约 5μm 的几何尺寸和小于约 0.075g/cm^3 的振实密度。在本发明的一个方面，颗粒包含磷脂。在本发明的另一个方面，颗粒包含盐。在本发明的又一个方面，颗粒包含表面活性剂或聚合物。

[0019] 在一个实施方案中，本发明的颗粒具有大于 10m^2/g 的外表面积。在另一个实施方案中，外表面积大于 15m^2/g、大于 20m^2/g 或约 10m^2/g 至约 50m^2/g。

[0020] 在一个具体实施方案中，本发明为用于肺部递送的药物组合物，所述药物组合物包含左旋多巴颗粒，所述左旋多巴颗粒具有约 8μm 至约 12μm 的几何尺寸和约 0.025g/cm^3 至约 0.050g/cm^3 的振实密度。在一些情况下，本具体发明的特征在于，颗粒具有在约 2.5μm 和 5μm 之间的空气动力学直径，颗粒具有约 10m^2/g 至约 50m^2/g 的外表面积，或所述颗粒还包含盐和磷脂。在一个非常具体的实施方案中，本发明为用于肺部递送的药物组合物，所述药物组合物包含左旋多巴、二棕榈酰磷脂酰胆碱和氯化钠的颗粒，其中所述颗粒具有约 8μm 至约 12μm 的几何尺寸和约 0.025g/cm^3 至约 0.050g/cm^3 的振实密度。在甚至更具体的实施方案中，本发明为用于肺部递送的药物组合物，所述药物组合物包含左旋多巴、二棕榈酰磷脂酰胆碱 (DPPC) 和氯化钠的颗粒，其中所述颗粒具有约 8μm 至约 12μm 的几何尺寸，和约 0.025g/cm^3 至约 0.050g/cm^3 的振实密度，在约 2.5μm 和 5μm 之间的空气动力学直径，以及约 10 至约 50m^2/g 的外表面积。

[0021] 吸入粉末可以含有另外的赋形剂。赋形剂的实例包括盐，如氯化钠 (NaCl)、柠檬酸钠、乳酸钠和氯化钾；以及磷脂，如二棕榈酰磷脂酰胆碱 (DPPC)、二月桂酰磷脂酰胆碱 (DLPC)、二饱和的磷脂酰胆碱 (DSPC)。在一个实施方案中，如以在粉末中的干固体的％所测量，药物组合物含有包含 90％的左旋多巴、8％的二棕榈酰磷脂酰胆碱和 2％的氯化钠的粉末。在一个实施方案中，药物组合物含有具有干重比率 90:8:2 的左旋多巴 :DPPC:NaCl 的可吸入粉末。在另一个实施方案中，胶囊含有具有干重比率 90:5:5 的左旋多巴 :DPPC:NaCl 的可吸入粉末。

[0022] 使用阶式冲击取样器的重量分析，是一种测量空气传播颗粒的尺寸分布的方法。Andersen 阶式冲击取样器 (ACI) 是可以根据空气动力学尺寸将气雾剂分为九个不同级分的八平台冲击取样器。各平台的尺寸截断值取决于操作 ACI 时的流速。优选地，在 60L/min 下校准 ACI。在一个实施方案中，二平台折叠 ACI 用于颗粒优化。二平台折叠 ACI 由八平台 ACI 的平台 0、2 和 F 构成，并且允许收集两个分开的粉末级分。在每个平台气雾剂流穿

过喷嘴并且撞击表面。具有足够大惯性的气雾剂流中的颗粒将撞击到板上。不具有足够的惯性撞击到板上的较小颗粒将保留在气雾剂流中，并被携带至下一个平台。

[0023] 校准 ACI，以便在第一平台上收集的粉末的分数在此被称为“细粒分数”或“FPF”。FPF 对应于具有小于 5.6μm 的空气动力学直径的颗粒的百分率。通过 ACI 的第一平台并沉积在收集过滤器上的粉末的分数被称为“FPF(3.4)”。其对应于具有小于 3.4μm 的空气动力学直径的颗粒的百分率。

[0024] FPF 分数已证实与沉积在患者肺部的粉末的分数相关联，而 FPF(3.4) 已证实与到达患者肺部深处的粉末的分数相关联。按照本发明，包含在胶囊中的标称剂量的可吸入粉末的 FPF（即，包含在胶囊中的具有小于 5.6μm 的空气动力学直径的粉末中的颗粒的百分率）为约 40％或更多。在一个实施方案中，包含在胶囊中的标称粉末剂量的可吸入粉末的 FPF 为约 50％、60％、或 70％、或 80％、或 90％。在一个实施方案中，包含在吸入器中的标称粉末剂量的可吸入粉末的 FPF 为约 50％至约 60％。在一个实施方案中，包含在吸入器中的标称粉末剂量的可吸入粉末的 FPF 为约 55％至约 65％。在一个实施方案中，包含在吸入器中的标称粉末剂量的可吸入粉末的 FPF 为约 50％至约 70％。在一个实施方案中，包含在吸入器中的标称粉末剂量的可吸入粉末的 FPF 为约 57％至约 62％。在一个实施方案中，包含在吸入器中的标称粉末剂量的可吸入粉末的 FPF 为约 50％至约 69％。在一个实施方案中，包含在吸入器中的标称粉末剂量的可吸入粉末的 FPF 为约 50％、51％、52％、53％、54％、55％、56％、57％、58％、59％、60％、61％、62％、63％、64％或 65％。

[0025] 如本文所使用的，术语“标称粉末剂量”为保持在胶囊中的粉末的总量。如本文所使用的，术语“标称药物剂量”为包含在标称粉末剂量中的药物（例如左旋多巴）的总量。标称粉末剂量通过粉末中药物的负载百分比与标称药物剂量相关。

[0026] 在一个实施方案中，标称粉末剂量按干重计为 25-50mg。在另一个实施方案中，标称粉末剂量按干重计为 25-40mg。在又一个实施方案中，标称粉末剂量按干重计为 30-35mg 或按干重计 32-38mg。

[0027] 另一种用于测量空气传播颗粒的尺寸分布的方法是多平台液体撞击取样器 (MSLI)。多平台液体撞击取样器 (MSLI) 与 Anderson 阶式冲击取样器 (ACI) 以相同的原理来工作，但是在 MSLI 中具有五个平台而非八个平台。另外，每个 MSLI 平台由甲醇润湿的玻璃料构成，代替每个平台由实心板构成。润湿平台用于防止使用 ACI 时可能发生的反弹和二次夹带。MSLI 用于提供粉末的流速相关性的指示。这可以通过以下方式来实现：在 30、60 和 90L/min 下操作 MSLI 并且测量在平台 1 上和收集过滤器上收集的粉末的分数。如果在不同流速下每个平台上的分数保持相对恒定，则粉末被认为是接近流速无关性。

[0028] 在一个实施方案中，本发明的可吸入粉末具有小于约 0.075g/cm^3的振实密度。例如，颗粒具有在 0.02g/cm^3和 0.075g/cm^3之间、在 0.02g/cm^3和 0.05g/cm^3之间、在 0.03g/cm^3和 0.06g/cm^3之间、在 0.03g/cm^3和 0.04g/cm^3之间、或小于约 0.05g/cm^3的振实密度，或小于约 0.04g/cm^3的振实密度、小于约 0.03g/cm^3的振实密度。可以通过使用本领域技术人员已知的仪器测量振实密度，如双平台微处理器控制的振实密度测试仪 (Dual Platform Microprocessor Controlled Tap Density Tester)(Vankel,N.C.) 或

[0029] GEOPYC™仪器 (Micrometrics Instrument Corp.,Norcross,GA,30093)。振实密度是对包封质量密度的标准量度。可以使用 USP Bulk Density and Tapped Density,United

States Pharmacopia Convention,Rockville,Md., 第 10 次增刊,4950-4951,1999 的方法来测定振实密度。可以有助于降低振实密度的特征包括不规则表面纹理和多孔结构。各向同性颗粒的包封质量密度被定义为,颗粒的质量除以其可以被封闭在内的最小球体包封体积。在本发明的一个实施方案中,颗粒具有小于约 0.4g/cm^{3}的包封质量密度。

[0030] 本发明的可吸入粉末具有优选的颗粒尺寸,例如至少约 1 微米(μm)的体积中值几何直径(VMGD)。在一个实施方案中,VMGD 大于 5μm。在其它实施方案中,VMGD 在约 5μm 和 30μm 之间、在约 5μm 和 10μm 之间、在约 7μm 和 15μm 之间,以及在约 7μm 和 12μm 之间。喷雾干燥颗粒的直径,例如 VMGD,可以使用激光衍射仪测量(例如 Helos,由 Sympatec,Princeton,N.J. 制造)。其它用于测量颗粒直径的仪器是本领域熟知的。样品中的颗粒的直径范围将取决于诸如颗粒组成以及合成方法等这些因素。可以选择样品中颗粒尺寸的分布以允许最佳沉积至呼吸道内的靶向位点。

[0031] 本发明的可吸入粉末的颗粒优选具有“质量中值空气动力学直径”(MMAD),本文也称为“空气动力学直径”,其在约 1μm 和约 5μm 之间或包括在约 1μm 和约 5μm 之间的任何子区间。例如,MMAD 在约 1μm 和约 3μm 之间,或 MMAD 在约 3μm 和约 5μm 之间。在一个实施方案中,MMAD 在 1.5μm 和 2.5μm 之间。在实验上,可以通过采用重力沉降法,由此使用全部粉末颗粒沉降一定距离的时间来直接推断颗粒的空气动力学直径来确定空气动力学直径。用于测量质量中值空气动力学直径(MMAD)的间接方法是多平台液体撞击取样器(MSLI)。可以由以下公式计算空气动力学直径 d_{aer}

[0032] $$d_{aer} = d_g \sqrt{\rho_{tap}}$$

[0033] 其中,d_g是几何直径,例如 MMGD,而 ρ 是粉末密度。

[0034] 通常通过喷雾干燥生产用于本发明的胶囊中的粉末。在一些情况下,喷雾干燥可以产生极干燥颗粒,所述干燥颗粒可能具有差的处理特性,并且可能很难以密集方式压成胶囊。具有指定水分含量的氮源可以流过、穿过或通过干粉以为干粉增加特定水分含量。这种水分可以提供所需的粉末工作密度。根据本发明的喷雾干燥方法描述于本文的实施例和美国专利号:6,848,197 和 8,197,845 中,所述美国专利以引用的方式并入本文。

[0035] 例如,如上所述的包含左旋多巴的可吸入粉末,用于填充适用于吸入器的胶囊。本文使用的术语“胶囊材料”指的是制成用于吸入的胶囊的外壳的材料。在一个实施方案中,根据本发明的胶囊材料选自明胶、纤维素衍生物、淀粉、淀粉衍生物、壳聚糖和合成塑料。

[0036] 如果使用明胶作为胶囊材料,根据本发明的实例可以选自聚乙二醇(PEG)、PEG-3350、甘油、山梨糖醇、丙二醇、PEO-PPO 嵌段共聚物和其它多元醇和聚醚。如果使用纤维素衍生物作为胶囊材料,那么根据本发明的实例可以选自羟丙基甲基纤维素(HPMC)、羟丙基纤维素、甲基纤维素、羟甲基纤维素和羟乙基纤维素。如果使用合成塑料作为胶囊材料,那么根据本发明的实例可以选自聚乙烯、聚碳酸酯、聚酯、聚丙烯和聚对苯二甲酸乙二醇酯。在一个实施方案中,胶囊材料还包含二氧化钛。在一个优选实施方案中,胶囊包含 HPMC 和二氧化钛。在一个实施方案中,胶囊包含角叉菜胶。在另一个实施方案中,胶囊包含氯化钾。在另一个实施方案中,胶囊包含 HPMC、角叉菜胶、氯化钾和二氧化钛。在一个实施方案中,胶囊尺寸选自 000、00、0、1 或 2。在一个具体实施方案中,胶囊尺寸为 00。

[0037] 在一个具体实施方案中,胶囊为羟丙基甲基纤维素(HPMC)胶囊。在另一个具体实施方案中,胶囊为羟丙基甲基纤维素 00 尺寸胶囊。在一个具体实施方案中,胶囊材料包含

HPMC 和二氧化钛，并且胶囊尺寸为 00。

[0038] 在一个实施方案中，00 胶囊含有按干重计在 15 和 50 克之间的左旋多巴。在另一个实施方案中，00 胶囊含有按干重计在 20 和 40 克之间的左旋多巴。在另一个实施方案中，00 胶囊含有在按干重计 25 和 35 克之间的左旋多巴。在另一个实施方案中，00 胶囊含有按干重计约 30、31、32、33、34、35、36、37、38、39 或 40 克的左旋多巴。

[0039] 在本发明的一个方面，粉末具有低静电荷以实现从胶囊中的高度分散。

[0040] 本发明的胶囊尤其适用于向患有例如帕金森病和需要用左旋多巴治疗的患者递送包含左旋多巴的干粉组合物的干粉吸入器。需要治疗的患者可能需要针对帕金森病的维持性治疗或针对帕金森病的挽救性治疗，这例如将是在由帕金森病引起的急性和 / 或僵冻发作的情况下所需要的。在一个实施方案中，胶囊用于干粉吸入器以向患者递送单次呼吸有效量的干粉组合物，如以引用的方式并入文本的美国专利号 6,858,199 和 7,556,798 所述。

[0041] 如本文所用，术语“有效量”意指达到期望效果或功效所需的量。药物的实际有效量可以根据所采用的具体药物或其组合、配制的特定组合物、施用方式和患者的年龄、体重和病状，以及所治疗的发作的严重程度而改变。就多巴胺前体、激动剂或其组合而言，有效量是减少了需要治疗的帕金森症状的量。用于特定患者的剂量在本文进行描述，并可由本领域的普通技术人员使用的常规考虑（例如借助于合适的、常规药理学方案）来决定。例如，口服左旋多巴的有效量范围为约 50 毫克 (mg) 至约 500mg。在许多情况下，正在进行（口服）的左旋多巴治疗方案通常为每日 100mg，八 (8) 次。

[0042] 可以在时间上同时或连续地施用不止一种多巴胺前体、激动剂或其组合，特别是左旋多巴、卡比多巴、阿朴吗啡和其它药物。例如，通常施用卡比多巴或苄丝肼以确保外围羧化酶活性被完全停止。可以采用肌内、皮下、口服和其它施用途径。在一个实施方案中，这些其它药剂被递送至肺部系统。可以之前、之后或同时施用这些化合物或组合物。在优选实施方案中，施用至呼吸道的颗粒包括左旋多巴和卡比多巴。本文使用的术语“共施用”意指间或施用特定的多巴胺前体、激动剂或其组合和 / 或其它组合物以治疗发作以及本文所述的潜在病状。

[0043] 在一个实施方案中，长期左旋多巴治疗包括使用在干粉吸入器中的用于肺部递送左旋多巴与口服卡比多巴的组合的本文所述药物组合物。在另一个实施方案中，在发作期间提供左旋多巴的肺部递送，而长期治疗可以采用左旋多巴 / 卡比多巴的常规口服施用。在另一个实施方案中，长期左旋多巴治疗包括使用在干粉吸入器中的用于肺部递送左旋多巴与口服苄丝肼的组合的本文所述药物组合物。在另一个实施方案中，在发作期间提供左旋多巴的肺部递送，而长期治疗可以采用左旋多巴 / 苄丝肼的常规口服施用。

[0044] 通过参照以下非限制性实施例可进一步理解本发明。

实施例

[0045] 实施例 1. 工艺一 :粉末制备

[0046] 使左旋多巴和 DPPC 在室温下 30 分钟，此后称重所需量的水和乙醇并分别转移至带夹套的水相进料容器和不带夹套的有机相进料容器中。将水相容器上的夹套设定为 55℃，并且使称重的水升温至 52.5℃，随后将所需量的氯化钠和左旋多巴加入至水相容器

中，并且将所需量的 DPPC 加入至有机相容器中，并且通过搅拌使它们都溶解。用维持在 70scfh 的氮气吹扫水相进料容器的顶部空间。

[0047] 通过发起干燥气流（设定为 95kg/h）和排气来启动喷雾干燥，并且将用于干燥气体的加热器设定至 125℃。打开产品过滤加热器并设定至 60℃，并且打开液体滑动加热器并设定至 55℃。在喷雾干燥器出口温度达到 80℃后，启动雾化气体（设定为 22g/min）和空白溶剂（水相流速＝ 28mL/min 并且有机相流速＝ 42mL/min）并使其稳定，并且使得系统冷却且稳定至出口温度为 52.5℃。启动产品过滤器脉冲，并且将产品过滤器的吹扫流量设定至 15scfh。在系统稳定在 52.5℃后，切换液体滑动入口至进料溶剂。表 1 总结了在整个操作期间维持的参数。

[0048]

工艺参数 (OC)	目标值
入口温度 (℃)	125.0
出口温度 (℃)	52.5
干燥气体流速 (kg/h)	95.0
腔室压力 ("wc)	-2.0
雾化气体流速 (g/min)	22.0
水相流速 (mL/min)	28.0
有机相流速 (mL/min)	42.0
产品过滤器吹扫流量 (scfh)	15.0

[0049] 表 1 :喷雾干燥的工艺参数

[0050] 在 20℃和 15％的相对湿度的控制条件下，每小时收集喷雾干燥粉末并转移至较大的容器。进料溶剂用完后，切换液体滑动入口至空白溶剂并允许进行约 10 分钟，在此期间收集并合并最终粉末。在空白溶剂 10 分钟后，通过关闭液体管线、雾化气体、干燥气体加热器、干燥气体入口，最后是排气装置来启动系统关闭。

[0051] 此过程产生含有约 3.4 重量％水的粉末。

[0052] 实施例 2. 工艺二 :利用特殊干燥的粉末制备

[0053] 使左旋多巴和 DPPC 在室温下 30 分钟，此后称重所需量的水和乙醇并分别转移至带夹套的水相进料容器和不带夹套的有机相进料容器中。将水相容器上的夹套设定为 55℃，并且使称重的水升温至 52.5℃，随后将所需量的氯化钠和左旋多巴加入至水相容器中，并且将所需量的 DPPC 加入至有机相容器中，并且通过搅拌使它们都溶解。用维持在 70scfh 的氮气吹扫水相进料容器的顶部空间。

[0054] 通过发起干燥气流（设定为 95kg/h）和排气来启动喷雾干燥，并且将用于干燥气体的加热器设定至 125℃。打开产品过滤器和优化的吹扫气体加热器并设定至 60℃，并且

打开液体滑动加热器并设定至55℃。在喷雾干燥器出口温度达到80℃后，启动雾化气体（设定为22g/min）、空白溶剂（水相流速＝28mL/min并且有机相流速＝42mL/min）和优化的干燥气体（设定为70kg/h）并使其稳定，并且使得系统冷却且稳定至出口温度为52.5℃。启动产品过滤器脉冲，并且将产品过滤器的吹扫流量设定至15scfh。在系统稳定在52.5℃后，切换液体滑动入口至进料溶剂。表2总结了在整个操作期间维持的参数。

[0055]

工艺参数(OC)	目标值
入口温度(℃)	125.0
出口温度(℃)	52.5
干燥气体流速(kg/h)	95.0
腔室压力("wc)	-2.0
雾化气体流速(g/min)	22.0
水相流速(mL/min)	28.0

[0056]

有机相流速(mL/min)	42.0
优化的干燥吹扫速率(kg/h)	70.0
优化的干燥吹扫温度(°C)	52.5
产品过滤器吹扫流量(scfh)	15.0

[0057] 表2：喷雾干燥的工艺参数

[0058] 在20℃和15％的相对湿度的控制条件下，每小时收集喷雾干燥粉末并转移至较大的容器。进料溶剂用完后，切换液体滑动入口至空白溶剂并允许进行约10分钟，在此期间收集并合并最终粉末。在空白溶剂10分钟后，通过关闭液体管线、优化的干燥气体、雾化气体、干燥气体加热器、干燥气体入口，最后是排气装置来启动系统关闭。

[0059] 此工艺产生包含约2.2重量％水的粉末。水含量的这种1％的降低使得产品稳定性显著改善。

[0060] 样品1：基于松散粉末（预先填充）：

[0061] VMGD＝10.2μm；并且

[0062] 振实密度＝0.033g/cm^3。

[0063] 样品2：相同但是使用在填充批次(60031)上测量的VMGD：

[0064] VMGD＝8.6μm；并且

[0065] 振实密度＝0.033g/cm^3。

[0066] 样品1.由阻抗为0.2的干粉吸入器发射的粉末(28.3LPM)：

[0067] VMGD＝9.4μm；并且

[0068] 振实密度＝0.048g/cm^3。

[0069] 样品2.由阻抗为0.2的干粉吸入器发射的粉末(60LPM)：

[0070] VMGD＝8.8μm；并且

[0071] 振实密度＝0.042g/cm^3。

[0072] 上述颗粒对于肺部产品是非常低密度的。这些非常低密度的颗粒对于包装到胶囊中是有利的。由于低密度，从吸入器发射之前这些颗粒可以被解聚或剪切。这些解聚/剪

切的颗粒具有良好的流动特性和至肺部的预期沉积。

[0073] 虽然本发明已参考其优选实施方案进行具体显示和描述，但是本领域技术人员应了解，可在不脱离由随附权利要求书所涵盖的本发明的范围的情况下在形式和细节方面在其中做出各种改变。还应理解本文所述的实施方案不是相互排斥的，而且根据本发明，来自各种实施方案的特征可全部或部分地组合。

Abstract

The invention provides pharmaceutical compositions for pulmonary delivery comprising particles containing a pharmaceutical agent and having a geometric size of greater than about 5 μm and a tap density of less than about 0.075 g/cm3. The invention also provides methods for delivering the pharmaceutical compositions of the invention to the respiratory tract of a patient.