(19) DANMARK

(10) DK/EP 2170348 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 31/573 (2006.01)* *A 61 K 9/46 (2006.01)* *A 61 K 9/72 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2016-11-07**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-08-10**

(86) Europæisk ansøgning nr.: **08784529.3**

(86) Europæisk indleveringsdag: **2008-06-20**

(87) Den europæiske ansøgnings publiceringsdag: **2010-04-07**

(86) International ansøgning nr.: **EP2008004993**

(87) Internationalt publikationsnr.: **WO2009000473**

(30) Prioritet: **2007-06-22 EP 07110896**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR**

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(54) Benævnelse: **BRUSETABLETTER TIL INHALATIONSBRUG**

(56) Fremdragne publikationer:
WO-A-03/035030
WO-A-03/086347
WO-A-2004/022132
WO-A-2005/011639

DESCRIPTION

Brief description of the invention

[0001] The present invention relates to effervescent tablets containing at least one micronized water-insoluble active principle for the extemporaneous preparation of a suspension suitable for inhalatory use.

[0002] Furthermore, it relates to the use of effervescent tablets containing water-insoluble active principles for the extemporaneous preparation of a suspension for inhalatory use.

[0003] The tablets are added to water or to a solution wherein they disaggregate until a fine suspension is obtained. The suspension maintains the initial particle size distribution of the active principle, ensuring the achievement of the therapeutic window of the breathed fraction.

Background of invention

[0004] Particle size is a very important factor to consider when administering inhalation preparations. It has been reported that the optimum particle size for penetration into the pulmonary cavity falls in the range 0.5 - 7.0 µm.

[0005] Smaller particles fail to settle in the bronchioles and bronchi and are mainly exhaled, while bigger particles get blocked in the respiratory tree before entering the bronchioles.

[0006] Water-insoluble drugs such as corticosteroids and mucolytic agents are often used by inhalatory administration in the form of suspensions for nebulisation, generally from a metered aerosol. This way of administration has the advantage that the drug exerts a topical effect on the lungs without a significant systemic activity at recommended doses.

[0007] For example, cortiscosteroids such as beclomethasone dipropionate, beclomethasone dipropionate, fluticasone propionate, budesonide, flunisolide, betamethasone, triamcinolone, mometasone, ciclesonide are widely used for the prophylaxis of the symptoms of asthma by inhalation.

[0008] However, commercial products of corticosteroid active principles, such as beclomethasone inhalatory suspensions, show the inconvenience of a very variable particle size distribution due to the formation of aggregates, this affecting the fraction of drug that actually reaches the lower parts of the respiratory tract. Furthermore, the formation of aggregates causes the sedimentation of the particles of active principle, thereby affecting also the dosing of the active principle.

[0009] WO 2004/022132 A2 discloses an insoluble carrier impregnated with the active substance in micronized form which is reconstituted prior to administration by addition of a solution for inhalation.

Summary of the Invention

[0010] The present invention is defined in the claims. The present inventors have surprisingly found that the problem of the wide granulometric dispersion of commonly used inhalatory suspensions can be overcome by the extemporaneous preparation of inhalatory suspension from effervescent tablets. In fact, as it will be shown in details in the experimental section hereibelow, it has now been found that suspensions made from effervescent tablets retain the original particle size of the drug substance.

[0011] Thus, object of the present invention are effervescent tablets comprising a micronised water insoluble active ingredient and their use for the preparation of a suspension for inhalatory administration.

[0012] The use of the effervescent tablets of the invention allows to obtain a suspension that retain the original particle size of the drug substance and, giving better particle size patterns, enhances the efficacy of the topical treatment..

[0013] The suspension, extemporarily reconstituted introducing an effervescent tablet into a nebulization device previously filled with an aqueous solution, preferably a physiological solution, is inhaled after the complete disintegration of the tablet, providing a

composition that falls into the therapeutical particle size range.

[0014] There are other advantages in using a solid formulation instead of a solution or a suspension; solid drug products in fact have a better chemical and physical stability, and a easier use and shipping.

[0015] Moreover, they do not need preservatives in the formulation, this raising the acceptability and tolerability of the administered product.

[0016] When the half dose is needed, tablets can be divided in two parts, and the stability of the residual half tablet is far bigger than the half dose of a solution or suspension.

Brief description of the figures

[0017] The specification is accompanied by the following figures:

Figures 1A and 1B show a comparison between the particle size distribution of beclometasone dipropionate (BDP) raw material and suspension from effervescent tablet;

Figures 2A and 2B show a comparison between the particle size distribution of beclometasone dipropionate (BDP) raw material and commercially available BDP aqueous suspension;

Figure 3A and 3B show a comparison between the particle size distribution of fluticasone propionate raw material and suspension from effervescent tablet.

Detailed description of the invention

[0018] A first object of the invention is an effervescent tablet for the extemporaneous preparation of a suspension for inhalatory administration comprising a micronized water-insoluble active principle.

[0019] The active principle present in the tablet of the present invention has been micronized before formulation into the tablet to a particle size between 0.5 and 7 µm.

[0020] According to the present invention, the term "water-insoluble active principle" indicates that the solubility of the active principle is such that from 100 mL to more than 10,000 mL of water are necessary to dissolve 1 gram of molecule

[0021] Preferred active principles for use in the tablet of the present invention are corticosteroids such as beclometasone dipropionate, fluticasone propionate, budesonide, flunisolide, betamethasone, triamcinolone, mometasone, ciclesonide or water-insoluble mucolytic agents such as sobrerol. These active principles can be used alone or in combination.

[0022] Most preferred compounds that can be vehicled the effervescent tablets are beclometasone dipropionate and fluticasone propionate.

[0023] The composition of excipients used in the effervescent tablet must be such that the tablet dissolves in short time, with a quick effervescence that does not leave remainders or slugs not completely dissolved.

[0024] The excipients of the composition have to be compatible with the administration route at issue (cfr. Inactive Ingredient Guide, FDA, 1996 - Inhalatory route).

[0025] In details the tablet of the invention comprises the following excipients:

Acidic compounds: citric acid (anhydrous, or monohydrate, or dihydrate), tartaric acid. Basic compounds: carbonate, bicarbonate, baked carbonate, or baked bicarbonate.

Surfactants: they are responsible for the wetting of the poor soluble drug substance in the aqueous medium, after the complete dissolution of the tablet. Non-ionic surfactants (e.g. polysorbates) as well as ionic surfactants (e.g. SDS) can be used.

[0026] Other optional excipients are the following:

Binders: if the wet granulation is chosen, a binding solution is necessary to form the granules. PVP and other common binders can be used, depending on the technique chosen.

Adsorbents: can be useful to adsorb the overwetting of granules.

Lubricants: they have to be compatible with the inhalation route. Sodium benzoate or similar substances can be effective in lubricating the mixtures before pressing.

Diluents: it is necessary to reach a suitable final weight of the tablet. Lactose, mannitol, starch and other diluents can be used for this purpose.

[0027] The excipients do not have to aggravate the overall flavor and odor of the tablet; in some cases they have to correct some unfavourable organoleptic properties of the drug substance.

[0028] For this purpose, a taste modifying agent could be necessary to mask the bad taste of the drugs. It has to be reminded, in fact, that the steam supplied by the nebulizer condense in the throat or in the nose, thus promoting the detection of bitterness, sourness ands so on.

[0029] Methods of production of effervescent tablets can be different, according to special needs of the drug substance that has to be formulated.

[0030] Production can occur by direct compression of drug substance and excipients or after a granulation step.

[0031] Drug substances can be either granulated with the excipients or added as powders to the granulated excipients, but tests showed that the best particle size profiles were obtained by granulating the drug substance with at least some of the excipients.

Examples of granulation techniques are the following:

1a. Wet granulation/fluid bed granulation

[0032] Usually, there is an acidic and a basic carbonic compound in the mixture. These excipients are responsible for the effervescence of the tablets, when they are placed in an aqueous environment. When choosing a wet or fluidized bed granulation technique, it is important to keep the acidic and the basic compound well separated (e.g. the acidic compound is granulated with the drug substance and/or some other excipients, while the basic compound is added to the dried granules, before the tablet pressing), in order to avoid the onset of effervescence process during the production.

Examples of wet granulation / fluidized bed granulations are the following:

a. Heated mixing on an oil bath or a sand heater.

[0033] Powders are mixed under heat. When excipients containing bound molecules of water are used, the water acts as a granulating agent in the bulk, while freeing itself from the crystalline structure. The mixing step aids the distribution of the water, thus providing an homogenous mixture of wet granules.

[0034] The granules are then sieved and dried until the desired water content.

b. Fluid bed granulation.

[0035] Part of the bulk (excipients and/or the drug substance) is granulated with water and a binding solution (e.g. polyvinylpyrrolidone). The granules are then dried in the fluid bed until the desired residual humidity is reached.

1b. ***Dry granulation***

[0036] Dry powders are mixed and pressed in big slugs or ribbons. These agglomerates are then crushed into smaller granules until the desired particle size.

[0037] The original powder mixture of drug substance and excipients has to be compressible and flowing to be easily compressed. It should not tend to pack in the feeders and the tooling of the tablet press, as well.

[0038] A further object of the present invention is the use of the effervescent tablet of the invention for the extemporaneous preparation of a suspension for inhalatory administration.

[0039] The suspension is prepared adding the effervescent tablet in water or in an aqueous solution, where it disintegrates. Preferably, said water or aqueous solution is sterile.

[0040] According to a preferred embodiment of the invention the aqueous solution is a physiological solution.

[0041] Tablets can alternatively be added also to a solution of at least one water-soluble active principle. Preferably said active principles are water-soluble mucolytic agents, preferably selected from the group consisting of ambroxol or sobrerol, or bronchodilators, preferably selected from salbutamol or ipratropium chloride.

Examples

Beclometasone dipropionate effervescent tablets.

[0042] Preparation of an effervescent tablet containing 0.8 mg of beclometasone dipropionate. The composition of the tablet prepared for the present study is reported in table 1.

Table 1 - composition of beclometasone dipropionate effervescent tablets.

Ingredient	***Amount per tablet***
Beclometasone dipropionate	0.8 mg
Sodium bicarbonate	31 mg
Citric acid anhydrous	25 mg
Lactose	8.4 mg
Polysorbate 20	2 mg
Sodium benzoate	2.8 mg

[0043] The above ingredients are mixed using the fluid bed granulation technique above described and granules are then pressed.

[0044] Once the tablet is put in the inhalation device vessel, previously filled with physiological solution, a suspension forms after the fast disintegration of the tablet. The technological properties of the tablet and the reconstituted suspension after disintegration are summarized in table 2.

Table 2 - properties of the tablet / reconstituted suspension.

Tablet	
Mean weight	70 mg
Diameter	5 mm

Tablet	
Thickness	2.0 - 2.2 mm
Water content	0.2 - 0.3%
Mean crushing strength	18 N
Colour	White
Mean disintegration time	150 seconds
Suspension	
pH	5.0-7.0
Colour	White
Opalescence	Yes
Residue or precipitate presence	No
Foaminess	Yes

[0045] A granulometric analysis was performed on the final suspension. The distribution curve was compared with the commercial raw material (material which is used for the preparation of commercial available BDP). As it can be seen from data displayed in table 3 and figures 1A-1B and 2A-2B, there is little or no difference between the particle size of the raw material and the suspension obtained by disintegration of the effervescent tablet.

Table 3 - granulometric analysis of beclometasone dipropionate of raw material and suspension from effervescent tablet.

Raw material	
Median	1.638 µm
Mode	1.654 µm
100% of particles	< 7.62 µm
Suspension from effervescent tablet	
Median	1.642 µm
Mode	2.031 µm
100% of particles	< 6.86 µm

[0046] As a proof of concept, here is reported the granulometric analysis and particle size distribution of a commercially available aqueous BDP inhalatory suspension. As it can be seen from table 4 and figures 2A and 2B, the particle size of the aqueous suspension is broader, and the mean values are considerably bigger than the raw material.

Table 4 - granulometric analysis of beclometasone dipropionate in a commercially available aqueous BDP inhalatory suspension.

Aqueous inhalatory suspension	
Median	14.239 µm
Mode	18.484 µm
100% of particles	< 50.47 µm

Fluticasone propionate effervescent tablets.

[0047] Preparation of an effervescent tablet containing 0.5 mg of fluticasone propionate. The composition of the tablet prepared for the present study is reported in table 5.

Table 5 - composition of fluticasone propionate effervescent tablets.

Ingredient	***Amount per tablet***
Fluticasone propionate	0.5 mg
Sodium bicarbonate	22.15 mg
Citric acid anhydrous	18.4 mg

Ingredient	*Amount per tablet*
Lactose	26.315 mg
Polysorbate 20	0.085 mg
Sodium benzoate	2.55 mg

[0048] The above ingredients are mixed using the fluid bed granulation technique above described and granules are then pressed.

[0049] Once the tablet is put in the inhalation device vessel, previously filled with physiological solution, a suspension forms after the fast disintegration of the tablet. The technological properties of the tablet and the reconstituted suspension after disintegration are summarized in table 6.

Table 6 - properties of the tablet / reconstituted suspension.

Tablet	
Mean weight	70 mg
Diameter	5 mm
Thickness	2.0 - 2.2 mm
Water content	0.2 - 0.3%
Mean crushing strength	28 N
Colour	White
Mean disintegration time	60 seconds
Suspension	
pH	5.0 - 7.0
Colour	White
Opalescence	Yes
Residue or precipitate presence	No
Foaminess	Yes

[0050] A granulometric analysis was performed on the final suspension. The distribution curve was compared with the commercial raw material (material which is used for the preparation of commercial available BDP). As it can be seen from data displayed in table 7 and figures 3A and 3B, there is little or no difference between the particle size of the raw material and the suspension obtained by disintegration of the effervescent tablet.

Table 7 - granulometric analysis of fluticasone propionate of raw material and suspension from effervescent tablet.

Raw material	
Median	1.664 µm
Mode	2.135 µm
100% of particles	< 5 µm
Suspension from effervescent tablet	
Median	1.89 µm
Mode	2.187 µm
100% of particles	< 7.5 µm

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO2004022132A2 [0009]

Patentkrav

1. Brusetablet til uforberedt fremstilling af en suspension der er egnet til inhalationsadministration omfattende mindst ét vand-uopløseligt aktivt aktivstof og excipienser der er egnede til inhalationsadministration omfattende:

en syreholdig forbindelse valgt fra citronsyre, vinsyre,

en basisk forbindelse valgt fra carbonat, bicarbonat, bagt carbonat og bagt bicarbonat; ikke-ioniske eller ioniske surfaktanter,

hvor det vand-uopløselige aktivstof er blevet mikroniseret til en partikelstørrelse mellem 0,5 til 7 µm og

hvor brusetabletten, når den tilsættes til vand eller til en vandig opløsning, skiller ad indtil opnåelse af den uforberedte suspension der er egnet til inhalationsadministration, i hvilken den originale partikelstørrelsesfordeling af det vand-uopløselige aktivstof opretholdes.

2. Brusetablet ifølge krav 1, hvor aktivstoffet er valgt fra corticosteroider og mucolytiske midler.

3. Brusetablet ifølge kravene 1 eller 2, hvor aktivstoffet er valgt fra gruppen bestående af beclomethasondipropionat, fluticasonpropionat, budesonid, flunisolid, betamethason, triamcinolon, mometason, ciclesonid og sobrerol.

4. Brusetablet ifølge kravene 1 to 3 hvor aktivstoffet er valgt fra beclomethasondipropionat og fluticasonpropionat.

5. Anvendelse af en brusetablet ifølge kravene 1 til 4 til fremstillingen af en uforberedt suspension til inhalationsadministration.

6. Anvendelse ifølge krav 5, omfattende trinnet af disintegration af brusetabletten i vand eller i en vandig opløsning.

7. Anvendelse ifølge krav 6, hvor den vandige opløsning er en fysiologisk opløsning.

8. Anvendelse ifølge kravene 6 to 7, hvor den vandige opløsning er en opløsning af mindst ét vand-opløseligt aktivstof.

9. Anvendelse ifølge krav 8, hvor det vand-opløselige aktivstof er et mucolytisk middel eller en bronchodilator.

10. Anvendelse ifølge krav 9, hvor det mucolytiske middel er valgt fra gruppen bestående af ambroxol eller sobrerol.

11. Anvendelse ifølge krav 9, hvor bronchodilatoren er salbutamol eller ipratropiumchlorid.

DRAWINGS

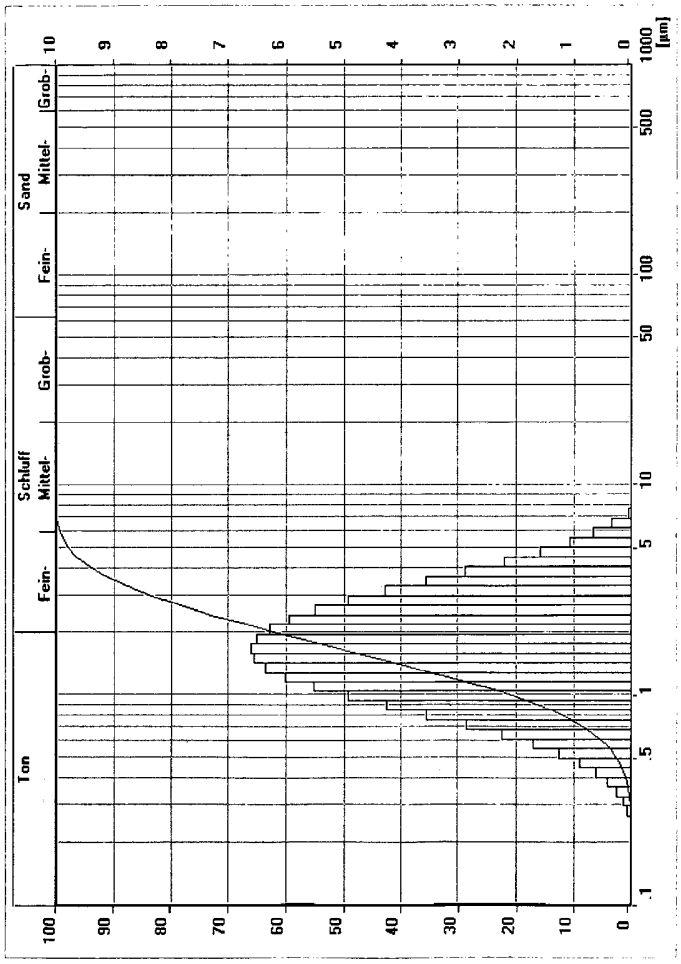
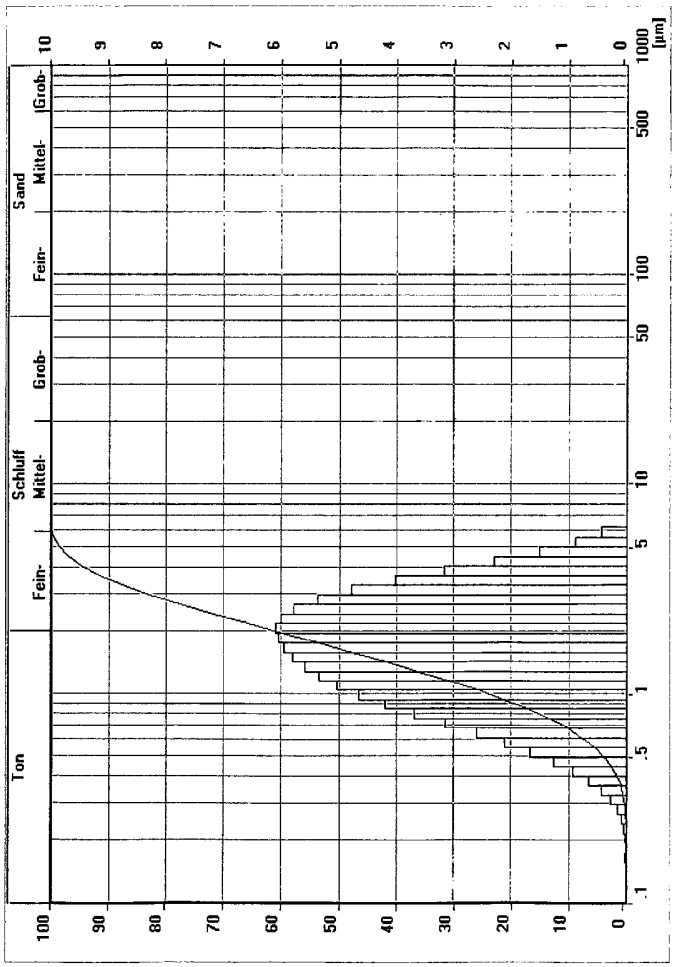
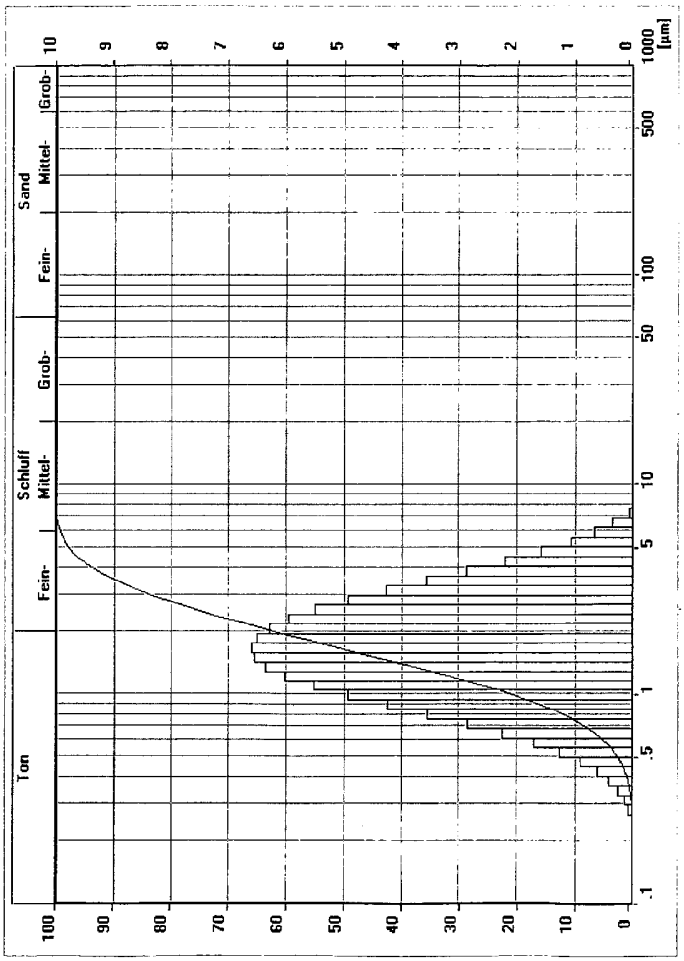


Figure 1A



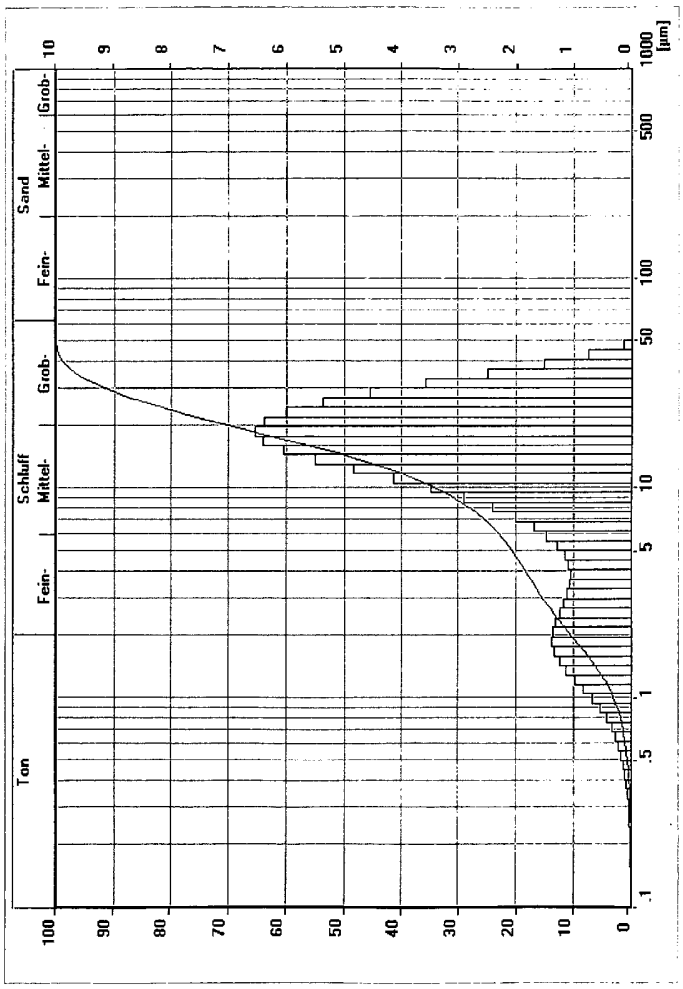
BDP suspension from effervescent tablet

Figure 1B



BDP raw material

Figure 2.A



commercially av.BDP aqueous suspension

Figure 2B

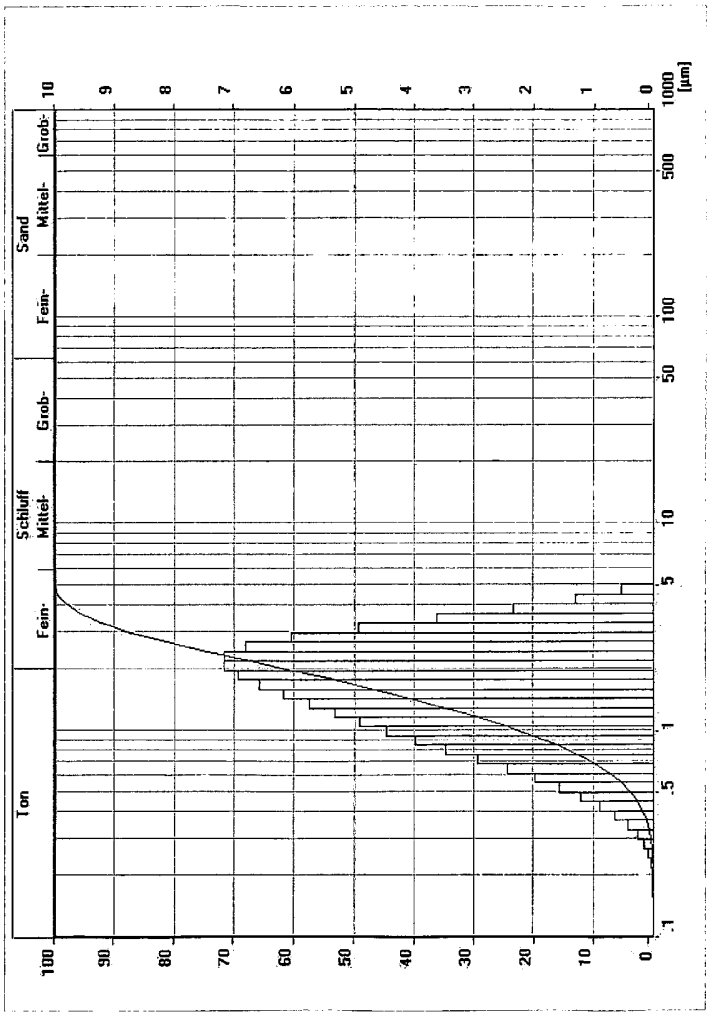

Ton
Schluff
Sand
Fein-
Mittel-
Grob-
Fein-
Mittel-
Grob-
[µm]
Fluticasone propionate raw material

Figure 3 A

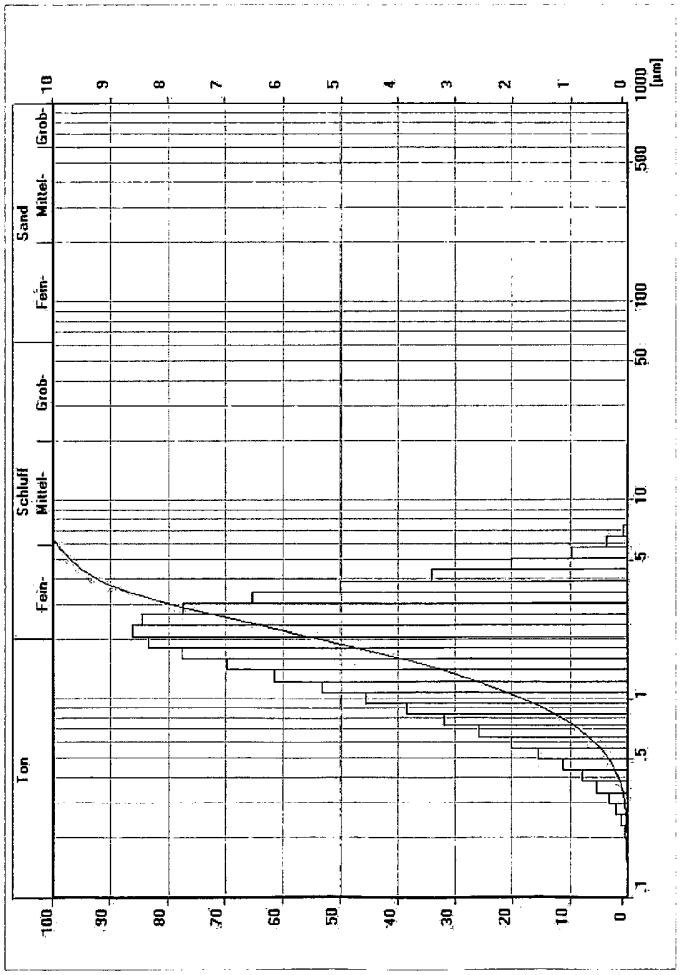


Figure 3B

Fluticasone propionate suspension from effervescent tablet