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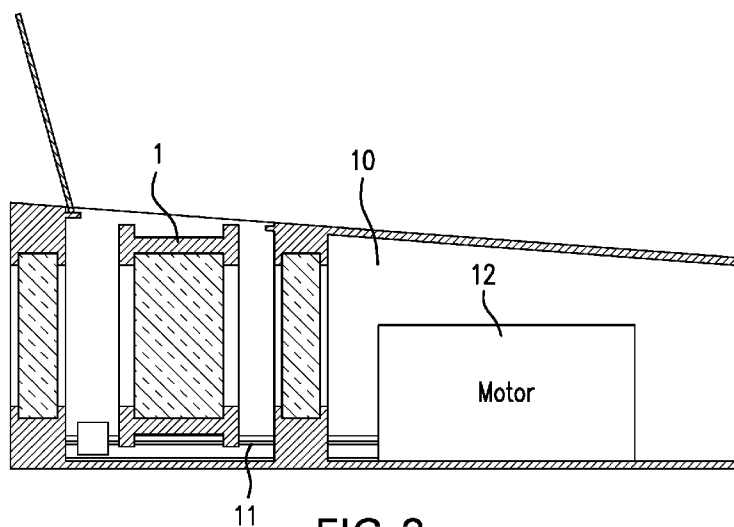
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(54) Title: CONTROLLED AGGLOMERATION OF MICRONIZED DRUG OR DRUG-EXCIPIENT MIXTURES

**FIG. 2**

(57) Abstract: The invention provides a process for preparing powder agglomerates from a rotating apparatus, comprising: loading dried particulate material having a diameter less than 5 μm into an enclosed chamber arranged about a horizontal axis; rotating the enclosed chamber around the horizontal axis for at least 300 revolutions to form the powder agglomerate; and discharging the powder agglomerate from the apparatus. The powder agglomerates are useful for preparation for common pharmaceutical dosage forms, especially dried powder dosage form for dry powder inhalers.



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CONTROLLED AGGLOMERATION OF MICRONIZED DRUG OR DRUG-EXCIPIENT MIXTURES

FIELD OF THE INVENTION

5 The present invention relates to a process for preparing powder agglomerates from a rotating apparatus. The powder agglomerates formed by the process of the present invention are useful for preparing common pharmaceutical dosage forms, especially dried powder dosage forms for dry powder inhalation.

BACKGROUND OF THE INVENTION

10 Micron-sized drug and/or excipient particles are widely used in the pharmaceutical industry in a multitude of applications. Common dosage forms which contain such particles include oral dosage forms, *e.g.*, tablets and capsules, topical dosage forms, *e.g.*, creams, injectable dosage forms, *e.g.*, suspensions, and inhalation dosage forms, *e.g.*, dry powder
15 dosage forms and metered dose inhaler forms.

 For oral dosage forms such as tablets, capsules and suspensions, micronization increases the effective surface area of the active pharmaceutical ingredient (API) and results in a better dissolution rate and bioavailability. Due to increased bioavailability of the API, the dosage form requires a smaller amount of API, which in turn results in a more cost-effective
20 product, and a lower exposure of the patient to the API.

 Likewise, drug particles administered in dry powder inhalers, metered dose inhalers, and nebulizers require drug particles to be in the micron size range to allow their passage into the deeper respiratory tract and thus, achieve the desired pharmacological effect.

 Comminuting drug and/or substances into small particles, and then processing the
25 particles into the desired dosage forms poses several challenges. As the mean size of the particles decrease to the lower micron range, inter-particulate forces exceed the gravitational forces exerted on these particles, which causes the powders to flow poorly in drug product processing steps. This phenomenon hinders the physical handling, storage and downstream processing through unit operations such as passage through hoppers, compression into tablets, filling of capsules or sachets, and metering into dry-powder inhalers. Poor flow characteristics of
30 micron-sized particles impede the accurate metering of drug-containing formulation into the dosage form or device, *e.g.*, an inhalation device.

 Agglomeration of powders enlarges the size of the materials to be processed and improves the flow properties of the complexed, micronized particles. Common agglomeration

methods often involve use of tertiary processes, such as addition of binders (*e.g.*, during wet granulation) or introduction of mechanical forces, *e.g.*, roller compaction, that cause the primary particles to bind to each other even more strongly. The properties of agglomerates resulting from such common methods hinder the dispersion into primary particles after administration to the patient. Ideally, an optimized agglomeration process results in particles which are strong enough to have adequate flow, storage, handling, and metering characteristics, yet are weak enough to readily disperse into primary particles upon interaction with physiological fluid (*e.g.*, disintegration for oral solid dosage forms upon contact with gastrointestinal fluids), or upon actuation of an inhaler.

A number of processes for controlled agglomeration exist or have been proposed. Typically, these processes include agitating a powder bed in a horizontal, parallel plane resulting in a circular or elliptical flow pattern of the powder bed. Interactive energy distributes into the powder bed contained in a vessel by vibrations and/or shear. These processes suffer from inhomogeneous distribution of the interactive energy throughout the powder bed which results in agglomerates having variable powder properties. In addition, the effective operating parameters that provide agglomerates of suitable properties often restrict the quantities of agglomerates that can be prepared since scale-up of such processes only exacerbates the variability in the resulting powder agglomerates' properties.

Prior art devices for preparing agglomerates frequently utilize spheronizers driven primarily by competing radial and inertial forces in the horizontal plane which coagulate particles into agglomerates and round them off by particle-particle and particle-wall interactions. For example, certain devices depicted in FIG. 1A have a spinning horizontal disc (1) with a vertical rotational axis (2) onto which a wet or dry mass of material is metered for agglomeration and/or spheronization. The metered mass spins with a spiral pathway and immediately fans out from the center of the disc only to be contained by the vertical wall (3) of the spheronizer. Inter-particle collisions and particle-wall interactions cause the particles to then coagulate, densify, and round off over time.

Another prior art device commonly used for preparing agglomerates is depicted in FIG. 1B. The device has a disc (1) which orbits in the horizontal plane, traveling in elliptical orbit (4) about a vertical rotational axis (2), causing the metered mass to travel in swirls (eddies) between the center of the disc and the wall of the spheronizer (3). In similar fashion to the spinning disc type device described above, inter-particle collisions and particle-wall interactions cause the particles to then coagulate, densify, and round off over time.

In both the aforementioned devices having a vertical rotational axis, due to inverse proportionality, radial forces attenuate with increasing distance from the center of rotation. This phenomenon effectively limits the size and capacity of any such spheronizer device and, hence, batch scaling is a last resort for increasing capacity.

5 U.S. Patent No. 4,161,516 to John H. Bell discloses, *inter alia*, a medicament in pellet form characterized in that the pellet form is soft, and comprises an agglomeration of individual medicament particles have a diameter of less than 10 microns. The patent discloses that the soft pellets can be prepared by controlled agglomeration of particles of medicament which are either intrinsically or have been rendered, self-agglomerative to a controlled
10 agglomeration.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a process for preparing powder agglomerates from a rotating apparatus comprising:

15 loading dried particulate material having a diameter less than 5 μm into a chamber arranged about a horizontal axis;

rotating the chamber around the horizontal axis for at least 300 revolutions to form the powder agglomerate; and

discharging the powder agglomerate from the chamber.

20 The present invention provides a process which is highly scaleable since it allows preparation of both small and large quantities of powder agglomerates with minimal process development. The inventive process also provides powder agglomerates of consistent quality which have excellent flow characteristics. In addition, the process results in powder agglomerates which have sufficient strength to withstand packaging and storage and yet, retain
25 sufficient softness to disperse into primary particles on mixing with physiological fluids or upon discharge from an inhaler or nebulizer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A is a depiction of a prior art spheronizing apparatus in which a chamber
30 charged with the granular material spins in the horizontal plane about a vertical rotational axis.

FIG. 1B is a depiction of a prior art spheronizing apparatus in which a chamber charged with the granular material spins with an elliptical orbit in the horizontal plane about a vertical rotational axis.

FIG. 2 depicts an apparatus (10) useful for conducting the process of the present invention.

FIG. 3 is an enlarged and cutaway view of the apparatus depicted in FIG. 2.

FIG. 4 is a cut-way view depicting an enclosed chamber used in one embodiment
5 of the process of the present invention.

FIG. 5 is a graph showing the size distribution of powder agglomerates obtained from lactose and resulting from the process of the present invention.

FIG. 6 is a graph showing the size distribution of powder agglomerates obtained from mometasone furoate and resulting from the process of the present invention.

FIG. 7 is a graph showing the size distribution of powder agglomerates obtained
10 from a blend of montelukast and lactose and resulting from the process of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

15 The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated.

20 As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

As used herein, a “patient” is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal.

25 As used herein, the term "therapeutically effective amount" as used herein, refers to an amount of the active pharmaceutical ingredient, or a composition thereof, that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a patient suffering from a disease or condition. .

30 As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

As used herein, “dried particulate material” refers to particles having a mean diameter of approximately 1-5 μm , wherein the particles have a moisture content of less than 5% by weight.

As used herein, the term “powder agglomerate” refers to a bound mass of small particulates.

Methods for Forming the Powder Agglomerates

As discussed above, the present invention involves, *inter alia* to a process where dried particulate material is rotated in an enclosed chamber arranged about a horizontal axis. In contrast to prior art processes for preparing agglomerates described above, the process of the present invention allows preparation of greater quantities of powder agglomerates with minimal process development upon scaling up.

FIG. 2 depicts an apparatus (10) useful for conducting the process of the present invention. FIG. 3 is an enlarged and cutaway view of the same apparatus where the chamber (1) rests on two cylinders (11). A motor (12), also housed in the apparatus, is connected to the cylinders. Operation of the motor drives the cylinders in a circular pathway which in turn spins the chamber in the opposite direction about its horizontal axis (2).

FIG. 4 depicts a cutaway view of the chamber of one embodiment used in the process of the present invention. The chamber (1) contains a powder bed (5) of the dried particulate material that rotates about a horizontal axis (2). At a critical incline, stress-strain vectors due to gravity and moment-induced shear surpass the cohesiveness of the granular material, causing a dislocation and subsequent cascade of particles down the incline of the powder bed. As such, the powder avalanche is a form of stress relaxation. This cascade is restricted to a small region which is the sliding plane at the top of the powder bed (exposed surface). The remainder of the granular bed remains essentially motionless. This point of the powder bed is referred to as the “curl” (5a). While not wishing to be bound by any specific theory, the applicants believe the scale-invariant nature of the inventive process results from the avalanche since the slip plane is irrespective of granular bed depth or chamber size. In a revolving vertical cylinder such as the one depicted in FIG. 2, continuous avalanching leads to a complete reshuffling of the powder bed so that essentially all of the material experiences a series of avalanches. Particle-particle interactions in the process of the present invention lead to coalescence, densification, and rounding off to yield the powder agglomerates.

In one embodiment the dried particulate material to be agglomerated is first passed through a coarse sieve to loosen the material before being loaded in the chamber. For instance the dried particulate material can be passed through an ASTM-16 sieve or a sieve having similar pore sizes. Typically, this sifting step is performed with gentle shaking which can be performed either mechanically or manually.

Prior to the agglomeration, adding water to the particulate material such as by providing a humidifying environment, is not required. The substantial absence of water in the process can result in a powder agglomerate which has a longer shelf-life than does powder agglomerate prepared with the addition of water to make the particulate material self-

5 agglomerative. The absence of water avoids physical, chemical, and microbial degradation processes which result from the presence of water in the final formulation (*e.g.*, mold processes, hydrolysis, capillary binding).

In some embodiments of the present invention, the dried particulate material is agglomerated in the presence of less than 3% by weight, *e.g.*, less than 1% by weight, of a

10 binder.

The dried particulate material is loaded into the chamber having a horizontally disposed longitudinal axis. The chamber is enclosed and can comprise a cylindrical shape or spherical shape. Alternatively, the enclosed chamber can be an ovoid, having an egg shape. In some embodiments, the chamber can be fitted with a wire mesh, for example, a metallic wire

15 mesh, to prevent wall effects, such as electrostatic attraction or particle-wall friction.

For preparing smaller scale quantities of powder agglomerates (*e.g.*, less than 200 g), the operator can simply manually load the desired quantity of the dried particulate material. For larger scale operations, conveyor or screw feeder systems introduce the material into the chamber. In some embodiments, the loading of the particulate powder fills about 20 to 75% of

20 the volume of the chamber. In certain embodiments, the particulate material fills no more than 60% of the chamber's volume. In specific embodiments, the particulate material fills no more than 50% of the chamber's volume.

In some embodiments of the present invention at least 200 g of dried particulate material is loaded into the chamber, such as 200 g to 200 kg of dried particulate material. In

25 certain embodiments, at least 500 g of dried particulate material is loaded into the chamber. In certain embodiments at least 10 kg of dried particulate material is loaded into the chamber.

The apparatus having the chamber includes a drive mechanism (*e.g.*, a rotating shaft) for rotating the enclosed chamber about the horizontal axis for at least 300 revolutions, for example, for about 300 to about 60,000 revolutions. In some embodiments the enclosed

30 chamber is rotated for at least 600 revolutions. The enclosed chamber is typically rotated about the horizontal axis at a speed of at least 5 rpm and no more than 150 rpm. For example, in some embodiments, the enclosed chamber is rotated at from 10 to 120 rpm, and in other embodiments, at from 30 to 100 rpm.

Counting the number of powder avalanches provides another alternative for determining the duration of the process of the present invention. Typically, the chamber is rotated until at least 600 powder avalanches occur before discharging the powdered agglomerate. In some embodiments, the chamber is rotated until at least 900 powder avalanches occur. If the chamber contains at least one glass wall, the powder avalanches can be counted manually or by using electronic sensing devices.

The powder agglomerate formed the process of the present invention can further include the step of agitating the discharged powder agglomerate from the chamber and on to a mesh screen to separate it from the residual particulate material (also referred as “fines”).

Typically, the screen has an aperture width between 200 to 1000 microns.

In some embodiments, the process of the present invention comprises transferring the discharged powder agglomerate into a container for storing or further processing a therapeutic agent. For example, the discharged powder agglomerate can be transferred into a dry powder inhaler reservoir, a tableting die, a capsule, a sachet, or a vial for injection.

Useful powder agglomerates produced by the process of the present invention include agglomerates ranging in size from between about 15 μm to 3 mm, such as from 100 to about 1500 μm . In some embodiments, the powder agglomerates have an average size of between about 300 and about 1,000 μm .

Typically, the bulk densities of the powdered agglomerates resulting from the process of the present invention are from 0.1 to 0.5 g/mL, preferably a bulk density of 0.2 to 0.4 g/mL.

Preferably, the powder agglomerates prepared by the present invention have a tight agglomerate size distribution. In some embodiments, no more than about 10% of the agglomerates are 50% smaller or 50% larger than the mean or target agglomerate size. For example, for an agglomerate of 300 μm , no more than about 10% of the agglomerates will be smaller than about 150 μm or larger than about 450 μm .

Dv stands for volume diameter of the agglomerates. DvX is the volume diameter below which X percent of the log normal cumulative size distribution falls. Dv90 is the volume diameter below which 90 percent of the log normal cumulative size distribution falls. Dv50 is the volume diameter below which 50 percent of the log normal cumulative size distribution falls. Dv10 is the volume diameter below which 10 percent of the log normal cumulative size distribution falls. Thus, Dv90 is defined to mean that at least about ninety percent of the powdered agglomerates have an agglomerate size of less than a certain agglomerate size. Thus,

Dv50 is defined to mean that at least 50% of the powdered agglomerates have an agglomerate size of less than a certain agglomerate size.

Various embodiments of the present invention provide for powdered agglomerates useful in dry powder inhalers or other dosage forms, wherein the agglomerate includes at least one excipient and at least one active pharmaceutical ingredient that have a Dv90 less than about 1200 microns (μm), or less than about 1000 microns (μm).

Various embodiments of the present invention provide for powder agglomerates useful in dry powder inhalers or other dosage forms, wherein the agglomerate includes at least one pharmaceutically acceptable excipient and at least one active pharmaceutical ingredient that has Dv50 of less than about 5 microns (μm) or less than about 3 microns (μm).

Such agglomerate formulations are useful in dry powder inhaler systems, such as the TWISTHALER®, sold by Merck Sharp & Dohme Corp., Whitehouse, New Jersey, U.S.A.

The powdered agglomerates resulting from the process of the present invention expand the available administration options for various pharmaceutical active ingredients as well as pharmaceutically acceptable excipients which are used in mixtures therewith. For example, suitable drugs include those having poor bioavailability due to the drugs' limited water-solubility. After being blended with excipients if necessary, and agglomerated, the drug-containing compositions are then formed into traditional oral dosage forms including tablets, capsules, and powder sachets.

In addition, the powdered agglomerates can be incorporated to form drug products where a smaller image size has a higher drug load, since the process results in agglomerates having a higher drug load due to the fact that agglomeration formed according to the process of the present invention require a lower concentration of excipients.

In some embodiments of the process of the present invention, powdered agglomerates are prepared which include drugs that require delivery deep in the respiratory tract, preferably through powder inhalation such as inhaled corticosteroids, long acting beta agonists, long acting muscarinic agents, medium acting beta agonists, spleen tyrosine kinase inhibitors (Syk), and combinations thereof. Other agents which may require delivery in the respiratory tract include drugs for the treatment of pulmonary hypertension, central nervous system disorders, asthma, and chronic obstructive pulmonary disease.

In some embodiments of the process of the present invention, the active pharmaceutical ingredients are selected from corticosteroids, dissociated steroids, β -agonists, anticholinergics, leukotriene antagonists, spleen tyrosine kinase (Syk) inhibitors, Janus kinase

(JAK) inhibitors, Phosphodiesterase (PDE) Inhibitors, Soluble Guanylate Cyclase (sGC) modulators, serotonergic agents, antibiotics, and inhalable proteins or peptides.

In another embodiment, the active pharmaceutical ingredients are selected from glycopyrrolate, ciclesonide, indacaterol, tiotropium, mometasone furoate, beclomethasone dipropionate, budesonide, fluticasone, dexamethasone, flunisolide, triamcinolone, salbutamol, albuterol, terbutaline, salmeterol, bitolterol, ipratropium bromide, oxitropium bromide, sodium cromoglycate, nedocromil sodium, montelukast, zafirlukast, pranlukast, formoterol, eformoterol, bambuterol, fenoterol, clenbuterol, procaterol, broxaterol, (22R)-6 α ,9 α -difluoro-11 β , 21-dihydroxy-16 α ,17 α -propylmethylenedioxy-4-pregnen-3,20-dione, TA-2005, tipredane, insulin, interferons, calcitonins, parathyroid hormones, sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, avitriptan, tobramycin, and granulocyte colony-stimulating factor.

In another embodiment, the active pharmaceutical ingredients are selected from glycopyrrolate, ciclesonide, indacaterol, tiotropium, mometasone furoate, budesonide, fluticasone, triamcinolone, salmeterol, montelukast, zafirlukast, pranlukast, rizatriptan, tobramycin, and formoterol.

In certain embodiments of the present invention the active pharmaceutical ingredient is a corticosteroid, such as mometasone furoate. Mometasone furoate is an anti-inflammatory corticosteroid having the chemical name, 9,21-Dichloro-11(β), 17-dihydroxy-16(α)-methylpregna-1,4-diene-3,20-dione 17-(2 furoate). It is practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone and chloroform; and freely soluble in tetrahydrofuran. Its partition coefficient between octanol and water is greater than 5000. Mometasone can exist in various hydrated (*e.g.*, as a monohydrate), crystalline and enantiomeric forms.

Several of these compounds could be administered in the form of pharmacologically acceptable esters, salts, solvates, such as hydrates, or solvates of such esters or salts, if any. The term is also meant to cover both racemic mixtures as well as one or more optical isomers. The drug in accordance with the present invention can also be an inhalable protein or a peptide such as insulin, interferons, calcitonins, parathyroid hormones, granulocyte colony-stimulating factor and the like. "Drug" as used herein may refer to a single pharmacologically active entity, or to combinations of any two or more, an example of a useful combination being a dosage form including both a corticosteroid and a β -agonist.

Percentages are expressed on a weight basis, unless the context clearly indicates otherwise. The mention of any specific drug substance in this specification or in the claims is

intended to encompass not only the base drug, but also pharmaceutically acceptable salts, esters, hydrates and other forms of the drug. Where a particular salt or other form of a drug is mentioned, it is contemplated that other salts or forms can be substituted.

The amount of drug administered will vary with a number of factors including, without limitation, the age, sex, weight, condition of the patient, the drug, the course of treatment, the number of doses per day and the like. For mometasone furoate, for instance, the amount of drug delivered per dose, *i.e.*, per inhalation, will generally range from about 10 µg to about 10,000 µg. Doses of 25 µg, 50 µg, 75 µg, 100 µg, 125 µg, 150 µg, 175 µg, 200 µg, 250 µg, 300 µg, 400 µg and/or 500 µg are preferred.

While it is possible that for use in therapy, that the active pharmaceutical ingredient as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides a pharmaceutical composition, which comprises an active pharmaceutical ingredient and a pharmaceutically acceptable excipient. The excipients must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In some embodiments of the process of the present invention, the dried particulate material to be agglomerated contains only the active pharmaceutical ingredient. In other embodiments of the process, the dried particulate material contains a blend of the active pharmaceutical ingredient and one or more pharmaceutically acceptable excipients.

In still other embodiments of the process, the dried particulate material contains only one or more pharmaceutically acceptable excipients. The resulting powder agglomerate containing the one or more pharmaceutically acceptable excipients can be used in further processing steps for preparing useful pharmaceutical dosage forms.

In one embodiment, the excipient used in the process is selected from polyhydroxy aldehydes, and polyhydroxy ketones. Preferred polyhydroxy aldehydes and polyhydroxy ketones include hydrated and anhydrous saccharides selected from lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, mannitol, melezitose, starch, xylitol, mannitol, myoinositol, their derivatives, and the like. In a specific embodiment, the process is conducted with lactose.

In another embodiment, the excipient is selected from sorbitol, xylitol, and mannitol.

The pharmaceutically acceptable excipient in accordance with the present invention is typically provided in, or reduced to, a particle size which is roughly congruent with the size of the particles of the active pharmaceutical ingredient as previously described.

For example, agglomerates of mometasone furoate anhydrous USP will preferably
5 be provided having particles of at least $80\% \leq 5 \mu\text{m}$ and at least $95\% \leq 10 \mu\text{m}$ (measured by volume distribution). The excipient, such as anhydrous lactose, NF will be provided having particles of at least $60\% \leq 3 \mu\text{m}$, at least 80% under $5 \mu\text{m}$, and at least $95\% \leq 10 \mu\text{m}$. The average particle size is roughly the same for both and is less than $5 \mu\text{m}$.

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical
10 composition for inhaled administration can be incorporated into a plurality of sealed dose containers (*e.g.*, containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of *e.g.*, the dry powder composition can be administered by inhalation via the device such as the DISKUS® device (GlaxoSmithKline). Other dry powder inhalers are well
15 known to those of ordinary skill in the art, and many such devices are commercially available, with representative devices including Aerolizer® (Novartis), Airmax™ (IVAX), ClickHaler® (Innovata Biomed), Diskhaler® (GlaxoSmithKline), Accuhaler (GlaxoSmithKline), Easyhaler® (Orion Pharma), Eclipse™ (Aventis), FlowCaps® (Hovione), Handihaler® (Boehringer Ingelheim), Pulvinal® (Chiesi), Rotahaler® (GlaxoSmithKline), SkyeHaler™ or Certihaler™
20 (SkyePharma), Twisthaler (Merck Sharp & Dohme Corp.), Turbuhaler® (AstraZeneca), Ultrahaler® (Aventis), and the like.

While the powdered agglomerates prepared by the process of the present invention are particularly useful for preparing powdered dosage form for dry powder inhalers, the agglomerates are also useful for preparing other dosage forms. Such dosage forms, for
25 example may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, topical, inhaled, nasal, ocular, or parenteral (including intravenous and intramuscular) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Dosage forms include tablets, troches, dispersions, suspensions,
30 solutions, capsules, creams, ointments, aerosols, and the like.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier

such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The active pharmaceutical ingredient can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Abbreviations and acronyms employed herein include the following:

aq = aqueous

g = grams

h = hour

μL = microliters

5 μm = micrometers

mg = milligrams

mL = milliliters

mm = millimeters

mmol = millimoles

10 min = minute

RT or rt = room temperature (ambient, about 25 °C)

EXAMPLES

While the present invention has been described in conjunction with the specific
15 embodiments set forth above, many alternatives, modifications and other variations thereof will
be apparent to those of ordinary skill in the art. All such alternatives, modifications and
variations are intended to fall within the spirit and scope of the present invention.

Preparation of Agglomerates

Three sets of powdered agglomerates were prepared. Sets 1 and 2 were simple
20 one component systems, where Set 1 contained lactose only, and Set 2 contained mometasone
furoate. Set 3 contained a uniformly blended binary mixture of montelukast and lactose in 40:60
w/w ratio. The components of all three sets had a particle mean size of 2-5 μm.

The components were passed through a 1.18 mm (ASTM-16M) sieve using gentle
manual shaking. For each of the three sets approximately 30 g of dried particulate material was
25 loaded into a transparent, plexiglass, cylindrical drum fitted with a a metallic wire grid on the
inner wall of the drum to prevent wall effects. The drum was part of an apparatus which was a
Revolution Powder Analyzer by Mercury Scientific, Model: Rev 2007. The drum was then
mounted on a rotating shaft and rotated about the horizontal axis at the defined speeds shown
below in Table 1. After completion of the rotations, the powdered agglomerates were emptied
30 on a 20M screen, and stored at ambient conditions prior to analysis. All runs were replicated
three times.

Table 1

Run	No. of Avalanches	Drum Speed (rpm)
-----	-------------------	------------------

1	1600	50
2	1600	25
3	1600	10

Bulk Density Determination

For bulk determination of the powdered agglomerates, a 10 mL graduated cylinder was filled with the powdered agglomerate. Bulk density values were calculated from the ratio of mass to volume of the agglomerates.

Determination of Size Distribution and Shape Factor

A QICPIC particle analyzer (Symnpattec GmbH, Clausthal-Zellerfeld, Germany) which analyzes size and shape using dynamic image analysis. Briefly, this instrument captures images of dry particles in a fast moving air stream with a high speed digital camera. For analysis of the size distribution of the powdered agglomerates, the volume diameter below which 90, 50 and 10 percent of the log normal cumulative size distribution of the agglomerate fell were measured.

For analysis of the shape factor distribution of the powdered agglomerates, sphericity is defined as the ratio between the perimeter of a circle that has the same projected area as the particle to the measured perimeter, and is thus a value between 0 and 1. The aspect ratio is defined as the ratio of the minimal and maximal Feret diameter, and is thus also between 0 and 1. Based on these definitions, both sphericity and aspect ratio of a sphere equal to 1. The sphericity distributions were determined at 90, 50, and 10 percent of the log normal cumulative sphericity distribution.

Results

Table 2A provides the physical characteristics of powdered agglomerate prepared from lactose (LAC) as the single component (Set 1) with the values in parentheses indicating the standard deviation. Figure 5 shows the size distribution of the Set 1 powdered agglomerates.

Table 2A

Run	Size (μm)			Bulk density (g/mL)	Shape		
	X10	X50	X90		X10	X50	X90
LAC-R1	389.52 (11.30)	589.38 (10.32)	804.55 (11.72)	0.36 (0.00)	0.65 (0.01)	0.87 (0.01)	0.95 (0.00)
LAC-R2	385.57 (30.72)	642.82 (22.58)	873.21 (3.27)	0.32 (0.00)	0.67 (0.01)	0.86 (0.00)	0.94 (0.01)
LAC-R3	380.89 (26.93)	625.78 (31.10)	856.09 (11.93)	0.32 (0.00)	0.73 (0.01)	0.88 (0.01)	0.93 (0.00)

Table 2B provides the physical characteristics of powdered agglomerate prepared from mometasone furoate (MF) as the single component (Set 2) with the values in parentheses indicating the standard deviation. Figure 6 shows the size distribution of the Set 2 powdered agglomerates.

5

Table 2B

Run	Size (μm)			Bulk density (g/mL)	Shape		
	X10	X50	X90		X10	X50	X90
MF-R1	345.53 (11.71)	620.84 (12.36)	886.40 (17.61)	0.26 (0.00)	0.66 (0.01)	0.83 (0.01)	0.94 (0.00)
MF-R2	336.12 (18.03)	675.15 (38.13)	929.94 (28.70)	0.23 (0.00)	0.63 (0.00)	0.79 (0.01)	0.89 (0.01)
MF-R3	400.23 (14.39)	721.79 (16.25)	956.21 (9.63)	0.22 (0.00)	0.62 (0.00)	0.77 (0.00)	0.90 (0.00)

Table 2C provides the physical characteristics of powdered agglomerate prepared from montelukast and lactose blend (MTL) (Set 3) with the values in parentheses indicating the standard deviation. Figure 7 shows the size distribution of the Set 3 powdered agglomerates.

10

Table 2C

Run	Size (μm)			Bulk density (g/mL)	Shape		
	X10	X50	X90		X10	X50	X90
MTL-R1	425.29 (30.38)	689.23 (23.29)	885.73 (7.38)	0.32 (0.00)	0.70 (0.00)	0.86 (0.00)	0.93 (0.00)
MTL-R2	408.41 (28.49)	723.35 (21.29)	941.42 (15.68)	0.31 (0.00)	0.65 (0.00)	0.80 (0.01)	0.91 (0.00)
MTL-R3	358.87 (34.66)	687.41 (22.21)	922.39 (11.11)	0.30 (0.00)	0.65 (0.00)	0.80 (0.00)	0.90 (0.00)

Conclusions

15

The results shown in Tables 2A-2C demonstrate that the process of the present invention provides powdered agglomerates of both active pharmaceutical ingredients, excipients, and blends thereof with substantial uniformity. Standard deviations are within 10% of the mean values, where up to 15% is considered acceptable. Particle size distribution width, measured as the ratio of X90 to X10, is less than 4 which is typical of narrow to medium size distributions.

20

WHAT IS CLAIMED IS:

1. A process for preparing powder agglomerates from a rotating apparatus, comprising:
loading dried particulate material having a diameter less than 5 μm into a chamber
arranged about a horizontal axis;
5 rotating the chamber around the horizontal axis for at least 300 revolutions to form the
powder agglomerate; and
discharging the powder agglomerate from the chamber.
2. The process of claim 1, further comprising;
10 agitating the discharged powder agglomerate on a mesh screen to separate the powder
agglomerate from residual particulate material.
3. The process of claim 1, wherein the chamber is rotated at speed of at least 5 rpm.
- 15 4. The process of claim 1, wherein the chamber is rotated at a speed of no more than 150
rpm.
5. The process of claim 1, wherein the chamber is rotated for a period until at least 600
powder avalanches occur.
20
6. The process of claim 1, wherein the chamber is rotated for at least 600 revolutions before
the powder agglomerate is discharged from the chamber.
7. The process of claim 1, wherein the chamber has a volume, wherein from 20% to 75% of
25 the chamber's volume is loaded with the dried particulate material.
8. The process of claim 1, wherein at least 200 g of dried particulate material is loaded into
the chamber.
- 30 9. The process of claim 1, wherein the chamber is a cylindrical chamber.
10. The process of claim 1, further comprising transferring the discharged powder
agglomerate into a container for storing or further processing a therapeutic agent.

11. The process of claim 1, wherein the discharged powder agglomerate is transferred into a container is a dry powder inhaler reservoir, a tableting die, a capsule, a sachet, or a vial for injection.
- 5 12. The process of claim 1, wherein the dried particulate material comprises mometasone, montelukast, or a pharmaceutically acceptable salt thereof.
13. The process of claim 1, wherein the dried particulate material comprises lactose.

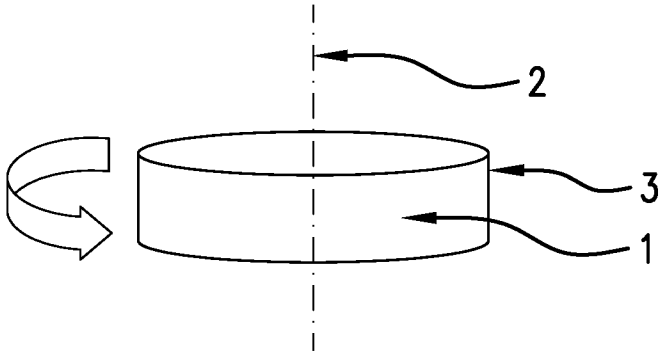


FIG. 1A

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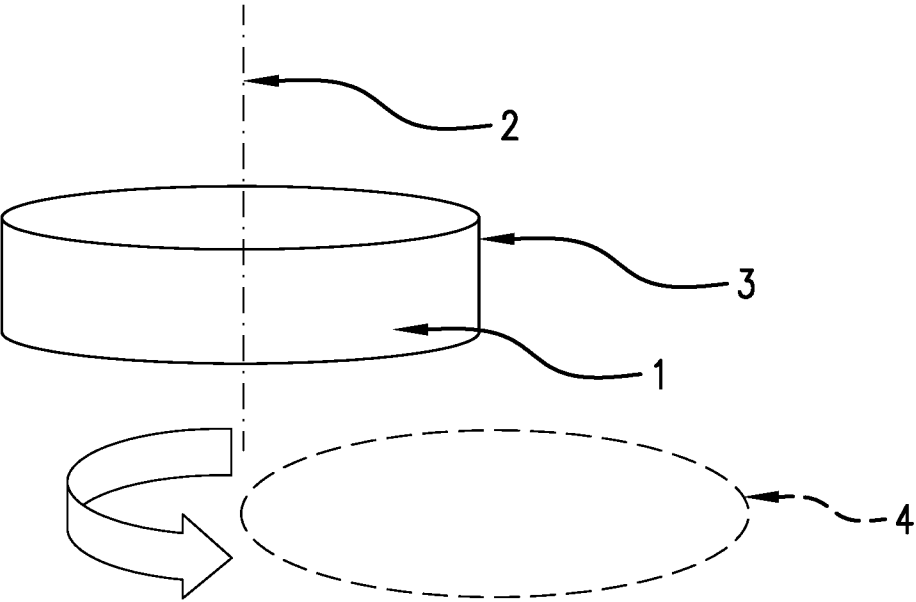


FIG. 1B

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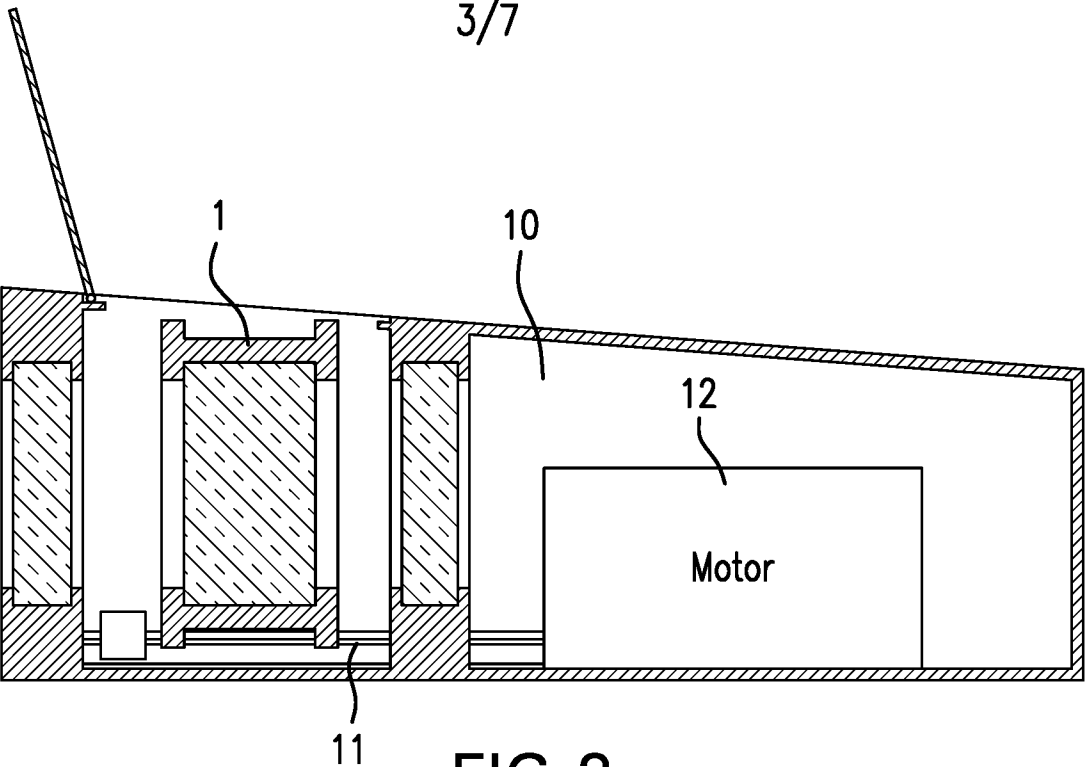


FIG. 2

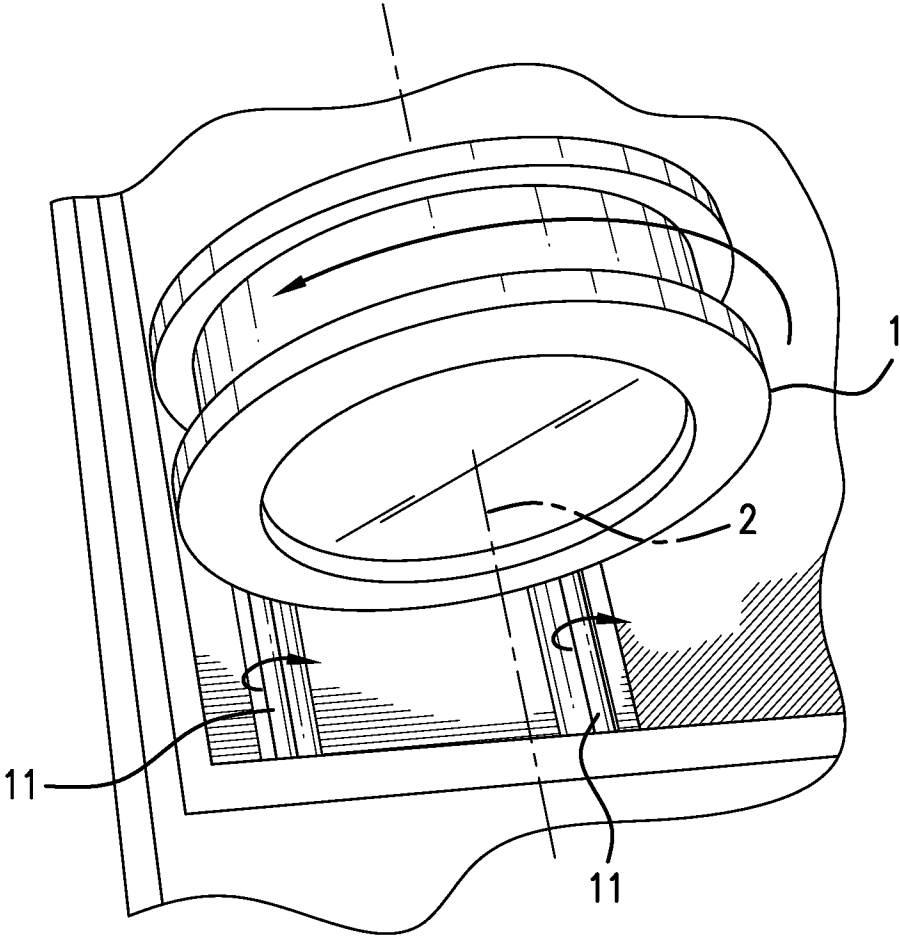


FIG. 3

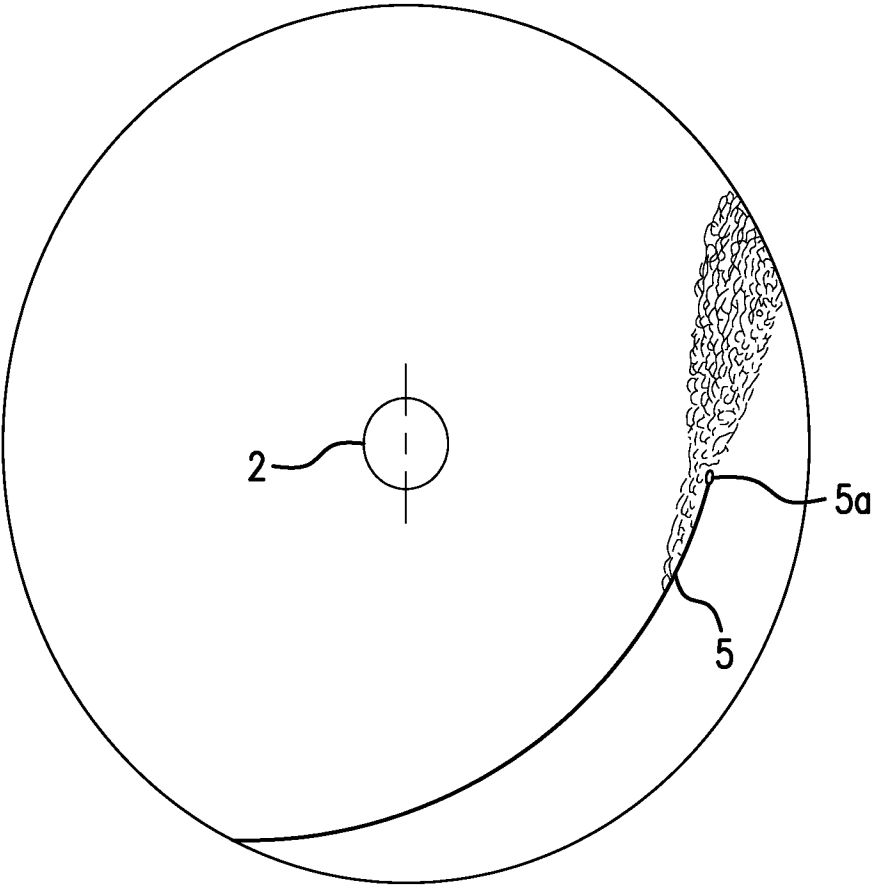


FIG.4

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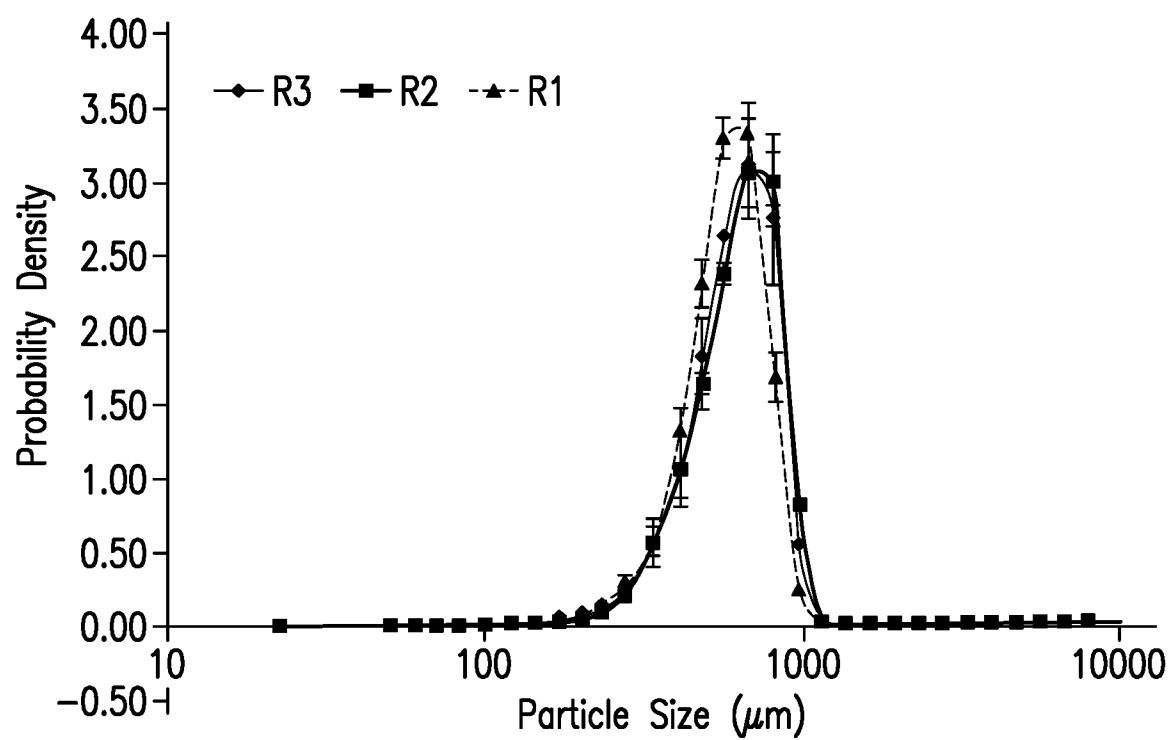


FIG.5

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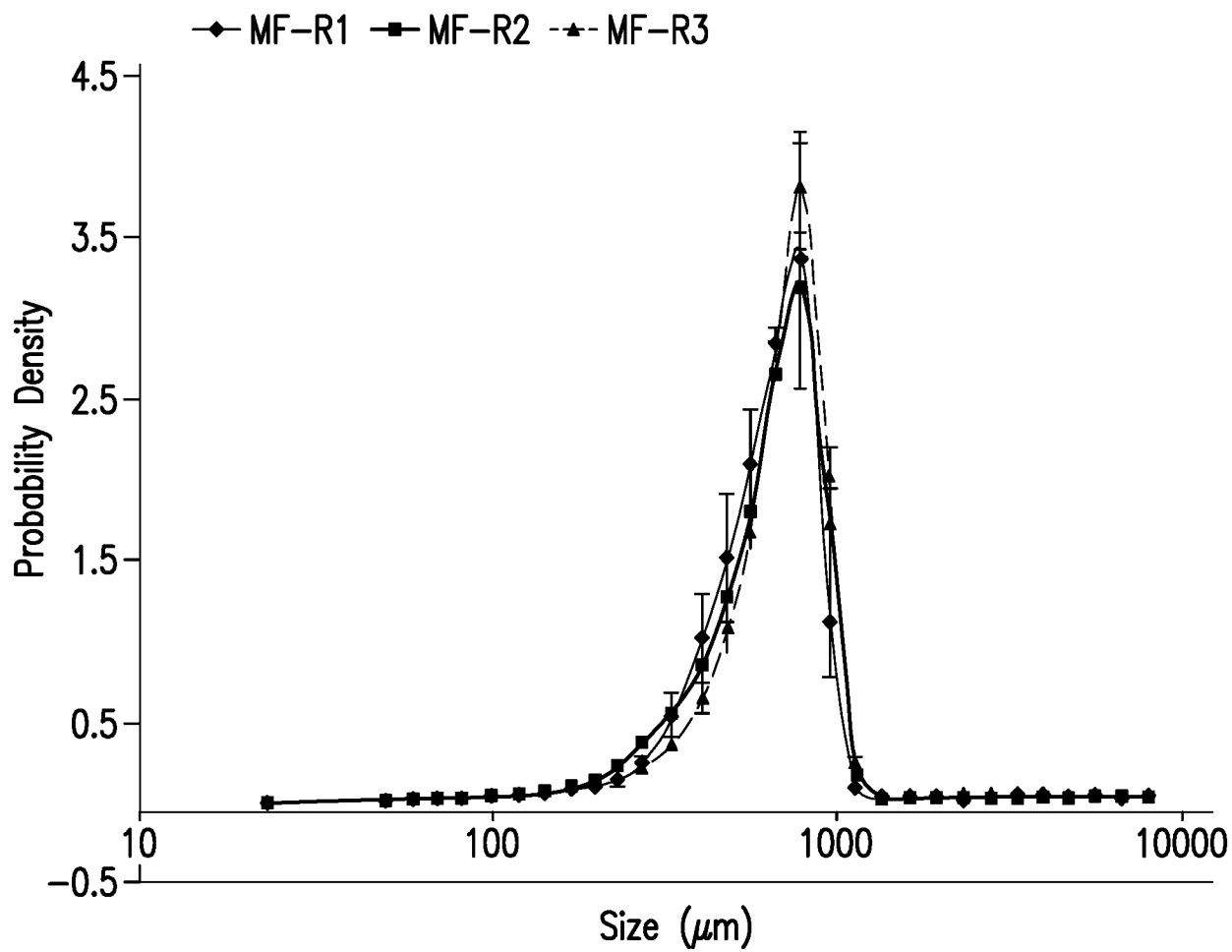


FIG.6

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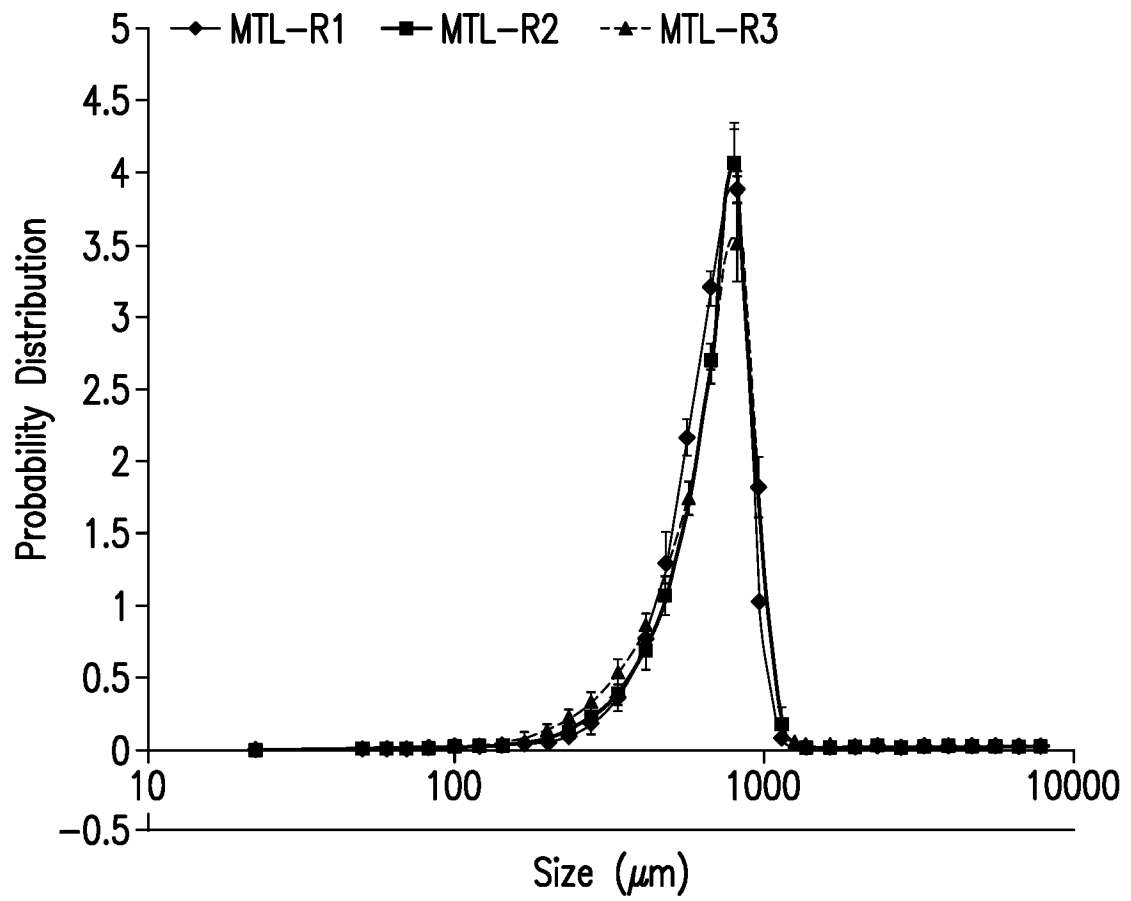


FIG.7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/18246

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K9/14, A61K9/16, A61J3/00, B01J2/12 (2017.01)

CPC - A61K9/14, A61K9/16, A61K9/1682, A61J3/00, B01J2/12

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)

See Search History document

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

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/0019411 A1 (COLOMBO, P et al.) 27 January 2005; paragraphs 28-30, 42, 62, 66, 72-73, 120	1, 3, 4, 6, 9, 11, 13
Y		7, 12
X	US 4,161,516 A (BELL, J) 17 July 1979; column 7, lines 65-68; column 8, lines 1-5, 61-68; column 9, lines 1-20, 28-40; column 10, lines 1-37, 45-60	1, 2, 8, 10
Y	US 2,561,055 A (HOOD, R) 17 July 1951; figure 2; column 1, lines 54-55; column 2, lines 1-15; column 4, lines 12-23	7
Y	US 2004/0198708 A1 (KAPLAN, L et al.) 7 October 2004; paragraphs 11-12, 19, 22	12
A	US 2011/0026760 A1 (MARTISKA, G et al.) 3 February 2011; entire document	5
A	US 2006/0159803 A1 (GOTTEMOLLER, T et al.) 20 July 2006; entire document	5
A	US 2010/0233276 A1 (RAFFIN, R et al.) 16 September 2010; entire document	1-13
A	US 5,551,489 A (TROFAST, E et al.) 3 September 1996; entire document	1-13
A	US 2003/0003229 A1 (WALTON, O) 2 January 2003; entire document	1-13

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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"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

12 April 2017 (12.04.2017)

Date of mailing of the international search report

10 MAY 2017

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