

METHOD FOR PREPARING DRY POWDER INHALATION COMPOSITIONS

Field of the Invention

The invention relates to a method for preparing dry powder inhalation compositions
5 which comprise two or more active ingredients and inert particulate excipient, and to
a method for adjusting the performance of such compositions.

Background of the Invention

Inhaled medicaments for the treatment of respiratory diseases such as asthma and
10 COPD are often formulated as dry powders and are delivered using a dry-powder
inhaler (DPI). The medicaments are micronized such as to have a respirable
aerodynamic diameter which is typically in the region of 0.5 to 10 μm . Such
micronized particles tend to be cohesive and have poor flow properties. To increase
flowability and dosing accuracy the fine drug particles of respirable size are typically
15 mixed with coarser excipient particles to form an ordered mixture, wherein fine drug
particles are attached to the coarser excipient particles. This technique necessitates
the break-up of the drug/excipient agglomerates before they enter the patient's mouth
and throat, where individual large particles and agglomerated large and small
particles tend to deposit. Effective aerosolization and deagglomeration of the powder
20 requires that forces exerted on particles (e. g. forces between particles and surfaces of
the device, between drug particles and excipient particles or between drug particles
themselves) must be overcome such that high fine particle dose (FPD) of
medicament particles in the respirable size is obtained. Improvements in FPD and
dose uniformity have been reported by suitably adjusting the size range of the
25 excipient particles.

The interaction between the drug and the excipient is further complicated when the
inhalation powder includes particles of two or more different active ingredients. In

the development of such combination products it is often desirable to adjust the FPD level of each active ingredient independently. However, this often proves to be difficult as attempts to affect the FPD level of one active ingredient affect the FPD of the other active ingredient(s) of the combination as well.

- 5 Efforts to control the performance of dry powder inhalation products having two or more active ingredients have been recently reported. EP 2221048 discloses a method of first preblending each different active ingredient with different excipient (differing in their particle size) and, thereafter, blending the obtained preblends together in a main blending procedure to obtain the final composition. The method allegedly
10 enables adhesion of each of the active ingredient to one excipient, but not to other. The FPD of one active substance could be then tuned independently from the other active substance by suitably adjusting the particle size of each excipient.

- The method of EP 2221048 suffers from the drawback that various lactose grades with different particle size distribution are required for each tuning step. Commercial
15 lactose grades may differ also in other characteristics than particle size and unexpected effects in the FPD may occur. Thus, there is a need for simplified methods for adjusting the FPD level of each active substance independently in inhaled dry powder combination products.

20 Summary of the Invention

- It has been found that FPD level of each active ingredient of the combination can be adjusted independently without the need to change the excipient grades used in the composition. This is achieved by providing two excipient grades which differ in their median particle size, mixing the first active ingredient and a portion of the second
25 active ingredient with a first excipient to provide a first preblend, mixing the remaining portion of the second active ingredient with a second excipient to provide a second preblend, and finally mixing the first and the second preblends together. The FPD level of second active ingredient can be adjusted simply by changing the ratio how it is divided between the first and the second excipient. Preblending with
30 coarser excipient is found to be associated with a lower FPD level. Thus, the FPD

value of the second active ingredient can be adjusted to the desired level by changing the portion of second active ingredient which is preblended with coarser excipient. At the same time, the FPD level of the first active ingredient is only minimally affected.

5 Brief Description of the Drawings

Figure 1a shows the observed changes in the fine particle dose (FPD) of salmeterol xinafoate by adjusting preblend parameters (percent of fine lactose and proportion of salmeterol xinafoate preblended with coarser excipient).

Figure 1b shows the observed changes in the FPD of fluticasone propionate in vitro
10 using various preblend parameters (percent of fine lactose and proportion of salmeterol xinafoate preblended with coarser excipient).

Detailed Description of the Invention

In one aspect, the present invention provides a method of preparing a dry powder
15 inhalation composition comprising a first and a second active ingredient in micronized form comprising the steps of:

- (a) mixing the first active ingredient and a portion of the second active ingredient with a first particulate excipient to provide a first preblend;
 - (b) mixing the remaining portion of the second active ingredient with a
20 second particulate excipient to provide a second preblend; and
 - (c) mixing the first and the second preblends together;
- wherein the first particulate excipient and the second particulate excipient differ in their median particle size, such that VMD (volume median diameter) of the finer particulate excipient is less than 90 % of the VMD of the coarser
25 particulate excipient.

The term “about” refers to a variation of 5 % from the indicated numeric value.

The term “finer particulate excipient”, as used herein, means the excipient selected
30 from the first and the second particulate excipients which has the lowest VMD value.

The term “coarser particulate excipient”, as used herein, means the excipient selected from the first and the second particulate excipients which has the highest VMD value.

- 5 The term “micronized form” means particle size lower than about 10 μm , for example in the range between 0.5 to 10 μm , particularly in the range between 1 and 6 μm .

The particle size, for example volume median diameter (VMD), of the particulate
10 material can be determined by a laser diffractometer (e.g. Malvern Instruments Ltd, UK) using dry dispersion method and Fraunhofer approximation.

In another aspect, the present invention provides a method of preparing a dry powder inhalation composition comprising a first and a second active ingredient in
15 micronized form comprising the steps of:

- (a) mixing the first active ingredient and a portion of the second active ingredient with a first particulate excipient having VMD within the range of from about 30 to about 70 μm to provide a first preblend;
- (b) mixing the remaining portion of the second active ingredient with a
20 second particulate excipient having VMD within the range of from about 80 to about 150 μm to provide a second preblend; and
- (c) mixing the first and the second preblends, optionally with additional first or second particulate excipient, together and
- (d) optionally mixing the obtained blend with additional first or second
25 particulate excipient.

The first and second active ingredients, which are understood herein to be different, can be generally any two active ingredients which are suitable for administration by inhalation in dry powders as a combination. In particular, the active ingredients may
30 be selected from those that are useful in the treatment of respiratory diseases such as asthma and COPD. The present method can be used also in the preparation of dry powder inhalation compositions which incorporate more than two different active

ingredients, for example in the preparation of a combination of three active ingredients.

According to one embodiment of the invention, the first and second active
5 ingredients are selected from anti-inflammatory steroids and bronchodilators. Examples of anti-inflammatory steroids include, but are not limited to, budesonide, fluticasone, beclomethasone, ciclesonide, fluticasone, mometasone and pharmaceutically acceptable salts thereof. Examples of bronchodilators include, but
10 are not limited to, formoterol, salmeterol, aclidinium, arformoterol, carmoterol, fenoterol, glycopyrronium, indacaterol, ipratropium, olodaterol, salbutamol, tiotropium, umeclidinium, vilanterol and pharmaceutically acceptable salts thereof.

According to one particular embodiment of the invention, the first active ingredient is an anti-inflammatory steroid and the second active ingredient is a bronchodilator.
15 According to another particular embodiment of the invention, the first active ingredient is a bronchodilator and the second active ingredient is an anti-inflammatory steroid. According to another particular embodiment of the invention, the first active ingredient is budesonide or a pharmaceutically acceptable salt thereof and the second active ingredient is formoterol or a pharmaceutically acceptable salt
20 thereof. According to still another particular embodiment of the invention, the first active ingredient is fluticasone or a pharmaceutically acceptable salt thereof and the second active ingredient is salmeterol or a pharmaceutically acceptable salt thereof.

The active ingredients should be in micronized form, i.e. having particle size lower
25 than about 10 μm , for example in the range from about 0.5 to about 10 μm , particularly in the range from about 1 to about 6 μm , such as to be able to deposit target areas in the lungs. Conventional methods, such as milling, can be used to provide the active ingredients in micronized form.

30 The amount of the active ingredient in the dry powder inhalation composition can vary depending e.g. on the active ingredient and the type of dry powder inhaler used. Generally, the amount of the active ingredient in the dry powder inhalation

composition is within the range of 0.02 to 30 %, typically from 0.05 to 10 %, more typically from 0.1 to 5 %, per weight of the composition.

According to one embodiment of the invention, the excipient used in the dry powder
5 inhalation composition is a mono- or disaccharide, particularly lactose or mannitol,
for example alpha lactose monohydrate. In general, the particle size of the excipient
is preferably such that it can be entrained in the air stream but not enter deeply into
the lung. However, a small proportion of particles with respirable size ($< 10 \mu\text{m}$) can
be present in the excipient as such fine particles of the excipient may help in attaining
10 higher FPD values. The VMD of the excipient, such as lactose, to be used in the
composition is suitably in the range of, for example, from about 30 to about $150 \mu\text{m}$.
The excipient of desired VMD can be obtained from commercial sources or can be
prepared using methods known in the art such as by blending together excipient
powders of known particle size or by sieving.

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In the present method two particulate excipients are used which differ in their median
particle size such that the VMD of the finer particulate excipient is less than 90 % of
the VMD of the coarser particulate excipient. According to one embodiment of the
invention, the VMD of the finer particulate excipient is less than 85 % of the VMD
20 of the coarser particulate excipients. According to another embodiment of the
invention, the VMD of the finer particulate excipient is within the range of from
about 30 to about $70 \mu\text{m}$, for example from about 35 to about $65 \mu\text{m}$, and the VMD
of the coarser particulate excipient is within the range of from about 80 to about $150 \mu\text{m}$,
for example from about 90 to about $120 \mu\text{m}$.

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The weight ratio of the finer particulate excipient to coarser particulate excipient in
the dry powder inhalation composition may vary within a wide range, but is typically
within the range of 0.2 to 5, more typically from 0.25 to 3, for example from 0.5 to
1.5.

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Preferably, the first and the second particulate excipient is lactose.

In the first step of the mixing process, the entirety of the first active ingredient and a portion of the second active ingredient are mixed with a first particulate excipient (e.g. the finer particulate excipient) to provide a first preblend. In this step the entirety or only a portion of the total first excipient may be used. If only a proportion
5 of the first excipient is used in this step, the proportion is typically 5 – 80 %, for example 10-75 %, of the total amount used in the composition. The rest of the first particulate excipient may then be used in subsequent blending steps. The components of the first preblend are mixed in a suitable blending device, for example a low shear powder mixer or high shear powder mixer. The mixing speed and mixing time may
10 vary within a broad range depending on the blending device used but are in general selected such as to produce homogenous powder composition. The mixing speed may be for example in the range of 10 – 50 rpm, for example 20 - 40 rpm. The mixing time may be for example in the range of 1 to 60 min, for example 3 to 15 min.

15 The second preblend is prepared by mixing the remaining portion of the second active ingredient with a second particulate excipient (e.g. the coarser particulate excipient) to provide a second preblend. In this step the entirety or only a portion of the total second excipient may be used. If only a proportion of the second excipient is used in this step, the proportion is typically 1-50 %, for example 1-30 %, of the total
20 amount used in the composition. The rest of the second particulate excipient may then be used in the final blending step. The same blending conditions as above can be utilized.

Next the first and the second preblends are suitably sieved and then mixed together.
25 If only a portion of the first excipient was used in the preparation of the first preblend, the rest of the first excipient (e.g. the rest of the finer particulate excipient) is mixed in this step with the first and the second preblends to obtain a blend containing the first and the second active ingredient. The blend is then preferably sieved. The same blending conditions as above can be utilized.

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If only a portion of the second excipient was used in the preparation of the second preblend, the rest of the second excipient (e.g. the rest of the coarser particulate excipient) can now be mixed with the previously obtained blend containing the first

and the second active ingredient such as to obtain the final dry powder inhalation composition. The same blending conditions as above can be utilized. The final composition can be filled in a suitable dry powder inhaler.

- 5 If desired, further excipients or active ingredients can be added to the composition during above mentioned mixing steps or during further mixing steps.

In the development of dry powder inhalation compositions incorporating a combination of active ingredients there often occurs a desire to adjust the fine
10 particle dose (FPD) of one active ingredient independently of the other active ingredient. According to the present method, the FPD of the second active ingredient of the composition can be independently adjusted by simply changing the proportion of the second active ingredient which is mixed with a first particulate excipient. Preblending the active ingredient with coarser excipient is found to be associated
15 with lower FPD level. Thus, in case the first particulate excipient is the finer particulate excipient, the FPD of the second active ingredient can be increased by increasing the proportion of the second active ingredient which is mixed with a first particulate excipient. Inversely, the FPD of the second active ingredient can be decreased by decreasing the proportion of the second active ingredient which is
20 mixed with the first particulate excipient.

The invention is illustrated further with the following Examples.

Example 1.

- 25 A dry powder formulation for inhalation according to Table 1 was prepared.

Table 1. Dry powder formulation for inhalation

Formoterol fumarate dihydrate	1.71 g
Budesonide	60.9 g
Lactose A (VMD = 55 μ m)	862 g
Lactose B (VMD = 105 μ m)	575 g

A first preblend was prepared by mixing 0.855 g of micronized formoterol fumarate dihydrate, 60.9 g of micronized budesonide and 287 g of lactose A in a swing-mix type powder mixer followed by sieving the mixture and blending it with the rest (575 g) of lactose A in a swing- mix type powder mixer. A second preblend was prepared
5 by mixing 0.855 g of micronized formoterol fumarate dihydrate and 192 g of lactose B in a swing-mix type powder mixer followed by sieving the mixture and blending it with 192 g of lactose B in a swing-mix type powder mixer. The two preblends were combined by sieving and then mixed with the rest (191 g) of lactose B in a swing-mix type powder mixer to obtain the final formulation. The mixing time of each step
10 was 5 min at 35 rpm.

Example 2. (Reference example)

A dry powder formulation for inhalation according to Example 1 was prepared with
15 the exception that all formoterol fumarate dihydrate was incorporated in the second preblend (with lactose B).

Example 3. (Reference example)

20 A dry powder formulation for inhalation according to Example 1 was prepared with the exception that all formoterol fumarate dihydrate was incorporated in the first preblend (with lactose A).

Example 4.

25 The formulations of Examples 1, 2 and 3 were filled in Easyhaler[®] powder inhaler device and the FPD values for the active ingredients (formoterol fumarate dihydrate and budesonide) were determined in vitro using methods well known in the art. The results are shown in Table 2.

Table 2. Fine particle dose (FPD) values of formulations of Examples 1-3.

Example No.	FPD of formoterol ($\mu\text{g}/\text{dose}$)	FPD of budesonide ($\mu\text{g}/\text{dose}$)
2	2.8	137
1	3.1	139
3	3.6	133

It can be seen that FPD of formoterol fumarate dihydrate can be adjusted by blending part of formoterol fumarate dihydrate with lactose B (coarser lactose) while the FPD of budesonide is only minimally affected. The change in FPD is dependent on the proportion of formoterol which is blended with lactose B (coarser lactose).

Example 5.

A dry powder formulation for inhalation according to Table 3 was prepared.

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Table 3. Dry powder formulation for inhalation

Salmeterol xinafoate	1.9 g
Fluticasone propionate	13.0 g
Lactose A (VMD = 55 μm)	145.5 g
Lactose B (VMD = 105 μm)	339.6 g

A first preblend was prepared by mixing 0.95 g of micronized salmeterol xinafoate, 13.0 g of micronized fluticasone propionate and 107.3 g of lactose A in a swing- mix type powder mixer. A second preblend was prepared by mixing 0.95 g of micronized salmeterol xinafoate and 7.3 g of lactose B in a swing- mix type powder mixer. The two preblends were combined by sieving and then mixed with 38.2 g of lactose A in a swing- mix type powder mixer. The resulting mixture was sieved and finally mixed with 332.3 g of lactose B in a swing- mix type powder mixer to obtain the final formulation. The mixing time of each step was 5 min at 35 rpm.

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Example 6. Effect of salmeterol/lactose ratio of the second preblend on fine particle dose (FPD)

It was studied how changes in the ratio of salmeterol/lactose B in the second preblend affects the fine particle dose (FPD) of the final salmeterol/fluticasone formulation. A series of salmeterol/fluticasone formulations were prepared as in the previous example with the exception that the proportion of salmeterol used in the second preblend was varied as well as the proportion of lactose A (of the total lactose) used in the formulation. The formulations were filled in Easyhaler[®] powder inhaler device and the FPD values for the active ingredients were determined in vitro using methods well known in the art. The results were fitted in a mathematical model which demonstrates the effect of the variables on the FPD of the active ingredients. The observed changes in the FPD of salmeterol xinafoate and fluticasone propionate are presented in Figure 1a and 1b, respectively. In the Figures the proportion (% of total) of salmeterol xinafoate (SX) mixed with lactose A (finer lactose) in the first preblend is shown in x-axis. The proportion of lactose A (% of total lactose) used in the composition is shown in y-axis. The resulting FPD value of salmeterol xinafoate is shown in Figure 1a as zones ranging from about 4 µg/dose to about 10 µg/dose. The resulting FPD value of fluticasone propionate is shown similarly in Figure 1b.

The Figures demonstrate that the FPD value (shown in a box) for each active ingredient of the composition can be increased by increasing the proportion of lactose A (finer lactose) in the composition. For example, the FPD of salmeterol can be increased from about 4 µg/dose to about 10 µg/dose by increasing the proportion of lactose A (finer lactose) from 0 % to 30 % (Figure 1a). At the same time, the FPD of fluticasone increases from about 60 µg/dose to about 100 µg/dose (Figure 1b).

On the other hand, when part of salmeterol of the composition is blended with lactose B (coarser lactose), the FPD value of salmeterol is decreased. The decrease is dependent on the proportion of salmeterol which is blended with lactose B (coarser lactose). For example, when the ratio of lactose A to lactose B is fixed to 10:90 (i.e. proportion of lactose A is 10 %) in the composition, the FPD of salmeterol can be linearly decreased from about 7.2 µg/dose down to about 5.5 µg/dose by increasing

the part of salmeterol which is blended with lactose B (coarser lactose) from 0 % to 100 %. This corresponds to a decrease of 24 % in the FPD of salmeterol. Importantly, at the same time the FPD value of fluticasone drops only 5 % (from about 74 $\mu\text{g}/\text{dose}$ to about 70 $\mu\text{g}/\text{dose}$). Thus, blending part of the second active ingredient of the

5 combination with a second lactose grade differing in the particle size from the first lactose grade provides a method of adjusting the FPD of the second active ingredient while only minimally affecting the FPD of the first active ingredient of the composition.

CLAIMS

1. A method of preparing a dry powder inhalation composition comprising a first and a second active ingredient in micronized form comprising the steps of:
 - 5 (a) mixing the first active ingredient and a portion of the second active ingredient with a first particulate excipient to provide a first preblend;
 - (b) mixing the remaining portion of the second active ingredient with a second particulate excipient to provide a second preblend; and
 - (c) mixing the first and the second preblends together;
- 10 wherein the first particulate excipient and the second particulate excipient differ in their median particle size, such that VMD (volume median diameter) of the finer particulate excipient is less than 90 % of the VMD of the coarser particulate excipient.
2. A method according to claim 1, wherein the VMD of the finer particulate excipient is less than 85 % of the VMD of the coarser particulate excipient.
3. A method according to claim 1 or 2, wherein the VMD of the finer particulate excipient is within the range of from about 30 to about 70 μm and the VMD of the coarser particulate excipient is within the range of from about 80 to about 150 μm .
4. A method of preparing a dry powder inhalation composition comprising a first and a second active ingredient in micronized form comprising the steps of:
 - 20 (a) mixing the first active ingredient and a portion of the second active ingredient with a first particulate excipient having VMD within the range of from about 30 to about 70 μm to provide a first preblend;
 - (b) mixing the remaining portion of the second active ingredient with a second particulate excipient having VMD within the range of from about 80 to about 150 μm to provide a second preblend; and
 - (c) mixing the first and the second preblends, optionally with additional first or second particulate excipient, together and
 - (d) optionally mixing the obtained blend with additional first or second particulate excipient.
- 30 5. A method according to any of claims 1 to 4, wherein the first and second particulate excipient is lactose.
6. A method according to any of claims 1 to 5, wherein the first and second

active ingredients are selected from anti-inflammatory steroids and bronchodilators.

7. A method according to any of claims 1 to 6, wherein the first active ingredient is an anti-inflammatory steroid and the second active ingredient is a bronchodilator.

5 8. A method according to any of claims 1 to 6, wherein the first active ingredient is a bronchodilator and the second active ingredient is an anti-inflammatory steroid.

9. A method according to any of claims 1 to 8, wherein the anti-inflammatory steroid is budesonide, fluticasone, beclomethasone or a pharmaceutically acceptable
10 salt thereof.

10. A method according to any of claims 1 to 9, wherein the bronchodilator is formoterol, salmeterol or a pharmaceutically acceptable salt thereof.

11. A method according to claim 7, wherein the first active ingredient is budesonide or a pharmaceutically acceptable salt thereof and the second
15 active ingredient is formoterol or a pharmaceutically acceptable salt thereof.

12. A method according to claim 7, wherein the first active ingredient is fluticasone or a pharmaceutically acceptable salt thereof and the second active ingredient is salmeterol or a pharmaceutically acceptable salt thereof.

13. A method according to claim 7, wherein the first active
20 ingredient is beclomethasone or a pharmaceutically acceptable salt thereof and the second active ingredient is formoterol or a pharmaceutically acceptable salt thereof.