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EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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Bogotá D.C, SEPTIEMBRE DE 2007

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Sarlikiotis et al.

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(45) **Date of Patent: *Sep. 4, 2001**

(54) **PARTICULATE FORMULATION FOR
ADMINISTRATION BY INHALATION**

(75) **Inventors: Werner Sarlikiotis, Frankfurt (DE);
Anne De Boer, Drachten (NL)**

(73) **Assignee: Asta Medica AG, Dresden (DE)**

(*) **Notice:** This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(58) **Field of Search 424/45, 46, 489**

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Primary Examiner—Raj Bawa

(74) *Attorney, Agent, or Firm*—Pillsbury Winthrop LLP

(57) **ABSTRACT**

A pharmaceutical formulation for administration by inhalation, a micronized active compound or micronized active compound mixture with a mean particle size of 0.1 μm to 10 μm being applied to a pharmaceutically acceptable excipient having a mean particle size of 200 μm to 1000 μm without the use of binders.

16 Claims, No Drawings

PARTICULATE FORMULATION FOR ADMINISTRATION BY INHALATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a pharmaceutical formulation for administration by inhalation, the micronized active compound or the micronized active compound mixture being applied to an excipient without binders being used.

2. Background Information

Active compounds which are administered by inhalation must penetrate deep into the lungs in order to show topical or alternatively systemic action. In order to achieve this, the particles of the active compound must have a diameter which does not exceed approximately 5 μm –10 μm . Additionally, the active compound or the active compound mixture is administered to the patient with the aid of a specially made device, an inhaler. The active compound here must first be either predosed, for example in capsules or blister packs, or stored in a relatively large amount in the inhaler in order then to be removed from a measuring device by the inhalation process of the patient and redispersed into the fine primary particles with a dispersing device, for example a fluidizing chamber, carried along with the breath and thus made available to the lungs.

On account of the particle size a high specific surface area of the particles and a distribution of forces resulting therefrom, the very fine-grained active compounds used for this purpose have very pronounced adhesive and cohesive properties, which in turn has the result that the processing of such powders regarding process technology runs into difficulties. Such process technology steps are the mixing of the active compounds in active compound mixtures, the storage and the transport of the powders, the filling of capsules, blister packs or inhalers, and the dosage of the therapeutic amounts.

The agglomeration processes customary in pharmacy, e.g. granulation, cannot be employed because the particles are so strongly bound to one another thereby that respirable active compound particles are no longer present or can no longer be generated. Additionally, at present most of the pharmaceutically customary auxiliaries cannot be used in pharmaceutical forms for inhalation, as the toxicological behavior of these substances on pulmonary administration is still largely unknown.

In order to solve the problems mentioned, it was proposed, for example, in EP 0 398 631 to grind the active compound down to a mean particle diameter of 5 μm to 10 μm and then either to mix it with a solid, pharmaceutically customary excipient, this having a mean particle diameter of 30 μm to 80 μm , or else to prepare round agglomerates of the active compound particles (so-called soft pellets), these disintegrating into the primary particles again during inhalation. A process for the preparation of such soft pellets is also described (GB 1,569,612 and GB 1,520,247). In this process, the moisture content of the active compound must be adjusted before the preparation of the soft pellets. The soft pellets can be filled into capsules as described, for example, in DE 25 35 258 and GB 1,520,247. In vitro experiments showed that on emptying these capsules with the aid of an inhaler at least 50% of the filled material was emptied.

However, these soft pellets, prepared according to the abovementioned procedures, have a dispersing rate (=proportion of the respirable active compound particles

after emptying, relative to the amount dispensed in the capsule), which may still not be satisfactory.

With a volume flow of 60 l/min, dispersing rates of 13.8–29.5% of the nominal dose were found for available systems in the cascade impinger (four-stage liquid impinger).

In another process (DE 22 29 981), the active compound is mixed with a pharmaceutically utilizable, water-soluble excipient, this excipient having a particle size of 80 μm to 150 μm .

The disadvantage here is the poor flow properties of the formulation.

DE 41 40 689 describes inhalation powders which consist of a physiologically acceptable auxiliary having a mean particle size of about 20 μm and a second component auxiliary having smaller particles of approximately 10 μm particle size.

This mixture can be filled into capsules and is inhaled using apparatuses which are described in DE 33 45 722. Here too the poor flow properties are a disadvantage.

EP 258 356 describes microparticles for inhalation purposes, which consist of a conglomerate of auxiliaries, for example lactose, xylitol and mannitol of a size between 30 μm and 150 μm . A problem in this process is the relatively complex preparation path in order to prepare auxiliary conglomerates having a specific particle size.

SUMMARY OF THE INVENTION

DE 28 51 489 A1 describes a formulation consisting of beclomethasone dipropionate whose particles to 90% by weight are smaller than 10 μm and of a powder excipient which consists of particles having an effective size of 90% by weight less than 400 μm and of at least 50% by weight greater than 30 μm . In addition to the active compound beclomethasone dipropionate, this formulation can additionally contain a bronchodilator of preferably the same particle size as beclomethasone dipropionate.

Designated bronchodilators are orciprenaline, terbutaline or salbutamol. Conversion to a pharmaceutical preparation is carried out by simple mixing.

WO 91/11179 A1 describes the use of excipient materials such as lactose, polysaccharides and others. As described, these excipient materials have a particle size of 5.0–1000 μm and a surface roughness of less than 1.75. Simple mixing of the excipient material with a pharmaceutical active compound leads to the powder preparation.

The object is thus, for the purposes of inhalation, to develop a powder which is simple to prepare, requires no complicated in-process controls of the moisture content of the active compounds and/or auxiliaries and has a high degree of redispersion. Furthermore, the formulation should have satisfactory flow properties and be easily disintegrable into respirable particles in the inhaler. Under identical conditions, at least 40% should be redispersed.

It has now surprisingly been found that by suitable mixing of the active compound or of the active compound mixture with a pharmaceutically utilizable excipient which has a mean particle size of 200 μm to 1000 μm , preferably between 300 μm and 600 μm , and a roughness of more than 1.75, the active compound particles having a particle size of 0.01 μm to 10 μm adhere to the excipient particles and thereby almost round excipient particles coated with active compound result. In the case of the formulation according to the invention, treatment, for example additional purification processes, of the excipient material employed can be dispensed with.

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The particles of the excipient are commercially available or can be obtained by fractionation (sieve) into a specific grain size or grain size range.

The determination of the particle size of the excipient particles was carried out by measurement of scanning electron microscope photographs and/or by sieve analysis. The determination of the particle size of the active compound particles was carried out by measurement of scanning electron microscope photographs and/or by laser diffraction spectrometry.

This powder formulation can be prepared simply and economically and has significantly better flow properties both in comparison to the untreated active compound powder and to the soft pellets. The results in Table 1 show this. A lower bed height means better flow properties of the formulation.

The more similar the bulk and compacted volumes are, the better the flow properties. However, even the emptying and subsequent redispersion is better in comparison to the previously known formulations (mixtures, soft pellets according to GB 1 569 612 or GB 1 520 247 or untreated active compound powder), i.e. the residues in the inhaler are lower and the yield of respirable particles is higher.

The formulation can contain various active compounds, for example analgesics, antiallergics, antibiotics, anticholinergics, antihistaminics, antiinflammatory substances, antipyretics, corticoids, steroids, antitussives, bronchodilators, diuretics, enzymes, cardiovascular substances, hormones, proteins and peptides. Examples of analgesics are codeine, diamorphine, dihydromorphine, ergotamine, fentanyl and morphine; examples of antiallergics are cromoglycic acid and nedocromil; examples of antibiotics are cephalosporins, fusafungin, neomycin, penicillins, pentamidine, streptomycin, sulfonamides and tetracyclines; examples of anticholinergics are atropine, atropine methonitrate, ipratropium bromide, oxitropium bromide and tropium chloride; examples of antihistaminics are azelastine, fexofenadine and methapyrilene; examples of anti-inflammatory substances are beclomethasone, budesonide, dexamethasone, flunisolide, fluticasone, triamcinolone; examples of antitussives are narcotine and noscapine; examples of bronchodilators are bambuterol, bitolterol, carbuterol, clenbuterol, ephedrine, epinephrine, formoterol, fenoterol, hexoprenaline, ibutanol, isoprenaline, isoproterenol, metaproterenol, orciprenaline, phenylephrine, phenylpropanolamine, pirbuterol, procaterol, reproterol, rimiterol, salbutamol, salmeterol, sulfoneterol, terbutalin and tolbuterol; examples of diuretics are amiloride and furosemide; an example of enzymes is trypsin; examples of cardiovascular substances are diltiazem and nitroglycerine; examples of hormones are cortisone, hydrocortisone and prednisolone; examples of proteins and peptides are cyclosporins, cetorelix, glucagon and insulin. Other active compounds which can be employed are adrenochrome, colchicine, heparin, scopolamine. The active compounds mentioned by way of example can be employed as free bases or acids or as pharmaceutically tolerable salts. Counterions which can be employed are, for example, physiologically tolerable alkaline earth metals or alkali metals or amines, as well as, for example, acetate, benzenesulfonate, benzoate, hydrogen carbonate, hydrogen tartrate, bromide, chloride, iodide, carbonate, citrate, fumarate, malate, maleate, gluconate, lactate, pamoate and sulfate. Esters can also be employed, for example acetate, acetonide, propionate, dipropionate, valerate.

The formulation according to the invention can also consist of a mixture of several finely ground active

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compounds, for example of sodium cromoglycate and reproterol hydrochloride. As already described, 100% of the active compound particles should be less than 10 μm , preferably in the range from 1 μm to 5 μm .

The excipient employed is a nontoxic material which has a mean particle size of 200 μm to 1000 μm , preferably between 300 μm and 600 μm . Excipients according to the invention inorganic salts such as sodium chloride and calcium carbonate, organic salts such as, for example, sodium lactate and organic compounds such as, for example, urea, monosaccharides such as, for example, glucose and its derivatives such as sorbitol, polyalcohols, sorbitol, mannitol, xylitol, disaccharides such as, for example, lactose, maltose and their derivatives, and polysaccharides such as, for example, starch and its derivatives, oligosaccharides such as, for example, cyclodextrins, and also dextrans can be employed. Mixtures of the auxiliaries can also be employed.

The ratio of active compound to the excipient material depends on the substances employed. By means of the examples, it has been shown that the use of 10 to 80 percent by weight of the active compound to 20 to 90 percent by weight of the excipient, preferably 30 to 70 percent by weight of the active compound to 30 to 70 percent by weight of the excipient, gives satisfactory results.

Additionally to the active compound and excipient, the formulations can also contain other constituents, such as flavor corrigents, for example saccharin or peppermint flavoring. The components can be, for example, 10–20% by weight relative to the active compound or to the active compound mixture.

The preparation of the formulation is carried out by mixing the constituents in a suitable mixer, for example tumble mixer, rotary mixer, high-speed mixer or fluidizing mixer. A possible tumble mixer is, for example, the Turbula mixer, W. A. Bachofen AG, Basle, CH; a high-speed mixer is the Diosna mixer, Dierks und Söhne, Osnabrück, FRG.

The constituents here are added to the mixer and mixed until the excipient crystals are coated with the fine active compound or active compound mixture, the fine fraction gradually disappearing and round, coated particles resulting.

However, other processes such as fluidized bed or vibration processes can also be used for the preparation of the powder formulations according to the invention. In these processes, the excipient particles are set into rotary motion in a container. The active compound particles are thereby able to deposit thereon and thus form the formulation according to the invention.

In order to demonstrate the advantages of the formulation according to the invention in comparison to the mixture of the two active compounds and the soft pellets according to specifications GB 1,569,612 and GB 1,520,247, these formulations were prepared and some physical measurements were determined.

DETAILED DESCRIPTION OF THE INVENTION

The preparation of the mixture of the two active compounds was carried out with the aid of a tumble mixer (Turbula mixer; W. A. Bachofen AG Basle). The soft pellets were prepared by transferring the fine active compounds to the bottom container of a sieve tower for particle size analysis (Retsch, FRG), and the container was exposed to vibrations until round active compound agglomerates resulted.

The following tables show some comparative measurement results.

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EXPERIMENT 1

Active Compound Mixture:
Two parts by weight of disodium cromoglycate and one part by weight of reproterol hydrochloride.

	Core agglomerates	Mixture	Soft pellets
Bulk volume (ml/g)	2.2	7.2	3.8
Compacted volume (20x) (ml/g)	2	5	3
Hausner factor	1,10	1,44	1,27
Bed height (mm)	24	35	29
Redispersion (%) at 60 l/min/volume flow [sic]	50	40	35
Redispersion (%) at 30 l/min/volume flow [sic]	30	10	15

The soft pellets were obtained according to the procedures of GB 1,569,612 and GB 1,520,247.

EXPERIMENT 2

Active Compound Mixture:
Three parts by weight of disodium cromoglycate and two parts by weight of reproterol hydrochloride.

	Core agglomerates	Mixture	Soft pellets
Bulk volume (ml/g)	2	7.2	3.8
Compacted volume (20x) (ml/g)	1.9	5	3
Hausner factor	1,05	1,44	1,27
Bed height (mm)	23	35	29
Flow angle (°)	48	59	54

Bulk volume and compacted volume were determined according to known processes.

100 g of formulation are carefully tipped into a measuring cylinder. The volume read off represents the bulk volume. The filled measuring cylinder is attached to a compacted volume meter. 20 compactions are carried out. The volume read off represents the compacted volume (see also Voigt R., Lehrbuch der pharmazeutischen Technologie [Textbook of Pharmaceutical Technology], Verlag Chemie, 5th Edition, page 148).

The Hausner factor is the ratio of bulk volume to compacted volume.

The bed height was determined with the aid of a cylinder of diameter 42 mm, powder slowly being tipped in until a heap of maximum height resulted, whose height was measured. Redispersion was determined with the aid of an inhaler and of a cascade impactor, by determining the contents in percent based on the initial weight which had been deposited on the second to fourth cascade. This experiment was carried out using two different volume flows.

EXAMPLE 1

266.8 g of micronized disodium cromoglycate and 133.2 g of micronized reproterol hydrochloride are sieved through a sieve of mesh width 0.125 mm and then added to a Diosna mixer PWC Dierks und Söhne, Osnabrück FRG). 600.0 g of commercially available lactose having a grain size distribution of 100%<800 μm, 12%–35%<400 μm and max 7%<200 μm are added thereto. Mixing is then carried out for 30 min.

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The core agglomerates thus resulting are readily flowable and can be filled into an inhaler. The properties of these core agglomerates can be seen from Experiment 1 (page 8).

EXAMPLE 2

3000 g of micronized disodium cromoglycate and 200.0 g of micronized reproterol hydrochloride are sieved through a sieve of mesh width 0.125 mm and then added to a tumble mixer (Turbula mixer; W. A. Bachofen AG Basle). 500.0 g of commercially available lactose having a grain size distribution of 100%<800 μm, 12%–35%<400 μm and max 7%<200 μm are added thereto. Mixing is then carried out for 30 min. The core agglomerates thus resulting are readily flowable and can be filled into an inhaler. The properties of these core agglomerates can be seen from Experiment 2 (page 9).

EXAMPLE 3

266.8 g of micronized disodium cromoglycate and 133.2 g of micronized reproterol hydrochloride are sieved with the aid of a 0.125 mm sieve and then added to a fluidizing mixer (Fukae Powtec Corporation, Japan).

600.0 g of commercially available sodium chloride having an average grain size of 300 μm are added thereto. Mixing is then carried out for 10 min. The core agglomerates thus resulting are readily flowable and can be filled into an inhaler.

EXAMPLE 4

30 g of micronized budesonide are sieved with the aid of a 0.125 mm sieve and then added to a tumble mixer (Tubula mixer; W. A. Bachkofen [sic] AG, Basle). 270 g of commercially available lactose having a grain size distribution of 100%<800 μm, 12%–35%<400 μm and at most 7%<200 μm are added thereto. Mixing is then carried out for 45 min. The core agglomerates thus resulting are readily flowable and can be filled into an inhaler, a cartridge or blister packs.

EXAMPLE 5

100 g of micronized salbutanol are sieved with the aid of a 0.125 mm sieve and then added to a tumble mixer (Tubula mixer; W. A. Bachkofen AG, Basle). 300 g of commercially available lactose having a grain size distribution of 100%<800 μm, 12%–35%<400 μm and at most 7%<200 μm are added thereto. Mixing is then carried out for 45 min. The core agglomerates thus resulting are readily flowable and can be filled into an inhaler, a cartridge or blister packs.

EXAMPLE 6

20 g of micronized hecclometasone-17,21-dipropionate are sieved with the aid of a 0.125 mm sieve and then added to a tumble mixer (Turbula mixer; W. A. Bachofen AG, Basle). 380 g of commercially available lactose having a grain size distribution of 100%<800 μm, 12%–35%<400 μm and at most 7%<200 μm are added thereto. Mixing is then carried out for 45 min. The core agglomerates resulting in this way are readily flowable and can be filled into an inhaler, a cartridge or blister packs.

EXAMPLE 7

20 g of micronized ipratropium bromide are sieved with the aid of a 0.125 μm sieve and then added to a tumble mixer (Turbula mixer; W. A. Bachofen AG, Basle). 380 g of commercially available lactose having a grain size distribu-

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tion of 100%<800 μm , 12%–35%<400 μm and at most 7%<200 μm are added thereto. Mixing is then carried out for 45 min. The core agglomerates resulting in this way are readily flowable and can be filled into an inhaler, a cartridge or blister packs.

What is claimed is:

1. A formulation comprising an active compound mixture having a mean particle size of 0.1 μm to 10 μm in combination with a physiologically acceptable excipient or excipient mixture having a mean particle size of 400 μm to 1000 μm and a rugosity greater than 1.75.

2. A formulation comprising an active compound mixture having a mean particle size of 1 μm to 5 μm in combination with a physiologically acceptable excipient or excipient mixture having a mean particle size of 400 μm to 600 μm and a rugosity greater than 1.75.

3. A process for the preparation of a formulation for production of medicaments for inhalation, comprising mixing an active compound or an active compound mixture having a mean particle size of 0.1 μm to 10 μm with a physiologically acceptable excipient or excipient mixture having a mean particle size of 400 μm to 1000 μm and a rugosity greater than 1.75.

4. The process according to claim 3 wherein the active compound or active compound mixture has a mean particle size of 1 μm to 5 μm and the physiologically acceptable excipient or excipient mixture has a mean particle size of 400 μm to 600 μm .

5. The process according to claim 3 or 4 wherein the excipient particles are covered by the active compound particles.

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6. The formulation according to claim 1 or 2 wherein the active compound or an active compound mixture is present in an amount between 5 and 80% by weight and the excipient or excipient mixture is present in an amount between 20 and 95% by weight.

7. The formulation according to claim 6 wherein the active compound or an active compound mixture is present in an amount between 30 and 70% and the excipient or excipient mixture is present in an amount between 30 and 70%.

8. The formulation according to claim 1 or 2 additionally comprising further physiologically acceptable auxiliaries.

9. The formulation according to claim 1 or 2 wherein the excipient contains at least one substance from the saccharides group.

10. The formulation according to claim 1 or 2 wherein the excipient contains lactose.

11. The formulation according to claim 1 or 2 wherein the active compound mixture is a mixture of reproterol and the disodium salt of cromoglycic acid.

12. The formulation according to claim 1 or 2 wherein the active compound is budesonide.

13. The formulation according to claim 1 or 2 wherein the active compound is salbutamol.

14. The formulation according to claim 1 or 2 wherein the active compound is cetorelex.

15. The formulation according to claim 1 or 2 wherein the active compound is beclometasone.

16. The formulation according to claim 1 or 2 wherein the active compound is ipratropium bromide.

* * * * *

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 A5B 741 74Y
 (72) Inventors STEPHEN RAYMOND GUNNING and
 PHILIP SAXTON HARTLEY



(54) PHARMACEUTICAL COMPOSITIONS FOR INHALATION

(71) We, FISON'S LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London, W.1. do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a pharmaceutical powder composition for inhalation.

It is known that powder compositions may be administered by inhalation, using a device such as is described in British Patent Specification No. 1,122,284. An example of such a form of device is one which comprises a hollow elongate housing having at both ends thereof one or more passageways adapted to permit the passage of air and having one end thereof adapted for insertion into the mouth and a propeller-like device rotatably mounted in the said housing on a rigid shaft mounted in said housing and co-axial with the longitudinal axis of the housing; said propeller-like device, having on the part thereof furthest from the end of the housing adapted for insertion into the mouth, mounting means adapted to receive a container, such as a gelatine or like capsule for the medicament to be inhaled.

Medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs; a suitable particle size range being 0.01 to 10, preferably 1 to 10 microns. However powders in this particle size range are not in general readily fluidised by the above technique because of cohesive forces between the individual particles. A means of overcoming this problem is described in British Patent Specification No. 1,242,211.

According to our invention there is provided a pharmaceutical powder composition, which comprises a mixture of a solid inhalation medicament having an effective particle size, as hereinafter defined, in the range 0.01 to 10 microns and a solid carrier acceptable in the lungs, having an effective particle size,

as hereinafter defined, in the range of from 80 to 150 microns.

For the purpose of the present invention there is no distinction between a single particle of given size and an agglomerate of the same size which is composed of finer individual particles. The term 'effective particle size' is therefore used herein, where the context permits, to denote the apparent particle size of a body without distinction as to the number of individual particles which go to make up that body. The effective particle sizes quoted herein for the fine particles of medicament are those as measured with a Coulter counter and those for the coarse material are as measured by sieve analysis (sieving method BS 1796).

In measuring particle sizes with a Coulter counter, the sample to be analysed is dispersed in an electrolyte into which dips a glass tube. The glass tube has a hole through the wall thereof with electrodes mounted on either side of the hole in the tube wall. The tube is immersed sufficiently for the hole and electrodes to be submerged in the liquid. The suspension is made to flow through the hole in the glass tube and as each particle passes through the orifice it displaces its own volume of electrolyte, thus changing the resistance across the hole. The change in resistance is converted into a voltage pulse with an amplitude proportional to the particle volume. The pulses are fed to an electronic counter with an adjustable threshold level such that all pulses above the threshold are counted. By setting the threshold level at different values it is possible to determine the number of particles falling within given size range and thus the proportion of particles in a sample which fall outside a desired particle size range.

The composition may contain any of a wide variety of medicaments suitable for administration by inhalation e.g. medicaments intended for alleviation of disorders of the bronchial tract or medicaments administered for systemic action. Particular examples of medicaments which may be employed in the composition of the invention are antianaphy-

lactic agents such as the di-sodium salt of 5,5' - [[5,5' - (2 - hydroxytrimethylene) dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]] tetrazole and sodium cromoglycate, i.e. the di-sodium salt of 1,3 - bis(2 - carboxy - chromon - 5 - yloxy) - propan - 2 - ol, bronchodilators such as isoprenaline, ephedrine, adrenaline or theophylline, antibiotics such as tetracycline, steroids, enzymes, vitamins, antihistamines, mucolytics such as N-acetyl cysteine or its salts, diagnostic agents such as propylidone or tantalum, and analgesics such as paracetamol. The composition may contain more than one medicament in finely divided form. Thus, a composition may contain for example, a mixture of sodium cromoglycate and isoprenaline sulphate. As stated above, the medicament should be in finely divided form having an effective particle size in the range 0.01—10, preferably 1—10 microns, and suitably at least 50% by weight of the finely divided medicament is in the effective particle size range 2—6 microns. Where the medicament is one of high specific activity, it may be desirable to dilute the medicament with an inert diluent of similar particle size. Such a composition should, of course, also contain a coarser carrier having an effective particle size in the range 80 to 150 microns.

The solid diluent or carrier in the composition will generally be a non-toxic water soluble material chemically inert to the medicament and will of course be acceptable for inhalation. The carrier has an effective particle size in the range 80 to 150 microns preferably 80 to 120, especially 80 to 100 microns. Examples of solid diluents or carriers which may be used in the composition of the invention include inorganic salts, e.g. sodium chloride or calcium carbonate; organic salts, e.g. sodium tartrate or calcium lactate; organic compounds, e.g. urea, propylidone; monosaccharides, e.g. lactose or dextrose monohydrate; disaccharides, e.g. maltose or sucrose; polysaccharides e.g. starches, dextrans or dextrans. A particularly preferred diluent or carrier is lactose, e.g. crystalline lactose.

The ratio of medicament to carrier may vary depending upon the materials used. The optimum ratio will depend upon the medicament and carrier and the method by which the composition is to be applied. We have found that the use of from 10 to 75% by weight of finely divided material to 90 to 25% by weight of carrier, preferably from 20 to 60% by weight of finely divided materials, e.g. about 25 to 60% by weight of medicament to 75 to 40% by weight of carrier, in general provides satisfactory results.

The finely divided medicament may be prepared by crystallisation, direct milling down to the desired particle size range and/or particle classification. The particulate

carrier may be prepared by grinding the carrier and subsequently separating out the desired fraction by conventional methods, e.g. by air classification and sieving. The surface characteristics of individual particles of both the medicament and carrier may be modified by such conventional techniques as crystallisation, spray drying and precipitation.

The composition may be prepared from the fine and coarse ingredients by mixing the ingredients together in a mixer, e.g. a planetary mixer or a rotating blender. If desired, the surfaces of the particles of medicament and/or diluent and/or carrier may be coated with a pharmaceutically acceptable material such as stearic acid, or polymers such as polyvinyl pyrrolidone. This coating procedure may serve incidentally to give a sustained release action to the medicament.

In addition to the medicament and carrier, the composition may contain other ingredients, such as colouring matter of flavouring agents such as saccharin, which are normally present in inhalant compositions. It is, however, preferred to use the minimum of such other ingredients.

The compositions according to the invention will generally be put up in gelatine, plastic or other capsules.

There is also provided, therefore, as a further feature of the invention, a dosage unit comprising a gelatine or like capsule containing a pharmaceutical composition according to the invention.

The amount of composition contained in the capsule will, of course, depend on the desired dosage. However, the capsule suitably contains from 10 to 300, preferably from 10 to 100 mg. of the composition.

The invention is illustrated, but in no way limited by the following Examples.

Example 1.

Commercially available ground crystalline lactose was sieved to remove material having an effective particle size of less than 80 microns. This product was then sieved through a sieve having a mesh aperture of about 110 microns to produce lactose product with an effective size in the range 80 to 110 microns.

The medicament or other material which was intended to form a finely divided material was passed through a fluid energy mill in an air stream until the product contained at least 50% by weight of particles in the effective size range 2—6 microns as determined on a Coulter counter.

Compositions containing the desired proportions of the coarse and fine materials were mixed together in a planetary mixer and the mixture then passed through a 30 mesh sieve to remove or break up agglomerated particles.

The compositions were then put up in gelatine capsules containing about 40 mg of

the composition (capsules approximately 1/3 full) and the ease of emptying of the composition from the capsule determined. The ease of emptying was assessed by mounting a pierced capsule in the capsule holder of the powder insufflator of French Patent Specification No. 1,471,722 (which corresponds to British Patent Specification No. 1,122,284). The insufflator was then mounted in a hole in the side wall of a chamber connected to bellows. The bellows were designed to suck air through the chamber; the insufflator acting as the air inlet thereto.

The capsule was weighed prior to mounting in the insufflator. The bellows were then operated to give seven one second sucks and the capsule reweighed to determine the amount of powder removed from the capsule. The amount of powder removed is related to the ease of fluidisation of the powder.

By way of comparison a composition containing no coarse diluent was prepared and tested. Those compositions containing the coarse carrier were all found to empty from the capsule at a satisfactory rate, whereas in the absence of the coarse diluent the emptying rates were much lower, about 15% or less, and were unpredictable.

Example 2

Compositions consisting of a mixture of 20 mg. of fine disodium cromoglycate produced by the fluid energy milling procedure described in Example 1, and 20 mg of coarse lactose of varying particle size were put up in gelatine capsules and their ease of emptying assessed by the following procedure:

A series of 20 of the powder insufflators of British Patent Specification No. 1,122,284 were mounted simultaneously in an air flow device which is adapted to reproduce one form of a human inhalation cycle. The weighed capsules were mounted in the insufflators, pierced and the insufflators were then subjected to 4 inhalation cycles and the capsules were then removed and re-weighed. The difference in weight between the capsules before and after the 4 inhalation cycles is then expressed thus:—

$$\% \text{ emptying} = \frac{\text{Weight emptied}}{\text{Weight of contents}} \times 100$$

The results are given in Table I.

TABLE I
Size Ranges of Lactose in Microns

	80—150	80—120	120—150
% emptying mean of 20 capsules	96.8%	95.5%	97.9%

WHAT WE CLAIM IS:—

1. A pharmaceutical powder composition,

which comprises a mixture of a solid inhalation medicament having an effective particle size, as hereinbefore defined, in the range 0.01 to 10 microns and a solid carrier acceptable in the lungs, having an effective particle size, as hereinbefore defined, in the range of from 80 to 150 microns.

2. A composition according to Claim 1, wherein the medicament is a medicament for the alleviation of a disorder of the bronchial tract.

3. A composition according to Claim 1, wherein the medicament is an antianaphylactic agent.

4. A composition according to any one of the preceding claims, wherein the medicament is the di-sodium salt of 5,5' - [[5,5' - (2 - hydroxytrimethylene)dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]] tetrazole.

5. A composition according to any one of Claims 1 to 3, wherein the medicament is sodium cromoglycate.

6. A composition according to Claim 1 or Claim 2, wherein the medicament is a bronchodilator, antibiotic, steroid, enzyme, vitamin, antihistamine, mucolytic, diagnostic agent, or analgesic.

7. A composition according to any one of the preceding claims, wherein the medicament has an effective particle size, as hereinbefore defined, in the range 1 to 10 microns.

8. A composition according to any one of the preceding claims, wherein at least 50% by weight of the medicament is in the effective particle size range 2 to 6 microns.

9. A composition according to any one of the preceding claims, wherein the carrier is a water soluble material chemically inert to the medicament.

10. A composition according to any one of the preceding claims, wherein the carrier has an effective particle size in the range 80 to 120 microns.

11. A composition according to any one of the preceding claims, wherein the carrier has an effective particle size in the range 80 to 100 microns.

12. A composition according to any one of the preceding claims, wherein the carrier is an inorganic salt, an organic salt, urea, propylidone, a monosaccharide, a disaccharide or a polysaccharide.

13. A composition according to any one of the preceding claims, wherein the carrier is lactose.

14. A composition according to Claim 13, wherein the carrier is crystalline lactose.

15. A composition according to any one of the preceding claims comprising from 10 to 75% by weight of medicament and from 90 to 25% by weight of carrier.

16. A composition according to Claim 15 comprising from 25 to 60% by weight of medicament and 75 to 40% by weight of carrier.