(54) Title: PROCESS FOR PREPARING PHARMACEUTICAL FORMULATIONS FOR INHALATION COMPRISING A HIGH-DOSAGE STRENGTH ACTIVE INGREDIENT

(57) Abstract: The invention concerns a process for dispersing a cohesive high-dosage strength micronized active ingredient in dry powder formulations for inhalation comprising carrier particles, and an apparatus thereof. A dispersion capsule is provided, said capsule comprising a cylindrical room (1) with a lateral boundary made of a sieving mesh (2), said room (1) containing grinding balls (3), being closed by a screw cap (4) on the top, two longitudinal rods (6), and a disk (5), wherein the capsule is connected to said disk by said two longitudinal rods.

Fig. 1

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PROCESS FOR PREPARING PHARMACEUTICAL FORMULATIONS
FOR INHALATION COMPRISING A HIGH-DOSAGE STRENGTH
ACTIVE INGREDIENT

The present invention provides a process for dispersing a cohesive high-dosage strength micronized active ingredient in dry powder formulations for inhalation comprising carrier particles, and an apparatus thereof.

**Background of the invention**

The administration of pharmacologically active ingredients by inhalation to the airways is a widely used technique especially for the treatment of reversible airway obstruction, inflammation and hyper-responsiveness.

Some of the most widely used systems for the administration of drugs to the airways are represented by dry powder inhalers (DPIs) which, in turn, can be divided into two basic types: i) single dose inhalers, for the administration of single subdivided doses of the active compound; each single dose being usually filled in a capsule; ii) multidose inhalers pre-loaded with quantities of active ingredients sufficient for longer treatment cycles.

Drugs intended for inhalation as dry powders by means of DPIs should be used in the form of micronized particles. Micronization is generally achieved by conventional milling processes known to the skilled person.

Although micronization of the drug is essential for deposition into the lower respiratory tract during inhalation, it is also known that the finer are the particles, the stronger are the cohesion forces among them. Strong cohesion forces hinder the handling of the powder during the manufacturing process (pouring, filling). Moreover they reduce the flowability of the particles, while favoring in the multidose DPI's the agglomeration and the adhesion thereof to the walls reservoir. Said phenomena impair the loading of the powder from the reservoir to the metering chamber and, hence, give rise to handling and metering accuracy
problems.

Poor flowability is also detrimental to the respirable fraction of the delivered dose being the active particles unable to properly leave the inhaler, essentially because they remain adhered to the interior of the inhaler and/or leave the inhaler as large agglomerates; agglomerated particles, in turn, cannot reach the bronchiolar and alveolar sites of the lungs. The uncertainty as to the extent of agglomeration of the particles between each actuation of the inhaler and, also, among inhalers and different batches of particles, leads to poor dose reproducibility as well.

For this reasons, powders for inhalation are commonly formulated by diluting the micronized drug in a pharmacologically inert physiologically acceptable excipient of coarser particles to yield the so-called "interactive ordered mixtures".

However, it has been found that particularly cohesive active ingredients to be delivered at relatively high doses, e.g. equal to or higher than 100 µg per actuation, are difficult to disperse, and form agglomerates even though they are diluted by mixing with coarse excipient particles.

The presence of the agglomerates lead to problems in the manufacturing of inhalable powder formulations with a good uniformity distribution of the active ingredient in the blend as well as a good dosage reproducibility and high respirable fraction upon administration by DPI's.

In view of the problems outlined above, it would be highly advantageous to provide a process for preparing powder formulations for inhalation comprising cohesive active ingredients to be delivered at high doses per actuation able of achieving a good dispersion of active particles when properly diluted with coarse carrier particles.

The problem is solved by the process of the present invention.
Summary of the invention

According to a first aspect, the present invention provides a process for dispersing a cohesive high-dosage strength micronized active ingredient in dry powder formulations comprising carrier particles, said process comprising the steps of:

(i) providing a dispersion capsule comprising a cylindrical room (1) with a lateral boundary made of a sieving mesh (2), said room containing grinding balls (3), being closed by a screw cap (4) on the top, two longitudinal rods (6), and a disk (5) wherein the capsule is connected to said disk by said two longitudinal rods;

(ii) loading said active ingredient and an aliquot of the carrier particles in the capsule of step (i);

(iii) fitting said capsule to a drum, filled with the remaining part of the carrier;

(iv) inserting the drum into a rotating body mixer apparatus; and

(v) operating said rotating body mixer to mix the whole powder.

The invention is also directed to an apparatus in form of capsule for dispersing a cohesive high-dosage strength micronized active ingredient, said capsule comprising a cylindrical room (1) with a lateral boundary made of a sieving mesh (2), said room) containing grinding balls (3) being closed by a screw cap (4) on the top, two longitudinal rods (6), and a disk (5) wherein the capsule is connected to said disk by said two longitudinal rods.

Definitions

"Drum" refers to a tank of variable capacity, made of an inert material, usually of steel, preferably of stainless steel, having a porthole (opening) to be fitted with the screw top (4). The drum is typically used for the transport, process manipulation and storage of the product.

"Cohesive active ingredient" means a micronized powder having a Specific
Energy value equal to or higher than 10 mJ/g. The Specific Energy can be determined applying the Freeman technology and the FT4 universal powder rheometer that measures bulk, flow and shear properties. During dynamic testing the rotational and axial forces acting on a helical blade are measured as it passes through a sample. Basic flow energy (BFE) is determined from these data and is regarded as a measure of the rheology or resistance to flow of the powder. The Specific Energy (SE) is a measure of how powder will flow in an unconfmed or low stress environment and it is considered as a powder cohesion index. [see Zauner J et al Quantitative Study of Process and Material Parameters on Flow Behavior and Powder Binder Separation of Feedstocks: Experimental Design 3D Simulation Model and Balance Model for Separation in Suspensions; In ADVANCES IN POWDER METALLURGY AND PARTICULATE MATERIALS V 1-4 PTS 1-13 2008, 1-13). The Surface Energy is calculated from the energy required to establish a particular flow pattern in a conditioned, precise volume of powder as reported in Freeman R, Measuring the flow properties of consolidated, conditioned and aerated powders—a comparative study using a powder rheometer and a rotational shear cell, - Powder Technology, 2007, 174, 25 -33). The flow pattern is an upward clockwise motion of the blade, generating gentle lifting and low stress flow of the powder.

"Rotating body mixer" refers to an apparatus which creates particle movement by rotation of the entire mixer shell or body.

"Carrier particles" refers to particles constituted of any pharmacologically-inert (not-therapeutically active) physiologically acceptable material.

For the purpose of the invention, "high-dosage strength active ingredients" are those to be delivered using a dry powder inhaler (DPI) device whose nominal dose delivered after each actuation of the inhaler is equal to or higher than 100 microg \(^{\text{g}}\). "Actuation" means the release of active ingredients from the device by a single activation (e.g. mechanical or breath).
The term "dispersing", refers to obtaining a good homogeneity of the active ingredient in the powder formulation, wherein no agglomerates of micronized particles of said active ingredient are present as visually determined or as determined by other methods known to the skilled person in the art such as sieving or Near Infrared Spectrophotometry provided with a microscopy imaging system (Near Imaging).

The expression "good homogeneity" refers to a powder wherein, upon mixing, the uniformity of distribution of a component, expressed as coefficient of variation (CV) also known as relative standard deviation (RSD), is less than 5.0%. It is usually determined according to methods known to the skilled person, for instance by taking samples from different parts of the powder and testing the component by HPLC or other equivalent analytical methods.

The term "coarse" means a substance having a size at least of few tens of micron. In general terms, the particle size of the particles is quantified by measuring a characteristic equivalent sphere diameter, known as volume diameter, by laser diffraction.

The particle size can also be quantified by measuring the mass diameter by means of suitable known instrument such as, for instance, the sieve analyzer.

The volume diameter (VD) is related to the mass diameter (MD) by the density of the particles (assuming a size independent density for the particles).

The particle size of the active ingredients and of the fraction of excipient fine particles is expressed in terms of volume diameter, while that of the coarse particles is expressed in terms of mass diameter.

The particles have a normal (Gaussian) distribution which is defined in terms of the volume or mass median diameter (VMD or MMD) which corresponds to the volume or mass diameter of 50% by weight of the particles, and, optionally, in terms of volume or mass diameter of 10% and 90% of the particles, respectively.
Another common approach to define the particle size distribution is by means of three values: i) the median diameter $d(0.5)$ which is the diameter where 50% of the distribution is above and 50% is below; ii) $d(0.9)$, where 90% of the distribution is below this value; iii) $d(0.1)$, where 10% of the distribution is below this value.

Upon aerosolisation, the particle size is expressed as mass aerodynamic diameter (MAD), while the particle size distribution is expressed in terms of mass median aerodynamic diameter (MMAD) and Geometric Standard Deviation (GSD). The MAD indicates the capability of the particles of being transported suspended in an air stream. The MMAD corresponds to the mass aerodynamic diameter of 50% by weight of the particles.

The term "hard pellets" refers to spherical or semispherical units whose core is made of coarse excipient particles.

The term "spheronisation" refers to the process of rounding off of the particles which occurs during the treatment.

The term "good flowability" refers to a formulation that is easy handled during the manufacturing process and is able to ensure for an accurate and reproducible delivering of the therapeutically effective dose.

Flow characteristics can be evaluated by different tests such as angle of repose, Carr's index, Hausner ratio or flow rate through an orifice.

The flow properties were tested by measuring the flow rate through an orifice according to the method described in the European Pharmacopeia (Eur. Ph.) 7.3, 7th Edition.

The expression "respirable fraction" refers to an index of the percentage of active particles which would reach the lungs in a patient.

The respirable fraction is evaluated using a suitable *in vitro* apparatus such as Andersen Cascade Impactor (ACI), Multi Stage Liquid Impinger (MLSI), Next Generation Impactor (NGI) or other apparatus known to the skilled person.

It is calculated by the percentage ratio of the fine particle mass (formerly fine particle dose) to the delivered dose.

The delivered dose is calculated from the cumulative deposition in the apparatus, while the fine particle mass is calculated from the deposition of particles having a diameter < 5.0 micron or by other methods known to the skilled person in the art.

**Figures**

Figure 1 shows a front elevation view of the dispersion capsule according to the invention;

Figure 2 is a perspective view of the dispersion capsule of figure 1.

**Detailed description of the invention**

The present invention concerns a process for the preparation of a powder formulation for inhalation comprising carrier particles, said process providing a good dispersion of cohesive, high-dosage strength micronized active ingredients in the powder formulation, and hence a good homogeneity.

The process of the invention turned out to be faster and more reproducible than processes based on other systems of mixing.

In the powder formulation obtained by the process of the invention, agglomerates of the active ingredient are not present, giving rise to an improved uniformity of distribution of the active ingredient, and hence of the reproducibility of the delivered dose.

No loss of active ingredient was observed either.

Furthermore, powder formulations obtained by the process of the invention turned to be more flowable than those processed based on the different systems of mixing as a lesser amount of fine carrier particles are produced during the dispersion step.
The carrier particles may comprise any pharmacologically-inert, physiologically acceptable substance, amorphous or crystalline, or combination thereof; preferred materials are crystalline sugars and for example monosaccharides such as glucose or arabinose, or disaccharides such as maltose, sucrose, dextrose and lactose. Polyalcohols such as mannitol, sorbitol, maltitol, lactitol may also be used.

The preferred material is lactose, more preferably a-lactose monohydrate. Examples of commercial a-lactose monohydrate are Capsulac® and Pharmatose®. An example of commercial mannitol is Pearlitol®.

The carrier particles usually comprise coarse carrier particles.

Said coarse particles shall have a mass median diameter equal to or higher than 80 micron, preferably equal to or greater than 125 micron, more preferably equal to or greater than 150 micron, even more preferably equal to or greater than 175 micron.

Advantageously, all the coarse particles have a mass diameter in the range 50-1000 micron, preferably comprised between 60 and 500 micron.

In certain embodiments of the invention, the mass diameter of said coarse particles might be comprised between 80 and 200 micron, preferably between 90 and 150 micron, while in another embodiment, the mass diameter might be comprised between 200 and 400 micron, preferably between 210 and 355 micron.

Preferably, the mass diameter of the coarse particles is comprised between 210 and 355 micron.

In general, the skilled person shall select the most appropriate size of the coarse excipient particles by sieving, using a proper classifier.

When the mass diameter of the coarse particles is comprised between 200 and 400 micron, the coarse excipient particles preferably have a relatively highly fissured surface, that is, on which there are clefts and valleys and other recessed regions, referred to herein collectively as fissures. The "relatively highly fissured"
coarse particles can be defined in terms of fissure index or rugosity coefficient as described in WO 01/78695 and WO 01/78693 which are incorporated herein by reference, and they could be characterized according to the description therein reported. Advantageously, the fissure index of said coarse particles is of at least 1.25, preferably of at least 1.5, more preferably of at least 2.0, while the rugosity coefficient is of at least 1.25.

The carrier may also comprise fine particles of a physiologically acceptable material in admixture with the coarse particles. Typically, said physiologically acceptable materials are those reported above for the coarse carrier particles, and preferably, both the coarse and fine particles are constituted of the same physiologically acceptable active material, more preferably alpha-lactose monohydrate.

Generally, the fine carrier particles have a MMD of less than 35 micron, preferably of less than 15 micron.

The carrier may further comprise one or more additives to promote the release of the active particles from the carrier particles on actuation of the inhaler. The additive may include a given material or a combination of more materials.

Advantageously the additive is a material with anti-adherent properties such as the amino acids leucine and isoleucine. The additive may also consist of one or more water-soluble surface active materials, for example lecithin, in particular soya lecithin.

Preferably, the additive is a water-insoluble lubricant such as magnesium stearate, sodium stearyl fumarate, sodium lauryl sulfate, stearyl alcohol, stearic acid and sucrose monopalmitate. More preferably, the additive is magnesium stearate.

In a particular embodiment of the invention, the carrier consists of:

i) a fraction of microparticles having a MMD lower than 15 micron constituted of a mixture of particles of alpha-lactose monohydrate and
particles of magnesium stearate (the fine carrier fraction);
ii) a fraction of particles of alpha lactose monohydrate having a diameter higher than 175 micron.

The microparticles (i) could be prepared according to the methods disclosed in WO 01/78693 which is incorporated herein by reference.

For example, said microparticles could be prepared by mixing and then micronizing the two components together by milling. Alternatively, each component can be micronized individually and then combined by mixing.

In certain embodiments of the invention, the microparticles fraction is composed from 90 to 99% by weight of a-lactose monohydrate particles and from 10 to 1% by weight of magnesium stearate particles; in a particularly preferred embodiment, the microparticles fraction is composed by 98% of a-lactose monohydrate particles and by 2% of magnesium stearate particles. The weight ratio between the microparticles fraction and the coarse particles is from 15:85 to 5:95 respectively, even more preferably 10:90.

As a first step, the process of the invention comprises the use of a dispersion capsule comprising a cylindrical room (1) with a lateral boundary made of a sieving mesh (2), said room containing grinding balls (3) and being closed by a screw cap on the top (4), wherein the dispersion capsule is connected to a disk (5) by two longitudinal rods (6).

The skilled person shall use a cylindrical room and a screw (4) cap of a size able of passing through the porthole of the drum.

The dispersion capsule is advantageously connected to the drum by fastening clamp.

The skilled person shall also adjust the length of the cylindrical room (1) and of the rods (6) depending on the product batch size.

The size of the meshes of the sieving screen shall be suitable selected by the skilled person depending on the size of the coarse carrier particles. Preferably, the
mesh size is comprised between 600 µm and 1200 µm (micron).

The disk (5) and the rods (6) can be made of any suitable inert material, advantageously of steel, preferably of stainless steel.

Also the balls inside the dispersion capsule may be made of any suitable inert material such as steel or hard Teflon®, preferably of stainless steel, more preferably of stainless steel type AISI 316.

Advantageously, their diameter is less than 5 cm, preferably of 2 cm.

In a second step, one or more micronized active ingredients and an aliquot of the carrier particles are loaded in the dispersion capsule.

The ratio between the micronized active ingredient particles and said part of the carrier particles might advantageously be comprised between 1:0.5 and 1:10 by weight, preferably between 1:2 and 1:5 by weight.

In a third step, the dispersion capsule of the invention is fitted to a drum filled with the remaining part of the carrier and fixed with a clamp.

Depending on the size of the batch, the skilled person shall select a drum of the proper capacity.

The drum is then inserted into a mixer apparatus.

Any rotating body mixer apparatus commercially available can be suitably used. Said mixers include V-shaped and double cone apparatus.

Mixers of this type such as Turbula™ or DynaMIX™ are commercially available from Bachofen AG (Muttenz, Switzerland).

Afterwards, all the powder is mixed for a time not longer than 40 minutes, advantageously not longer than 30 minutes, preferably not longer than 20 minutes, in such a way as that the portion comprising the active ingredient(s) is forced through the meshes of the sieve screening.

In a general way, the skilled person shall suitably adjust the speed of rotation of the mixer depending on the size of the processed batch.

At the end of the process, the resulting powder can be harvested and used as
Otherwise, optionally, the powder can be poured into a sieving machine available from Frewitt (Fribourg, Switzerland).

The skilled person shall select the proper mesh size of the sieving screen depending on the particle size of the coarse carrier particles.

The powder collected from the Frewitt machine can be subjected to a further mixing step in suitable known apparatus, such as a Turbula™ mixer or DynaMIX™ mixer. In a general way, the skilled person shall adjust the time of mixing and the speed of rotation of the mixer depending on the desired degree of homogeneity.

When the particle size of the coarse carrier particles is comprised between 150 and 400 micron, preferably between 212 and 355 micron, the powder formulation are preferably in the form of "hard pellets". This can be obtained by subjecting the powder mixture to a spheronization step that shall be carried out for at least two hours, even more preferably for four hours.

The active ingredient particles referred to throughout the specification will comprise an effective amount of at least one high-dosage strength active substance that can be delivered to the lungs in the form of a powder for inhalation by means of a DPI. Advantageously, the high-dosage strength active agents are those active ingredients whose nominal dose is equal to or higher than 100 µg (microg), more advantageously equal to or higher than 200 µg, preferably equal to or higher than 400 µg.

In some embodiments of the invention, nominal dose might be of 600 µg, 800 µg or 1200 µg.

Suitable therapeutically active agents include drugs which are usually administered by inhalation for the prevention and/or treatment of respiratory diseases. Examples of said respiratory drugs are the phosphodiesterase inhibitors disclosed in WO 2008/006509, WO 2009/077068, WO 2009/127320,
WO 2009/018909 and WO 2010/089107 or the anti-muscarinic agents disclosed in WO 2011/161018, WO 2011/160918, WO 2011/160919. WO 2010/015324 and WO 2010/072338. In certain embodiments of the invention, the aforementioned active agents can be used in combination with additional active ingredients selected from the group of corticosteroids and/or beta2-agonists, provided that they are compatible with one another under conditions of storage and use.

Typically, at least 90% of the particles of each micronized active ingredient have a diameter equal to or lower than 6 micron.

Advantageously, the process of the invention is applied to micronized active ingredients having a cohesivity expressed as Specific Energy value equal to or higher than 10 mJ/g, preferably higher than 15 mJ/g, more preferably higher than 20 mL/g. The Specific Energy shall be determined according to reported in the 'Definitions' paragraph.

The invention is illustrated by the following examples.

**Examples**

**Example 1 - Preparation of a powder formulation comprising an anti-muscarinic agent as active ingredient**

The composition of the powder formulation is reported in Table 1.

**Table 1 - CI dry powder formulation**

<table>
<thead>
<tr>
<th>Components</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per shot of the inhaler</td>
</tr>
<tr>
<td></td>
<td>mg (% µg)</td>
</tr>
<tr>
<td>Compound CI</td>
<td>0.2 (2.0)</td>
</tr>
<tr>
<td>Alpha-lactose monohydrate 212-355 µm</td>
<td>8.82 (88.2)</td>
</tr>
<tr>
<td>Microparticles</td>
<td>0.98 (9.8)</td>
</tr>
<tr>
<td>Total weight</td>
<td>10</td>
</tr>
</tbody>
</table>

A 4 kg batch size of the dry powder formulation was prepared as described as follows.

The anti-muscarinic compound (R)-3-[bis-(3-fluoro-phenyl)-
methoxycarbonyloxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-
bicyclo[2.2.2]octane chloride, quoted as CI in WO 2010/015324, was subjected to micronization according to standard milling techniques.

Particles of a-lactose monohydrate having a mean particle size of less than 250 micron, and magnesium stearate particles having a mean particle size of less than 35 micron in a ratio 98:2 percent by weight were co-micronized by milling in a jet mill operating under nitrogen to obtain the fraction of co-micronized particles indicated as microparticles.

Said microparticles were mixed in a Turbula mixer for 4 hours with fissured coarse particles of a-lactose monohydrate having a mass diameter comprised between 212-355 micron in the ratio 90:10 percent by weight, to obtain the Carrier.

The micronized compound CI and an aliquot of the Carrier in a 1:1 ratio by weight with CI were loaded in the dispersion capsule fitted with sieving mesh (2) of size of 1 mm. The whole apparatus is made of stainless steel. The grinding balls are made of stainless steel as well and have a diameter of 2 cm.

The dispersion capsule was fitted to a 22 l stainless steel drum, filled with an aliquot of remaining part of the Carrier.

The drum was inserted into a DynaMIX™ mixer apparatus which was operated for 20 minutes.

The collected powder does not show any agglomerate upon visual inspection. It was characterized in terms of the uniformity of distribution of the active ingredients and aerosol performances after loading it in the multidose dry powder inhaler described in WO 2004/012801.

The uniformity of distribution of the active ingredients was evaluated by withdrawing 20 samples from different parts of the powder and determined by HPLC. Each sample has a mass unit comprised between 1 and 3 doses of the active ingredient.

The results (mean value ± RSD) are reported in Table 2.
The evaluation of the aerosol performance was carried out using the New Generation Impactor (NGI) according to the conditions reported in the European Pharmacopeia 6th Ed 2008, par 2.9.18.

After aerosolization of 3 doses from the inhaler device, the ACI apparatus was disassembled and the amounts of drug deposited in the stages were recovered by washing with a solvent mixture and then quantified by High-Performance Liquid Chromatography (HPLC). The following parameters, were calculated: i) the delivered dose which is the amount of drug delivered from the device recovered in the all parts of impactor; ii) the fine particle mass (FPM) which is the amount of delivered dose having a particle size equal to or lower than 5.0 micron; Hi) the fine particle fraction (FPF) which is the percentage of the fine particle dose; iv) the MMAD.

The results (mean ± RSD) are reported in Table 2.

<table>
<thead>
<tr>
<th>Uniformity of distribution</th>
<th>98.2 (± 1.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivered Dose [μg]</td>
<td>160.4</td>
</tr>
<tr>
<td>Fine Particle Mass &lt; 5 μm [μg]</td>
<td>81.5</td>
</tr>
<tr>
<td>Fine Particle Fraction &lt; 5 μm [%]</td>
<td>50.8</td>
</tr>
</tbody>
</table>

As it can be appreciated, the powder formulation processed according to the process of the invention shows a good uniformity of distribution of the active ingredient as demonstrated by the low RSD as well as good aerosol performances.

Example 2 - Preparation of a powder formulation comprising a phosphodiesterase inhibitor as active ingredient

The composition of the powder formulation is reported in Table 3.
Table 3 - C2 dry powder formulation

<table>
<thead>
<tr>
<th>Components</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per shot of the</td>
</tr>
<tr>
<td></td>
<td>inhaler</td>
</tr>
<tr>
<td></td>
<td>mg</td>
</tr>
<tr>
<td>Compound C2</td>
<td>0.4</td>
</tr>
<tr>
<td>Alpha-lactose monohydrate 212-355 μm</td>
<td>9.0</td>
</tr>
<tr>
<td>Microparticles</td>
<td>0.96</td>
</tr>
<tr>
<td>Total weight</td>
<td>10</td>
</tr>
</tbody>
</table>

A batch size of the dry powder formulation is prepared as described as follows.

The phosphodiesterase inhibitor (-)-3-cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-l-oxy-pyridin-4-yl)-ethyl ester quoted as C2 in WO 2010/089107 is micronized by methods known in the art, to prepare the active substance in the form of particles having a typical particle size suitable for inhalation.

The carrier is prepared as reported in the Example 1.

The micronized active ingredient and the Carrier are processed as reported in Example 1.
CLAIMS

1. A process for dispersing a cohesive high-dosage strength micronized active ingredient in dry powder formulations comprising carrier particles, said process comprising the steps of:
   (i) providing a dispersion capsule comprising a cylindrical room (1) with a lateral boundary made of a sieving mesh (2), said room (1) containing grinding balls (3), being closed by a screw cap (4) on the top, two longitudinal roads (6), and a disk (5), wherein the capsule is connected to said disk by said two longitudinal rods;
   (ii) loading said active ingredient and an aliquot of the carrier particles in the capsule of step (i);
   (iii) fitting said capsule to a drum, filled with the remaining part of the carrier;
   (iv) inserting the drum into a rotating body mixer apparatus; and
   (v) operating said rotating body mixer to mix the whole powder.

2. The process according to claim 1, wherein the active ingredient is delivered at a nominal dose equal to or higher than 100 μg.

3. The process according to claim 2, wherein the nominal dose is equal to or higher than 200 μg.

4. The process according to claim 3, wherein the nominal dose is equal to or higher than 400 μg.

5. The process according to any one of claims 1 to 4, wherein the active ingredient is selected from the drugs which are usually administered by inhalation for the prevention and/or treatment of respiratory diseases.

6. The process according to claim 5, wherein the drug is a phosphodiesterase inhibitor or an anti-muscarinic agent.

7. The process according to any one of the preceding claims, wherein the
carrier comprises a pharmacologically-inert, physiologically acceptable substance.

8. The process according to claim 7, wherein the substance is a crystalline sugar selected from the group consisting of glucose, arabinose, maltose, sucrose, dextrose and lactose.

9. The process according to claim 8, wherein the sugar is alpha-lactose monohydrate.

10. The process according to any one of claims 7 to 9, wherein the carrier particles have a mass median diameter equal to or higher than 80 micron.

11. The process according to claim 10, wherein the mass median diameter is equal to or greater than 175 micron.

12. The process according to claim 7, wherein the carrier further comprises one or more additives.

13. An apparatus in form of capsule for dispersing a cohesive high-dosage strength micronized active ingredient, said capsule comprising a cylindrical room (1) with a lateral boundary made of a sieving mesh, said room (2) containing grinding balls (3) and be closed by a screw cap (4) on the top, two longitudinal rods (6), and a disk (5) wherein the capsule is connected to said disk by said two longitudinal rods.

14. The apparatus according to claim 13, wherein the sieving mesh have a size comprised between 600 μm and 1200 μm (micron).

15. The apparatus according to claim 13 or 14, wherein the grinding balls (3), the disk (5) and the rods (6) are made of stainless steel.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. B02C17/02 B01F9/00 B01F13/00

ADD.

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)

B02C B01F

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

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

EPO-Internal

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>WO 95/11666 AI (CO ORGINTED DRUG DEV LTD [GB]; STANIFORTH JOHN NICHOLAS [GB]) 4 May 1995 (1995-05-04) page 8, line 18 - page 9, line 16</td>
<td>1-12</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  * A: document defining the general state of the art which is not considered to be of particular relevance
  * E: earlier application or patent but published on or after the international filing date
  * L: document which may throw doubts on priority claim(s) or on which it is cited to establish the publication date of another citation or other special reason (as specified)
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  * 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
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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
  * Z: document member of the same patent family

Date of the actual completion of the international search

19 December 2014

Date of mailing of the international search report

13/01/2015

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Swiderski, Piotr
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