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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-031216-00005-0000

Trámite : 011 Evento : 379 Actuación : 444

Fecha: 2008-02-05 16:54:55 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 12

347.

Referencia : Expediente No. **03.031.216**
Asunto : Solicitud de patente para **"PROCEDIMIENTO PARA LA PREPARACIÓN DE FORMULACIONES DE POLVOS"**
Solicitante : **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**
Fecha de Solicitud : 11 de Abril de 2003

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. **12064** notificado por fijación en lista del 28 de septiembre de 2007.

2. Mediante mi memorial de fecha 21 de diciembre de 2007 solicité un plazo de 30 días para atender el Oficio No. **12064**.

3. Mediante el Oficio No. **12064** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente.

Atiendo a las observaciones de la manera siguiente:

3.1. CLARIDAD DE LA SOLICITUD

Para subsanar las objeciones que sobre claridad hizo su Despacho, presento nuevo capítulo reivindicatorio con 8 reivindicaciones en el cual se han hecho los cambios

respectivos, sugeridos por su Despacho. Las modificaciones realizadas fueron los siguientes:

- La expresión "aproximadamente" ha sido eliminada de este pliego reivindicatorio de manera tal que se definen con claridad la cantidad de sustancia y la distribución del tamaño de partícula. Adicionalmente el valor de N ha sido especificado de acuerdo con las características preferidas descritas en la descripción de la solicitud de patente.
- Por otro lado, respetuosamente ponemos de presente que las expresiones "mayor" y "menor" que se dejaron en el nuevo pliego reivindicatorio no afectan la concisión del mismo, toda vez que como se anotó anteriormente, una persona medianamente versada en la materia puede determinar con claridad la cantidad de sustancia y la distribución del tamaño de partícula, y de esta forma llevar a cabo la invención.
- La reivindicación 9 ha sido eliminada de este pliego reivindicatorio.
- Adicionalmente, tanto el procedimiento como el producto están correctamente caracterizados. Eso es, por sus etapas y condiciones y por las propiedades de los componentes de la composición respectivamente.

De esta manera es claro que con las anteriores modificaciones del capítulo reivindicatorio no solamente queda subsanada la objeción que por claridad hizo su Despacho, sino que al haberse limitado el alcance de la protección solicitada, la misma es fácilmente determinable por un técnico medio y por ende, el mismo estaría en capacidad de compararla frente al estado del arte, de acuerdo con las disposiciones del artículo 30 de la Decisión 486.

3.2. NIVEL INVENTIVO

A este respecto, es importante poner de presente que el examen de nivel inventivo está dirigido a determinar si la invención reivindicada había sido sugerida o enseñada en el estado del arte, de acuerdo con el conocimiento de un técnico medio en la materia. Para los anteriores efectos, el método problema-solución le indica al Examinador que al realizar el examen de nivel inventivo debe verificar las enseñanzas del arte previo sin adoptar la posición de un inventor que se preguntaría cómo solucionar el problema técnico en cuestión.

Lo anterior, por cuanto si se adopta la posición del inventor y se tiene conocimiento tanto del arte previo como de la forma como efectivamente se solucionó el problema técnico, la invención en todos los casos le resultará obvia y evidente.

Adicionalmente, se debe tener en cuenta que el mencionado método problema-solución también señala que los documentos del estado del arte frente a los cuales se debe efectuar el examen de nivel inventivo son aquellos que dentro del mismo campo técnico estén dirigidos a solucionar el mismo problema. Lo anterior, por cuanto estos son los documentos que se presume debieron ser de conocimiento del inventor para a partir de ellos formular su invención. Así los documentos relacionados con otro campo técnico o dirigidos a solucionar cualquier otro problema no serían relevantes para estos efectos en la medida que no harían parte del grupo de documentos de los cuales el inventor hubiera podido derivar de manera obvia y evidente su invención.

De acuerdo con lo anterior, procederemos a indicar las razones por las cuales los documentos citados no afectan el nivel inventivo de la presente solicitud de patente. Veamos:

Ese Despacho afirma que los documentos **D1** y **D2** afectan el nivel inventivo de la presente invención pues considera que el experto en la materia podría llegar al procedimiento reivindicado al combinar las enseñanzas de dichos documentos.

A este respecto, respetuosamente ponemos de presente que dichas anterioridades no revelan aspectos específicos con respecto a cómo las formulaciones en polvo descritas en la presente solicitud de patente fueron preparadas. En dichos documentos no se revela una descripción de la técnica de mezcla llevada a cabo. Por consiguiente, dichas anterioridades no puede tenerse como anterioridades válidas capaces de afectar el nivel inventivo de la presente invención.

Por lo tanto, no resulta posible derivar ninguna enseñanza técnica de las enseñanzas de D1 y D2 con respecto al proceso de producción de las formulaciones en polvo descritas en la presente invención; hecho este que refuerza nuestra conclusión de que se trata de documentos que no hace parte del estado del arte más próximo y que por ende, resultan irrelevantes para determinar la patentabilidad de la presente invención.

Adicionalmente deseamos llamar la atención del Examinador a los datos adjuntos (ver anexo 4.2.) que demuestran la relación de dependencia entre la uniformidad de contenido del ingrediente activo y el número de capas empleadas en el proceso de acuerdo a la intención. Tal y como lo demuestra la información adjunta, **la uniformidad del contenido es directamente proporcional a la cantidad de capas, toda vez que la primera se incrementa al incrementarse la segunda**, efecto inesperado que no podía ser deducido a partir de las anterioridades citadas.

En vista de lo antes expuesto, los documentos D1 y D2 ni anticipan la materia de la presente invención, ni dan sugerencia con respecto al efecto inesperado de tal materia. Por lo cual no se puede considerar que sean documentos que afecte de algún modo el nivel inventivo de esta invención.

4. ANEXOS:

- 4.1. Nuevo pliego reivindicatorio con 8 reivindicaciones;
- 4.2. Documento titulado "Influencia del número de capas sustancia medicamentosa/portador en el procedimiento de mezcla de polvo sobre la uniformidad del contenido de mezclas en polvo de tiotropio/lactosa";
- 4.3. Formulario de modificaciones;
- 4.4. Recibo por valor de \$103.000 por concepto de modificaciones en solicitud pendiente.

Señora Jefe,



EMILIO FERRERO

T.P.A. No. 31.929

✓ COLO-13736-841-006-4
NNJ\NNJ\ID-118133\WPC13736
No. M-2008-118133\NNJ

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG Sociedad constituida y existente bajo las leyes de Alemania. Dirección: 55216 Ingelheim, Alemania Domicilio: Ingelheim, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@cavelier.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019 TP 31.929</u>
4	Número de expediente: <u>03.031.216</u>	
5	Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 8 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho y pido atentamente que el examen de patentabilidad sea efectuado sobre estas nuevas reivindicaciones.	
6	Comprobante de pago No. <u>08-7.441</u> Fecha: <u>29 de enero de 2008</u>	
7	Anexos ☒ Comprobante de pago de la tasa por \$103.000.00 por concepto de modificaciones. ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929	

f

Reivindicaciones

- 1) Procedimiento para la preparación de polvos para inhalación, caracterizado porque $N + m$ porciones de una sustancia con un tamaño de partícula promedio de 10 a 100 μm (excipiente) y N porciones de una sustancia que tiene un tamaño de partícula promedio de 0.5 a 10 μm (sustancia activa) son colocadas en capas intercaladas dentro de un recipiente de mezcla adecuado y una vez se han adicionado todas, las $2N + m$ capas de los dos componentes se mezclan conjuntamente empleando una mezcladora adecuada, efectuándose primeramente la adición de una porción de la sustancia con un mayor tamaño de partícula, en donde N es un número entero > 5 y m denota 0 o 1.
- 2) Procedimiento según la reivindicación 1, caracterizado porque las fracciones individuales son adicionadas en capas a través de un dispositivo de tamizado adecuado.
- 3) Procedimiento de acuerdo a la reivindicación 1 o 2, caracterizado porque m denota el número 1.
- 4) Polvos para inhalación caracterizados porque contienen menos de 5%, preferiblemente menos de 2% de sustancia activa.
- 5) Polvos para inhalación según la reivindicación 4, caracterizados porque la sustancia activa tiene un tamaño de partícula de entre 1 a 6 μm .
- 6) Polvos para inhalación según una de las reivindicaciones 4 a 5 caracterizados porque el excipiente tiene un tamaño de partícula promedio de entre 15 a 80 μm .

- 7) Polvos para inhalación según una de las reivindicaciones 4 a 6, caracterizados porque el excipiente consiste de una mezcla de un excipiente más grueso con un tamaño de partícula promedio de 15 a 80 μm y un excipiente más fino con un tamaño de partícula promedio de 1 a 9 μm , en donde la proporción del excipiente más fino constituye del 1 al 20% de la cantidad total de excipiente.
- 8) Polvos para inhalación según una de las reivindicaciones 4 a 7, caracterizados porque la sustancia activa consiste de uno o más compuestos seleccionados de entre los betamiméticos, anticolinérgicos, corticoesteroides y agonistas de dopamina.

Anexo 4.2. Caso 1/1237: Influencia del número de capas sustancia medicamentosa/portador en el procedimiento de mezcla de polvo sobre la uniformidad del contenido de mezclas en polvo de tiotropio/lactosa

Introducción:

Se realizaron pruebas de mezclas de n capas de sustancia medicamentosa micronizada, en donde n = 1, 6, 9 y 18, con n + 1 capas de portador de lactosa (en donde n + 1 = 2, 7, 10 y 19, respectivamente) para investigar la influencia del número de capas de sustancia medicamentosa usadas en el procedimiento de mezcla de polvo sobre la uniformidad de contenido de las mezclas de polvos para inhalación de tiotropio.

Métodos: Fabricación

Para las pruebas, la concentración de la sustancia medicamentosa en la mezcla fue del 0.4%, Como portador de lactosa, se empleó lactosa 200 M (Farmatosa DMV) con una mezcla al 5% de lactosa micronizada (lactosa 5 µm).

Se cribó primeramente una capa del portador de lactosa dentro del recipiente de mezcla seguido por los números respectivos de capas de sustancia medicamentosa micronizada y portador de lactosa respectivamente (observación: para las mezclas con 6, 9 y 18 capas de sustancia medicamentosa, se cribó para la primera capa una doble cantidad de portador de lactosa del recipiente de mezcla para un mejor recubrimiento de las superficies del equipo).

El polvo en el recipiente de mezcla fue mezclado por 900 revoluciones y se evaluó la uniformidad del contenido. Posteriormente, esta mezcla de polvo fue cribada /re-mezclada por otras 900 revoluciones (esto es 1800 revoluciones en total) y nuevamente evaluada.

Tamaño del lote:	11kg
Criba:	granulador de criba Comil, tamaño tamiz:0,5mm

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Mezclador:	mezclador Rhoenrad /recipiente de 50l
Revoluciones de Mezcla:	900/1800

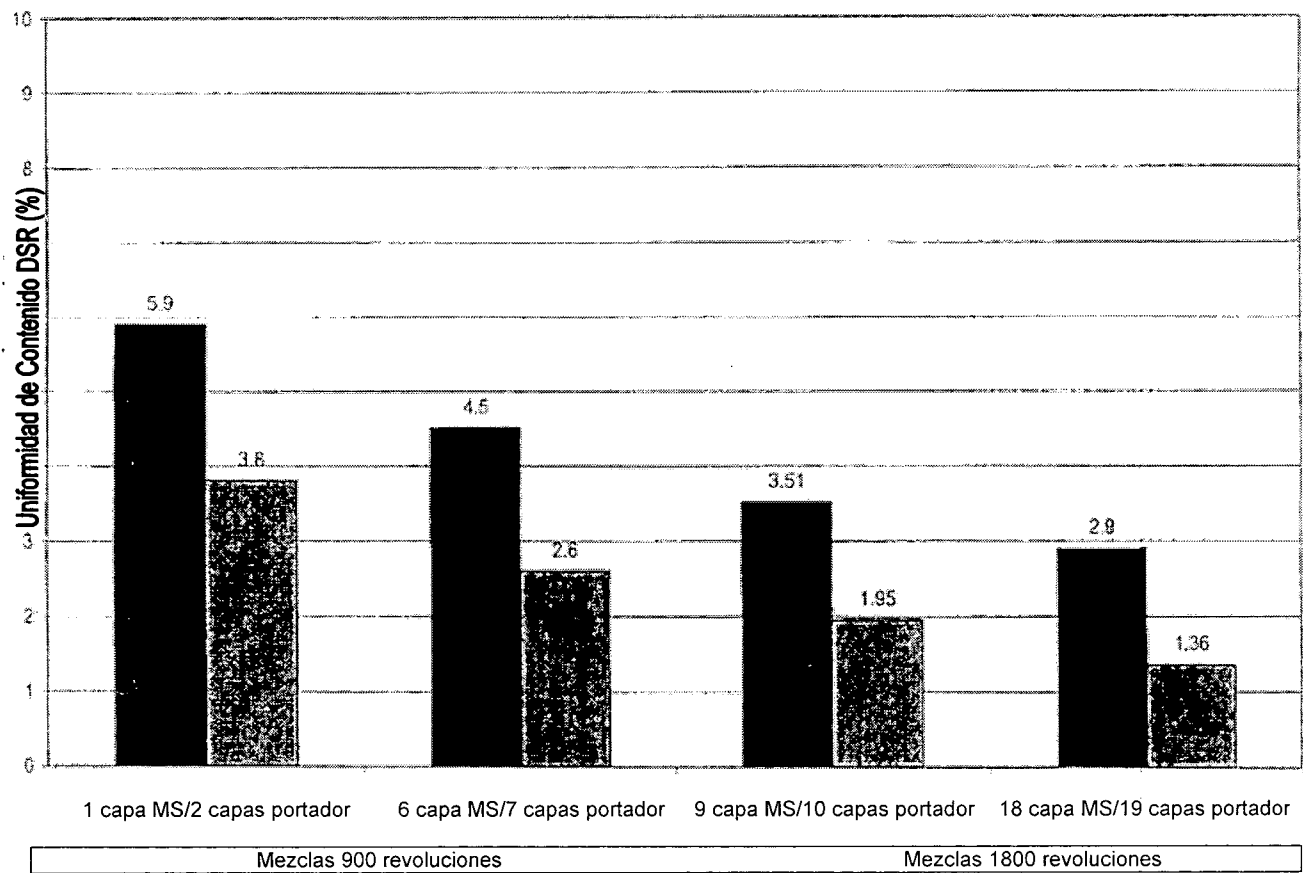
Métodos: Pruebas

Para la prueba de la uniformidad de contenido para cada una de las mezclas de polvo, se tomaron 10 muestras en lugares diferentes y fueron analizadas usando un método HPLC (Cromatografía Líquida de Alta Presión).

Evaluación

Para demostrar la influencia del número de capas de sustancias medicamentosa/portador se escogieron los valores de la RSD (= desviación estándar relativa) del contenido de ingrediente activo como parámetro de evaluación: un menor valor de RSD representa una mejor uniformidad de contenido/ mejor calidad de mezclado.

Gráfico: Influencia del número de capas sustancia medicamentosa/portador en el procedimiento de mezcla de polvo sobre la uniformidad del contenido de mezclas en polvo de tiotropio/lactosa



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 7,441
FECHA : ENERO 29 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 12

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CHAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2808480	29/01/2008	22,233,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 13736-841-006-4

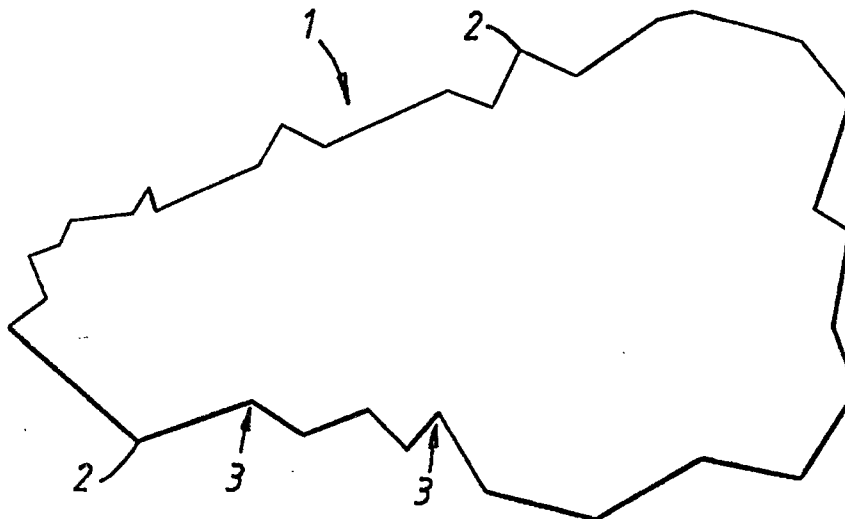
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00	A1	(11) International Publication Number: WO 95/11666 (43) International Publication Date: 4 May 1995 (04.05.95)
(21) International Application Number: PCT/GB94/02353 (22) International Filing Date: 26 October 1994 (26.10.94) (30) Priority Data: 9322014.3 26 October 1993 (26.10.93) GB (71) Applicant (for all designated States except US): CO-ORDINATED DRUG DEVELOPMENT LTD. [GB/GB]; 30 Gay Street, Bath BA1 2PA (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): STANFORTH, John, Nicholas [GB/GB]; High Trees, 170 Bloomfield Road, Bath BA2 2ST (GB). (74) Agents: BARDO, Julian, Eason et al.; Abel & Imray, Northum- berland House, 303-306 High Holborn, London WC1V 7LH (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>

(54) Title: **IMPROVEMENTS IN AND RELATING TO CARRIER PARTICLES FOR USE IN DRY POWDER INHALERS**

(57) Abstract

In a method of producing particles suitable for use as carrier particles in dry powder inhalers, particles (1) of a size suitable for use as carrier particles in dry powder inhalers are treated so as to dislodge small grains from the surface of the particles, without substantially changing the size of the particles during the treatment. The treatment gives improved efficiency of redispersion of active particles from the surfaces of carrier particles.



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Improvements in and relating to carrier particles for
use in dry powder inhalers.

This invention relates to carrier particles for use
in dry powder inhalers. More particularly the invention
5 relates to a method of producing such particles, to a dry
powder incorporating the particles and to the particles
themselves.

Inhalers are well known devices for administering
pharmaceutical products to the respiratory tract by
10 inhalation. Inhalers are widely used particularly in the
treatment of diseases of the respiratory tract.

There are a number of types of inhaler currently
available. The most widely used type is a metered dose
inhaler (MDI) which uses a propellant to expel droplets
15 containing the pharmaceutical product to the respiratory
tract. Those devices are disadvantageous on
environmental grounds as they use CFC propellants.

An alternative device to the MDI is the dry powder
inhaler. The delivery of dry powder particles of
20 pharmaceutical products to the respiratory tract presents
certain problems. The inhaler should deliver the maximum
possible proportion of the active particles expelled to
the lungs, including a significant proportion to the
lower lung, preferably at the low inhalation capabilities
25 to which some patients, especially asthmatics, are
limited. It has been found, however, that, when
currently available dry powder inhaler devices are used,

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in many cases only about 10% of the active particles that leave the device on inhalation are deposited in the lower lung. More efficient dry powder inhalers would give clinical benefits.

5 The type of dry powder inhaler used is of significant importance to the efficiency of delivery of the active particles to the respiratory tract. Also, the physical properties of the active particles used affect both the efficiency and reproducibility of delivery of
10 the active particles and the site of deposition in the respiratory tract.

On exit from the inhaler device, the active particles should form a physically and chemically stable aerocolloid which remains in suspension until it reaches
15 an alveolar or other absorption site preferably in the lungs. Once at the absorption site, the active particle should be capable of efficient collection by the pulmonary mucosa with no active particles being exhaled from the absorption site.

20 The size of the active particles is particularly important. For effective delivery of active particles deep into the lungs, the active particles should be small, with an equivalent aerodynamic diameter substantially in the range of 1 to 5 μ m, approximately
25 spherical and monodispersed in the respiratory tract. Small particles are, however, thermodynamically unstable due to their high surface area to volume ratio, which provides significant excess surface free energy and

of the particles and little fracture of particles. Fracture of the particles, which occurs with aggressive milling conditions, for example at higher milling speeds such as 60 revolutions per minute and/or long milling 5 times, may result in agglomerates of fractured particles of carrier material. The use of agglomerates of particles as carrier particles has been found to lead to good deposition of active particles in the lower lung.

Advantageously, the particles are milled for at 10 least one hour, preferably the particles are milled for about six hours. That time has been found to be suitable when milling with balls made from plastics material. When using denser balls, shorter milling times may be used. Alternatively, a different milling technique may 15 be used, for example using a re-circulated low fluid energy mill, or other method that results in the removal of grains from the surfaces of the particles e.g. sieving.

The carrier particles may include may acceptable 20 pharmacologically inert material or combination of materials. Advantageously, the carrier particles are crystalline sugar particles. Preferably, the carrier particles are lactose particles.

Advantageously, the diameter of the carrier par- 25 ticles lies between $50\mu\text{m}$ and $1000\mu\text{m}$. Preferably, the diameter of the carrier particles is less than $355\mu\text{m}$ and lies between $60\mu\text{m}$ and $250\mu\text{m}$, more preferably $90\mu\text{m}$ and

250 μ m. The relatively large diameter of the carrier particle improves the opportunity for active particles to become attached to carrier particles which is controlled by the above technique to provide good flow and

5 entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The size of the carrier particles is an important factor in the efficiency of the inhaler, and an optimum, or near optimum, range of size of carrier particles is preferably selected. The optimum range of size of carrier particles may differ according to the inhaler device and active particles used. Thus, the method preferably includes the step of selecting an advantageous

10 range of size of carrier particles prior to the treatment step. That step of selecting an advantageous range of size may be a sieving step.

According to the invention, there is also provided a method of producing a dry powder for use in dry powder inhalers, the method including the steps of treating carrier particles to dislodge small grains from the surfaces of the carrier particles without substantially changing the size of the carrier particles during the treatment step, and mixing the treated carrier particles

20 with active particles such that active particles adhere to the surfaces of carrier particles.

Advantageously, the small grains become reattached

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to the surfaces of the carrier particles.

Advantageously, the method includes the steps of treating carrier particles according to the present invention and mixing the treated carrier particles with the active particles such that active particles adhere to the surfaces of carrier particles. The treatment of the carrier particles may be carried out before the active particles are added, but it may also be carried out in the presence of the active particles.

10 Advantageously, the carrier particles and the active particles are mixed in a container made from a plastics material. That has been found to give an unstable mixture of salbutamol and lactose and thus increases the deposition of salbutamol in the lungs. A container of
15 different material may be used when using a mixture containing a different type of active particles.

Advantageously, the carrier particles and the active particles are mixed for at least five minutes. Preferably, the carrier particles and the active
20 particles are mixed for about thirty minutes. The mixing should be for a time sufficient to give a homogeneous mixture of the active particles and the carrier particles, during mixing, rearrangement of the sites of particles may also occur, even when the system
25 is homogeneous.

Advantageously, the mixing is interrupted and the mixture of carrier particles and active particles is

flow properties.

- (a) The lactose was sieved by the following method conforming to British Standard No. 410 to give samples having particles with a range of diameter from 90 to 125 μ m. Samples of 30 g of Lactose EP D30 were sieved mechanically for 20 minutes using a stack of woven wire stainless steel sieves of mesh aperture diameters 90 μ m, 125 μ m and 180 μ m. The mesh was vibrated at high speed to reduce the binding of lactose particles to the mesh of the sieve. After ten minutes of the sieving process, the sieving was stopped and each of the sieves was dismantled individually and the powder on the sieve was removed, the sieve brushed and the powder replaced in the sieve from which it was removed. The sieve stack was then reassembled and the sieving resumed. This was done in an attempt to improve the efficiency of the sieving process.

50 g samples of the lactose EP D30 were taken from the particles that had passed through the 125 μ m mesh sieve but had remained on the 90 μ m sieve. Those particles could be considered to have a diameter between 90 μ m and 125 μ m.

- (b) The samples obtained in step (a) above were milled in a porcelain ball mill (manufactured by Pascal Engineering Company). Plastics grinding balls having an approximate diameter of 10 mm were used and the mill which had a diameter of

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approximately 150 mm was revolved at a slow speed of 6 revolutions per minute for six hours. During the milling process, the mill was periodically stopped and any powder adhered to the mill wall or to the plastics grinding balls, was scraped free.

(c) Small samples of the milled lactose particles were mounted for scanning electron microscope (SEM) analysis and were sputtered with gold. The SEM analysis showed the extent of grinding of the lactose particles and the alteration of the surfaces of the lactose particles.

Figure 1a shows a representation of an untreated particle 1 having asperities 2 and clefts 3. Figure 1b shows the effect of a milling treatment on the particle of Figure 1a. Shaded areas 4 represent the sections removed from the surface of the particle as small grains during the milling.

In Figure 1c small grains 5 have become reattached to the surface of the particle, mostly at active sites on the surface.

(d) Samples of the milled lactose particles were mixed with the active particles. 0.4 g of salbutamol sulphate (mass median diameter $4.6\mu\text{m}$) were added to 50 g of the milled lactose particles in a plastics container. After blending for ten minutes using an Erweka AR400 cube blender, the mixture was removed from the container and screened

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through a sieve of mesh aperture diameter $250\mu\text{m}$ to remove any large agglomerations of active particles which may have formed. The mixture was returned to the container and blended for a further twenty
5 minutes. The mixture was stored in the plastics container for five days to allow the decay of any accumulated electric charges.

The blending process was repeated for a 50 g sample of lactose particles which had been taken
10 from the sieved sample of particles of diameter between $90\mu\text{m}$ and $125\mu\text{m}$, but which had not been milled, to give a comparative example.

(e) After five days, six samples each of 100mg of mixture were taken from the container
15 containing the milled carrier particles, and four samples each of 100mg were taken from the container containing the unmilled carrier particles. Each sample was used to fill a respective one of ten size three capsules (size 3 opaque, Elanco BN 3D056D).
20 Those capsules were allowed to stand for two days to allow the decay of any accumulated electric charge.

(f) In order to assess the effectiveness of the mixing method, ten 100mg samples were taken randomly from each of the two mixes (and were made up to
25 250ml with distilled water) and were analyzed using spectrofluorimetry on a Shimadzu RS S40 spectrofluorimeter at an excitation wavelength of 223nm and an emission wavelength of 303nm as described below.

(12) **United States Patent**
Keller et al.

(10) **Patent No.:** **US 6,645,466 B1**
(45) **Date of Patent:** **Nov. 11, 2003**

(54) **DRY POWDER FOR INHALATION**

(75) Inventors: **Manfred Keller**, Bad Krozingen (DE);
Rudi Müller-Walz, Schopfheim (DE)

(73) Assignee: **Jago Research AG**, Muttentz (CH)

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

(21) Appl. No.: **09/831,011**

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(57) **ABSTRACT**

The aim of the invention is to improve the moisture resistance of dry powder formulations for inhalation which contain a pharmaceutically ineffective carrier of not-inhalable particle size and a finely divided pharmaceutically active compound of inhalable particle size and to also improve the storage stability of said formulations. To this end, magnesium stearate is used in said formulations. One of the features of the inventive dry powder is that a high fine particle dosage or fine particle fraction can be maintained also under relatively extreme temperature and humidity conditions.

15 Claims, No Drawings

DRY POWDER FOR INHALATION

This application claims priority to International Patent Application No. PCT/CH99/00528, filed Nov. 10, 1999.

FIELD OF THE INVENTION

The invention relates to the improvement of the resistance to moisture of dry powder formulations for inhalation, and to the novel dry powder formulations.

BACKGROUND OF THE INVENTION

Dry powder formulations for inhalation must fulfil a number of demands which are partially contradictory to one another, where the following, in particular, are to be taken into account:

~~The active compound must be inhalable. In order to be able to pass into the lungs, it must be present in particles of size about 1 to 10 μm . Such microfne particles can be obtained, for example, by micronization, controlled precipitation from suitable solvents or by spray drying if the process conditions are suitably selected, controlled and carried out. Microfne particles, however, have a very unfavorable, i.e. large, ratio of surface to volume or mass and therefore a large surface energy. This is manifested in strong adhesion and cohesion tendencies which in turn lead to poor flow properties and to powder aggregation. Microfne powders of this type are therefore difficult to handle and are strongly influenced by electrostatic charge, processing, atmospheric humidity and the like.~~

In order to guarantee consistent production of the formulation, mechanical filling of the powder inhaler and correct dosage and release by the powder inhaler, the powder must be free-flowing. Good flow properties are as a rule expected with sufficiently large particles which are as spherical as possible and which have a low surface energy and small contact areas.

In the case of powder inhalers having a reservoir, the finished pharmaceutically preparation is filled into the reservoir in the form of a powder bed. A dose is withdrawn by means of a suitably designed dosage device. Withdrawal takes place volumetrically. The accurate volumetric dosage of the preparation for most active compounds necessitates dilution thereof with a pharmaceutically inactive excipient in order to obtain a dosable unit amount meeting the demands on dosage accuracy.

For powder inhalers which release the medicament from predosed units, e.g. capsules or blister packs, the same restriction applies for the frictionless operation of the filling machines for these unit doses.

In the case of a multidose dry powder inhaler which contains a powder reservoir from which the individual doses are withdrawn by means of a dosage mechanism, as a rule the pulverulent medicament is in contact with the surrounding area and can thus be influenced by atmospheric humidity. The quality of the medicament and of the inhalation system must not be significantly adversely affected, however, by the influence of external factors during the intended storage time and up to the use of the pack.

In order to meet these requirements, the inhalable, i.e. present in microfne particles, constituents (active compounds) are mixed with pharmacologically inactive substances in order to obtain flowable powders. The dilution is chosen here such that the amount applied from the powder inhaler exactly contains the desired dose. The predominant proportion of the pharmacologically inactive excipient is

present here intentionally in a particle size which is not inhalable. It serves not only for dilution, but also for establishing an acceptable, if possible a good to very good, flowability of the powder mixture. ~~In the case of these "interactive or ordered mixtures", it is the carrier substance, to which the microfne active compound particles are bound by adhesion in order to achieve and to maintain a suitable mixed material, i.e. homogeneity of the mixture.~~ By means of the mixing process, the particle size of the carrier can also be changed such that a certain proportion is inhalable. The particle size of the carrier employed in this case as a rule depends on the requirements and specifications of the powder inhaler which is intended for the administration of the formulation. It is true for these mixtures that during all required processing, transport, storage and dosage operations no demixing must take place, i.e. the active compound particles must not detach from their carrier particles. During dispersion in the inhaler, induced by the respiratory flow of the patient, the active compound particles, however, must be detached as effectively as possible, i.e. as quantitatively as possible, in order to be inhaled. The carrier is in most cases lactose, but can also be mannitol, trehalose or another suitable carrier material. In some inhalers obtainable on the market, glucose is also present as a carrier material.

It is known that the flow properties of ordered mixtures in the main depend on the physicochemical properties of the carrier, which in fact as a rule is admixed in an excess. It is likewise known that the effectiveness of the release of the inhalable primary particles of the active compound by shearing force especially also depends on the properties of the carrier, in addition to the physicochemical, substance-specific properties of the active compound and the physical, in particular aerodynamic, properties of the powder inhaler. For this purpose, as an analytical parameter, the amount of active compound in fine, inhalable particles (fine particle dose, subsequently also designated by FPD) or the fine particle fraction (subsequently also designated by FPF) is determined relative to the total amount of released active compound in vitro in so-called cascade impactors or liquid impingers, such as are described in various pharmacopeias.

Recent studies show that the FPF is all the higher, the smaller the particle size of the admixed lactose [M. J. Clarke, U. J. Potter, P. Lucas, M. J. Tobyn and J. N. Staniforth: Poster presentation to the conference "Drug Delivery to the Lungs VIII" of the Aerosol Society, London, 12.15-16.1997; and P. Lucas, M. J. Clarke, K. Anderson, M. J. Tobyn and J. N. Staniforth (1988): Presentation to the conference "Respiratory Drug Delivery VI", Hilton Head Island, 5.3-7.1998, published in: R. N. Dalby, P. R. Byron and S. J. Farr (editors): Respiratory Drug Delivery VI, Interpharm Press, 1998, 243 et seq.]. This process, however, comes up against a natural barrier, as the flowability with smaller particles rapidly becomes inadequate.

It was likewise shown that on comparison of identical screen fractions of various lactose grades a recrystallized lactose achieved the higher FPF [N. M. Kassam and D. Ganderton: J. Pharm. Pharmacol. 42 (1990), 11 et seq. (Suppl.) and EP-B-0 464 171]. This effect is based on the fact that the active compound particles preferably adhere to defects, cracks and breaks, i.e. to particularly activated centers ("active sites" or "hot spots") of the carrier particles. The adhesion forces are largest at these activated centers and thus the detachment is also least probable during inhalation. It was then shown by electron micrographs that the recrystallized lactose is very much more regular than the commercially available material.

It is furthermore known that crystalline α -lactose monohydrate also contains a small proportion of amorphous

lactose which interferes with the regular crystal structure and thus provides activated sites on the crystal surface [G. Buckton and P. Darcy: *Int. J. Pharm.* 123 (1995), 265 et seq.; E. M. Phillips: *Int. J. Pharm.* 149 (1997), 267 et seq.]. In the case of increased atmospheric humidity, water can preferably add to these amorphous centers and, as a plasticizer, cause a conversion into the thermodynamically more stable crystal form [B. C. Hancock and G. Zografi: *J. Pharm. Sci.* 86 (1997), 1 et seq.]. In turn, this has the result that the storage stability of powder preparations of this type is limited at increased atmospheric humidity.

In WO-A-95/11666, it was proposed to saturate the active centers by addition of microfine lactose with the aim of making available only a few energy-rich binding sites on the lactose to the active compound in the preparation of the final mixture. Since detachment during inhalation accordingly needs less energy, the FPF should significantly increase, which was clearly demonstrated. The same also applies to the process which is described in WO-A-93/11746.

In *J. Pharm. Pharmacol.* 34: 141-145 (1982), it was furthermore found that the addition of a third powder component to an ordered mixture of salicylic acid (1%) and sucrose formed beforehand can influence the physical stability of ternary mixtures in a different manner as a result of charge interactions. The addition of 0.5-4.0% of magnesium stearate adversely affected the adhesion of the salicylic acid particles to the sucrose carrier, the proportion of weakly bound active compound particles increasing with increasing magnesium stearate concentration. This finding was ascribed to a change in the charge interactions on the surface of the sucrose carrier particles as a result of the positive electrostatic charge of the magnesium stearate and the negative charge of the salicylic acid and sucrose particles. This effect and the fact that the addition of a third component, which preferably adds to the carrier particles, can displace the active compound particles from their adhesion sites has already been pointed out in *J. Pharm. Pharmacol.* 31: 800 (1979). In contrast, by addition of 2% cornstarch the adhesion of the active compound particles was intensified and the amount of active compound adhering to sucrose was increased, while by addition of 2% of talc the adhesion forces between the particles were generally increased. Similar effects were also found by N. M. Kassem [Thesis DX187842, University of London, 1990] and likewise explained by the electrostatic properties of the constituents.

In WO-A-87/05213, on the other hand, it was proposed to use carriers, consisting of microparticles of a conglomerate of one or more solid water-soluble diluents, such as lactose, xylitol, mannitol, arabinose or dextran, with a lubricant, such as magnesium stearate, sodium benzoate, colloidal silica, hydrogenated oil or fatty substances, for the preparation of inhalation powders. The microparticles preferably have a particle size of 30-150 μm and are prepared by adding the lubricant to an aqueous solution of a part of the solid diluent, granulating the remaining diluent together with this mixture and sieving the granules obtained. The use of such carriers should make possible, inter alia, improved flow properties and improved self-lubricating properties.

However, it has been shown that powder mixtures, in particular interactive powder mixtures, are sensitive to the moisture in the surrounding air. They are therefore only limitedly suitable for use in a multidose dry powder inhaler which contains a powder reservoir, since this is normally not a tight pack in the sense of a hermetic sealing-off of water vapor. This is usually manifested in a dramatic fall in the inhalable proportion of the released dose, which is deter-

mined in vitro as the FPD or FPF. The fall is based on a stronger adhesion of the micronized active compound particles to the carrier particles, as from a relative atmospheric humidity of about 60%, as a result of water vapor condensation, "liquid bridges" result in the intermediate spaces which contribute to a stronger binding energy. Visual signs of this process are crust or clump formation, which, however, do not necessarily have to be observed in each case. The process is irreversible, since on drying-up of the liquid bridges "solid bridges" are formed. Inter alia, the water absorption tendency or the water sorption ability of the substances involved is also crucial for the extent of the impairment of the powder properties in the case of high atmospheric humidity storage.

SUMMARY OF THE INVENTION

The invention is therefore based on the object of lowering the sensitivity of powder mixtures to moisture. The object is achieved according to the invention by use of magnesium stearate. It has in fact surprisingly been shown that magnesium stearate is able to minimize the influence of penetrating moisture on the FPD and the FPF during the storage of the inhalation powder, i.e. to prevent or at least considerably to slow down an adverse effect on the FPD and the FPF caused by moisture, and to stabilize the dry powder formulation. The original quality of the pharmaceutical preparation thus remains considerably better than in the case of conventional preparations even on storage under extreme conditions of temperature and humidity. The improvement is usually manifested in that the influence of moisture on the mass median aerodynamic diameter (subsequently also designated as MMAD) and on the accuracy and reproducibility of the released dose can be prevented or greatly slowed. These effects are particularly marked, especially for moisture-sensitive active compounds, since possible hygroscopicity of the active compound favors water absorption and thus the formation of the liquid bridges. Moreover, the use of magnesium stearate as a rule leads to a general improvement in the FPD and the FPF. It is conceivable that the magnesium stearate, in addition to general moisture protection, also stabilizes the carrier materials and active compounds by suppressing or slowing down undesirable morphological phase transitions.

The invention therefore relates to the use of magnesium stearate for improving the resistance to moisture, i.e. for lowering the sensitivity to atmospheric humidity, of dry powder formulations for inhalation. The use of magnesium stearate accordingly brings about an improvement in the storage stability and in particular a reduction of the influence of penetrating moisture on the FPF (and the FPD), which permits the maintenance of a high FPD and FPF even under comparatively extreme temperature and humidity conditions.

DETAILED DESCRIPTION OF THE INVENTION

The dry powder formulations obtainable according to the invention thus comprise a pharmaceutically inactive carrier of noninhalable particle size, a finely divided pharmaceutically active compound of inhalable particle size (i.e. having a mean particle diameter of preferably at most 10 μm , in particular at most 5 μm) and—to improve the resistance to moisture—magnesium stearate, and they are preferably present in the form of "interactive (or ordered or adhesive) mixtures". If desired, the dry powder formulations can also contain a proportion of carrier material of inhalable particle size.

The expression "interactive mixture" or "ordered mixture" or "adhesive mixture" is familiar to the person skilled in the art and in the context of the present invention comprises dry powder formulations in which the pharmacologically inactive carrier is present in a particle size which is noninhalable or mainly noninhalable, and in which microfine active compound particles are bound to the carrier particles by adhesion (i.e. are not contained in the carrier, e.g. in the form of granules).

It has been found that magnesium stearate is suitable for improving the moisture resistance of fundamentally any desired dry powder formulations, independently of the nature of the active compounds and carrier materials. The improvement is particularly marked, however, in the case of dry powders, whose combination of active compound and carrier—i.e. without addition of magnesium stearate—has a high sensitivity to the influence of atmospheric humidity and shows, for example, a decrease in the FPF by at least 50% within 10 days in the case of storage in the open at 40° C. and 75% relative atmospheric humidity. A high sensitivity of the FPF or FPD to atmospheric humidity is frequently observed if the active compound is present in the form of a salt or ester and/or is comparatively hygroscopic or hydrophilic.

An active compound is hygroscopic in this sense if it never completely dries out at a water vapor pressure in the drying air of >0, i.e. in contact with air having a moisture content of >0% relative humidity, but always contains a certain amount of absorptively bound water [H. Sucker, P. Fuchs and P. Speiser: Pharmazeutische Technologie [Pharmaceutical Technology], Georg Thieme Verlag, Stuttgart, New York, 2nd edition 1991, page 85]. The use according to the invention of magnesium stearate is particularly advantageous if the active compound is comparatively hygroscopic and, for example, absorbs or retains at least approximately 0.5% by weight of absorptively bound water on storage in drying air having a relative humidity of 50%.

An active compound powder is hydrophilic if it can easily be wetted by water, in the context of the present invention hydrophilic active compound powders in particular being understood as meaning those which have, for example, a wetting angle of less than 90° [Martin, Swarbrick and Cammarata: Physikalische Pharmazie [Physical Pharmacy], Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 3rd edition 1987, page 534]. The use according to the invention of magnesium stearate is particularly advantageous in the case of active compound powders which have a wetting angle of less than 70°.

The use of magnesium stearate for improving the resistance to moisture of dry powder formulations is thus particularly preferred in the case of dry powder formulations which contain a pharmaceutically active compound which is present in the form of a salt or ester and/or absorbs or retains at least approximately 0.5% by weight of absorptively bound water on storage in drying air having a relative humidity of 50% and/or has a wetting angle of less than 90°, in particular less than 70°.

The use according to the invention of magnesium stearate is furthermore especially advantageous for use in multidose dry powder inhalers which contain a powder reservoir from which the individual doses are withdrawn by means of a dosage mechanism. The use of magnesium stearate, however, is also suitable for improving the resistance to moisture of predosed units, which can be present, for example, in the form of capsules.

The active compound present in the formulations obtainable according to the invention can fundamentally be any

desired pharmaceutically active compound which can be administered by inhalation in dry powders. In order that the active compound is inhalable, i.e. can pass into the lung, it must be present in particles having a mean particle diameter (measured as MMAD) of at most approximately 10 μm , for example approximately 1 to 10 μm , and preferably approximately 1 to 6 μm . Such microfine particles can be obtained in a manner which is known or known per se, for example by micronization, controlled precipitation from suitable solvents (e.g. even from supercritical carbon dioxide) or by spray drying if the process conditions are suitably selected, controlled and carried out.

As active compound, the formulations obtainable according to the invention can preferably contain a β -mimetic, such as levalbuterol, terbutaline, reproterol, salbutamol, salmeterol, formoterol, fenoterol, clenbuterol, bambuterol, tulobuterol, broxaterol, epinephrine, isoprenaline or hexoprenaline, an anticholinergic, such as tiotropium, ipratropium, oxitropium or glycopyrronium, a corticosteroid, such as butoxycart, rofleponide, budesonide, ciclesonide, mometasone, fluticasone, beclomethasone, loteprednol or triamcinolone, a leukotriene antagonist, such as andolast, iralukast, pranlukast, imitroast, seratroast, zileuton, zafirlukast or montelukast, a phosphodiesterase inhibitor, such as flaminast or piclamilast, a PAF inhibitor, such as apafant, forapafant or israpafant, a potassium channel opener, such as amiloride or furosemide, a painkiller, such as morphine, fentanyl, pentazocine, buprenorphine, pethidine, tilidine, methadone or heroin, a potency agent, such as sildenafil, alprostadil or phentolamine, a peptide or protein, such as insulin, erythropoietin, gonadotropin or vasopressin, or a pharmaceutically acceptable derivative or salt of these compounds. In the case of chiral active compounds, this can be present in the form of an optical isomer, a diastereoisomeric mixture of racemate. If desired, the formulations according to the invention can contain two or more pharmaceutically active compounds.

As the moisture sensitivity is frequently a great problem, especially in the case of active compounds which are present as a salt or ester, the use of magnesium stearate is advantageous, in particular in the case of dry powder formulations which contain at least one pharmaceutically active compound in the form of a pharmaceutically acceptable salt, for example a chloride, bromide, iodide, nitrate, carbonate, sulfate, methylsulfate, phosphate, acetate, benzoate, benzenesulfonate, fumarate, malonate, tartrate, succinate, citrate, lactate, gluconate, glutamate, edetate, mesylate, pamoate, pantothenate or hydroxy-naphthoate, or a pharmaceutically active compound in the form of a pharmaceutically acceptable ester, for example an acetate, propionate, phosphate, succinate or etabonate.

The use of magnesium stearate in dry powder formulations which contain a β -mimetic and/or an anticholinergic and/or a corticosteroid is particularly preferred, and in particular in dry powder formulations which contain a β -mimetic and/or an anticholinergic and/or a corticosteroid in the form of a pharmaceutically acceptable salt or ester, for example a β -mimetic in the form of a salt, such as levalbuterol sulfate, formoterol fumarate, formoterol tartrate, salbutamol sulfate or salmeterol xinafoate (salmeterol 1-hydroxy-2-naphthoate), or an anti-cholinergic in the form of a salt, such as oxitropium bromide, glycopyrrolate (glycopyrronium bromide), ipratropium bromide or tiotropium bromide, or a corticosteroid in the form of an ester, such as beclomethasone dipropionate, fluticasone propionate, triamcinolone 16,21-diacetate, triamcinolone acetonide 21-acetate, triamcinolone acetonide 21-disodium

phosphate, triamcinolone acetonide 21-hemisuccinate, mometasone furoate or loteprednol etabonate, or a combination thereof, such as ipratropium bromide in combination with salbutamol sulfate.

According to a further preferred aspect, the formulations obtainable according to the invention can in particular also contain a corticosteroid, such as ciclesonide, rofleponide, fluticasone propionate, mometasone furoate or loteprednol etabonate, in combination with a beta-mimetic, such as formoterol fumarate, formoterol tartrate, levalbuterol sulfate or salmeterol xinafoate.

~~The amount of active compound in the~~ formulations obtainable according to the invention can vary within wide ranges and is to a high extent dependent on the respective active compound and up to a certain degree also on the powder inhaler used. Typically, the active compound concentration can be approximately 0.1 to 10% by weight, in particular, approximately 0.1 to 5% by weight, based on the total formulation. Occasionally, higher or lower concentrations can also be expedient, where, however, active compound concentrations of below 0.001% by weight or below 0.01% by weight rarely occur.

For the exact volumetric dosage of most active compounds or formulations, dilution of the active compound with a pharmaceutically inactive excipient is necessary in order to obtain a dosable unit amount meeting the demands on dosage accuracy. For this purpose, the microfine, inhalable active compound particles are mixed with pharmacologically inactive substances (carriers). The dilution is chosen here such that the amount applied from the powder inhaler exactly contains the desired dose. The pharmacologically inactive excipient preferably serves not only for dilution, but also for the adjustment of a flowability of the powder mixture which is as good as possible, and in the case of the "interactive or ordered mixtures" preferably used it is the carrier substance, to which the microfine active compound particles are bonded by adhesion in order thus to achieve and to maintain a suitable mixed material, i.e. homogeneity of the mixture.

The carrier is preferably present in the formulation obtainable according to the invention in a particle size which is not inhalable. The carrier particles, however, should on the other hand not be too large, as this can have a disadvantageous effect on the FPF. The optimum particle size of the carrier employed in this case as a rule depends on the demands and specifications of the powder inhaler which is intended for the administration of the formulation. In the context of the present invention, carriers having customary particle sizes can be used, and optimum particle sizes can easily be determined from case to case by the person skilled in the art. In general, however, the mean particle diameter (MMAD) of the carrier particles can be approximately 10 to 500 μm and preferably approximately 50 to 200 μm .

The adhesion of the active compound particles to the carrier particles should be sufficient that no demixing takes place during processing, transport, storage and dosage operations, but on the other hand not so high that a detachment of the active compound particles which is as quantitative as possible is no longer guaranteed during the dispersion in the inhaler induced by the respiratory flow of the patient. The effectiveness of the release of the active compound particles is especially dependent, in addition to the physicochemical properties of the active compound and the aerodynamic properties of the powder inhaler, on the properties of the carrier, in particular the nature of the carrier and its surface structure, mean particle size and particle size distribution.

In the context of the present invention, fundamentally all carrier materials customarily used in dry powder formulations are suitable, for example mono- or disaccharides, such as glucose, lactose, lactose monohydrate, sucrose or trehalose, sugar alcohols, such as mannitol or xylitol, polylactic acid or cyclodextrin, glucose, trehalose and in particular lactose monohydrate in general being preferred. If desired, the formulations can also contain two or more carrier materials. If desired, in addition to noninhalable carrier particles, the formulation can also contain a proportion of inhalable carrier particles; for example in addition to relatively coarse lactose monohydrate carrier particles it can contain a proportion of, for example, 0.1 to 10% by weight of micronized lactose monohydrate, which can have, for example, a particle size diameter of at most 10 μm , preferably at most 5 μm , for at least 50% of the particles.

The proportion of carrier material in the formulations obtainable according to the invention can vary within a wide range depending on the dilution necessary or desirable for the particular active compound and the amount of magnesium stearate used for improving the resistance to moisture. The proportion of carrier material to the total formulation can be, for example, approximately 80 to 99.9% by weight, where, however, higher or lower proportions can also be advantageous depending on the active compound.

The concentration of magnesium stearate can also vary within relatively wide limits and can be, for example, approximately 0.001 to 10% by weight, in particular approximately 0.01 to 5% by weight, based on the total formulation, a concentration of approximately 0.1 to 2% by weight as a rule being preferred. With a view to toxicological harmlessness, the magnesium stearate concentration, however, will not usually be over approximately 1% by weight, but on the other hand usually at least approximately 0.25% by weight, in order to guarantee a high efficacy, a concentration range of approximately 0.4 to 0.8% by weight, preferably approximately 0.5 to 0.75% by weight, having proven particularly suitable for most cases. The magnesium stearate is preferably employed as a pulverulent material; the particle size is not particularly critical.

If desired, the formulations obtainable according to the invention can contain further components. They preferably consist, however, of one or more pharmaceutically inactive carriers, one or more pharmaceutically active compounds and magnesium stearate.

The dry powder formulations can be prepared according to the invention by mixing together a pharmaceutically inactive carrier of noninhalable particle size (which, if desired, can contain a proportion of inhalable particle size), a finely divided pharmaceutically active compound of inhalable particle size, for example having a mean particle diameter of at most 10 μm (preferably at most 5 μm), and magnesium stearate. In principle, the constituents can be mixed with one another in any desired sequence, where, however, mixing should expediently be carried out in such a way that the particles of the constituents—apart from the adhesion to the carrier particles—are essentially retained as such, i.e. are not destroyed, for example, by granulation and the like. According to a preferred variant, however, a preliminary mixture of magnesium stearate with the carrier can first be prepared and then the active compound particles can be admixed. According to a further preferred variant, a preliminary mixture of the active compound with the carrier can first be prepared and then the magnesium stearate can be admixed. Mixing can be carried out in a manner known per se, for example in a tumble mixer. Preferably, in this process, however, pulverulent magnesium stearate having a mean

particle size of approximately 1 to 100 μm , in particular approximately 5 to 20 μm , can be added.

The dry powder formulations described can be used in all customary dry powder inhalers. They are particularly advantageously for use in multidose dry powder inhalers which contain a powder reservoir, in particular in multidose powder inhalers such as described in WO-A-97/20589.

The invention likewise relates to dry powder formulations for inhalation having improved resistance to moisture, comprising a pharmaceutically inactive carrier of noninhalable particle size, a finely divided pharmaceutically active compound in the form of a pharmaceutically acceptable salt or ester of inhalable particle size (preferably having a mean particle diameter of at most 10 μm , in particular at most 5 μm) and 0.25 to 1% by weight, based on the total formulation, of magnesium stearate. Preferred dry powder formulations are those which are present in the form of interactive mixtures. Preferred active compound salts and esters, carrier materials, ranges of amounts, methods and the like follow from the above description.

The invention is illustrated further by the following examples. In the examples, r.h. designates the relative atmospheric humidity; the notation n.d. indicates that the value concerned was not determined. The tests were in each case carried out using a dry powder inhaler of the SkyePharma mDPI type (SkyePharma AG, Switzerland) according to WO-A-97/20589. The FPD and the FPF were determined—if not stated otherwise—in each case using a twin impinger. Screenings were carried out—if not stated otherwise—in each case using a screen having a hole diameter of 180 μm . For the determination of the moisture sensitivity, the dry powders, apart from in example 7, were in each case stored in the open without moisture protection.

EXAMPLE 1

198.46 g of lactose monohydrate having a defined particle size of <200 μm for 100%, <125 μm for 50% and <75 μm for 10% of the particles (screen analysis) are screened and mixed with 1 g of screened magnesium stearate using a tumble mixer. Following this, 0.54 g of formoterol fumarate dihydrate and the preliminary mixture are screened and mixed. The mixture thus obtained is filled into a suitable metering dry powder inhaler. For the exact analytical determination of the particle size distribution and especially of the FPD and/or FPF, an adequate number of doses are released and collected in an impinger or impactor described in the European Pharmacopeia or other national pharmacopeias, e.g. the "twin impinger" or "multi-stage liquid impinger", according to procedures also described there. The active compound particles trapped and deposited are worked up in analytical standard procedures to give sample solutions and the amounts of active compound deposited in each size class are determined. To test the stability to moisture, samples of the inhalation powder are stored in the open at 40° C./75% r.h. or another suitable condition over a period of time of several days to weeks and then tested in the powder inhaler as described above.

The results obtained using the ternary mixture prepared (formulation 1-A) and using conventional mixtures (formulations 1-B and 1-C) in a 5-stage liquid impinger according to Ph. Eur., and the compositions of the mixtures (in % by weight) are listed in table 1. In comparison to the conventional interactive mixtures, the ternary mixture with magnesium stearate, according to the invention, shows the advantage of an increased FPD or FPF and a significantly improved stability of the FPD or FPF on storage at 40°

C./75% r.h. As the results for formulation 1-C show, an initial increase in the FPD and FPF can indeed be achieved in conventional formulations by addition of micronized lactose, but not protection against the influence of increased temperature and humidity. This is likewise evident from the MMAD values determined for the formulations 1-A and 1-C immediately after preparation or after 7 or 13 days' storage of the dry powder at 40° C./75% r.h.: for formulation 1-A after preparation 1.8 μm , after 7 days 1.9 μm and after 13 days 1.9 μm ; for formulation 1-C after preparation 2.2 μm , after 7 days 4.5 μm and after 13 days 5.5 μm . In contrast to the conventional formulation, the MMAD thus remains constant in the formulation according to the invention, which confirms the results of the FPD and FPF investigation.

TABLE 1

Formulation	1-A	1-B (comparison)	1-C (comparison)
Lactose monohydrate	99.23%	99.73%	97.24%
Lactose monohydrate, micronized	0.00%	0.00%	2.49%
Magnesium stearate	0.50%	0.00%	0.00%
Formoterol fumarate dihydrate, micronized	0.27%	0.27%	0.27%
FPD after preparation [μg per stroke]	4.7	1.3	3.3
FPD after 3-4 days at 40° C./75% r.h. [μg per stroke]	4.5	n.d.	1.0
FPF after preparation [% active compound found]	42.5	13.7	35.9
FPF after 3-4 days at 40° C./75% r.h. [% active compound found]	37.3	n.d.	11.0

EXAMPLE 2

97.23 g of lactose monohydrate having a defined particle size of <200 μm for 100%, <125 μm for 50% and <75 μm for 10% of the particles (screen analysis) are screened and mixed with 2.5 g of screened micronized lactose monohydrate (50% of the particle <5 μm) in a tumble mixer. Following this, 0.27 g of formoterol fumarate dihydrate and the preliminary mixture are sieved and mixed. The mixture thus obtained is mixed with 0.125 g of screened magnesium stearate and filled into a suitable metering dry powder inhaler. For the analytical determination of the FPD or FPF, an adequate number of doses are released and collected in a twin impinger or multi-stage liquid impinger. The active compound particles trapped and deposited are worked up to give sample solutions and the amounts of active compound deposited in each size class are determined. To test the stability to moisture, samples of the inhalation powder are stored in the open at 40° C./75% r.h. for a period of time of a few days and then tested in the powder inhaler as described above.

The results obtained with the prepared mixture (formulation 2) and with a conventional mixture (formulation 1-C) in a 5-stage liquid impinger according to Ph. Eur. and the compositions of the mixtures (in % by weight) are listed in table 2. In comparison to the conventional interactive mixture, the mixture with magnesium stearate, according to the invention, shows the advantage of an increased FPD or FPF and an improved stability of the FPD or FPF on storage at 40° C./75% r.h.

TABLE 2

Formulation	2	1-C (comparison)
Lactose monohydrate	96.75%	97.24%
Lactose monohydrate, micronized	2.48%	2.49%
Magnesium stearate	0.50%	0.00%
Formoterol fumarate dihydrate, micronized	0.27%	0.27
FPD after preparation [μg per stroke]	5.3	3.3
FPD after 3-4 days at 40° C./75% r.h. [μg per stroke]	n.d.	1.0
FPP after preparation [% active compound found]	41.4	35.9
FPP after 3-4 days at 40° C./75% r.h. [% active compound found]	n.d.	11.0

EXAMPLE 3

97 g of lactose monohydrate having a defined particle size of $<110\ \mu\text{m}$ for 90%, $<70\ \mu\text{m}$ for 50% and $<40\ \mu\text{m}$ for 10% of the particles (screen analysis) are screened and mixed with 0.5 g of screened magnesium stearate in a tumble mixer. Following this, 2.5 g of salbutamol sulfate and the preliminary mixture are screened and mixed. The mixture thus obtained is filled into a suitable metering dry powder inhaler. For the analytical determination of the FPD or FPF, an adequate number of doses are released and collected in a twin impinger. The active compound particles trapped and deposited are worked up to give sample solutions and the amounts of active compound deposited in each size class are determined. To test the stability to moisture, samples of the inhalation powder are stored in the open at 40° C./75% r.h. over a period of time of 7 days and then tested in the powder inhaler as described above.

The results obtained with the prepared ternary mixture (formulation 3-A) and with a conventional binary mixture (formulation 3-B) in a twin impinger according to Ph. Eur. and the compositions of the mixtures (in % by weight) are listed in table 3. The ternary mixture with magnesium stearate attains a higher FPD or FPF and is significantly more stable on storage at 40° C./75% r.h.

TABLE 3

Formulation	3-A	3-B (comparison)
Lactose monohydrate	97.00%	97.50%
Magnesium stearate	0.50%	0.00%
Salbutamol sulfate, micronized	2.50%	2.50%
FPD after preparation [μg per stroke]	39.5	26.2
FPD after 7 days at 40° C./75% r.h. [μg per stroke]	27.8	11.3
FPP after preparation [% active compound found]	37.4	25.3
FPP after 7 days at 40° C./75% r.h. [% active compound found]	35.6	9.7

EXAMPLE 4

1 196 g of lactose monohydrate having a defined particle size of $<315\ \mu\text{m}$ for 100%, $<150\ \mu\text{m}$ for 55-90% and $<63\ \mu\text{m}$

for at most 10% of the particles (screen analysis) are screened and mixed with 3 g of screened magnesium stearate in a tumble mixer (tumble blender TB). Following this, 1.44 g of formoterol fumarate dehydrate and the preliminary mixture are screened and mixed. Analogously, with variation of the batch size, the process parameters and the amounts of magnesium stearate and formoterol fumarate, further formulations are prepared in order to investigate their influence on the stability of the FPD. The mixtures obtained are filled—after preparation or after subsequent storage of the open mixture at elevated temperature and humidity—into a suitable metering dry powder inhaler. The in-vitro particle size distribution and the FPD or FPF are determined on an adequate number of doses using a multi-stage liquid impinger.

The results showed that on preparation of the powder mixtures using a tumble mixer virtually only the concentration of magnesium stearate is responsible for the stability with respect to the FPD, while the other parameters in the range investigated were virtually without significance for the stability under increased humidity. In table 4, the batch size, the concentration of magnesium stearate (MS) and the concentration of formoterol fumarate dihydrate (FF) for some representative mixtures and their FPF values measured in a 5-stage liquid impinger according to Ph. Eur., which were obtained immediately after preparation or after storage at 40° C./75% r.h. for 7 days, are compiled. The values indicated are mean values from three determinations each. The results show that the FPF is barely adversely affected any longer by increased temperature and humidity if the magnesium stearate concentration is adequate. The FPF of 32.3% measured for formulation 1-A after 3 weeks' storage at 40° C./75% r.h. moreover appears to indicate that even at a suboptimal magnesium stearate concentration a long-lasting protection against the influence of increased temperature and humidity is achieved.

TABLE 4

Formulation	Batch size [kg]	MS [%G/G]	FF [% G/G]	FPF after 0 d [%]	FPF after 7 d [%]
4-A	1.2	0.25	0.12	42.5	33.6
4-B	4.8	0.50	0.12	49.3	n.d.
4-C	4.8	0.75	0.12	56.9	56.8
4-D	1.2	0.25	0.34	50.0	33.5
4-E	4.8	0.50	0.34	58.1	n.d.
4-F	4.8	0.75	0.34	59.2	57.2
1-C (comparison)	0.2	0.00	0.27	39.7	12.3
1-A	0.2	0.50	0.27	44.8	32.5

EXAMPLE 5

49.5 g of lactose monohydrate having a defined particle size of $<200\ \mu\text{m}$ for 100%, $<125\ \mu\text{m}$ for 50% and $<75\ \mu\text{m}$ for 10% of the particles (screen analysis) are screened and mixed with 0.25 g of screened magnesium stearate in a tumble mixer. Following this, 0.25 g of salbutamol sulfate and the preliminary mixture are screened and mixed. Analogously, with variation of the concentration of magnesium stearate (MS) and salbutamol sulfate (SS), further mixtures are prepared according to table 5. The mixtures obtained are filled immediately after preparation or after storage at 40° C./75% r.h. for 5 or 21 days into a suitable metering dry powder inhaler. For the determination of the FPD or FPF, an adequate number of doses are released in a twin impinger according to Ph. Eur., collected and the active compound content of the individual fractions is determined analytically.

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The FPF values indicated in table 5 (mean values of two measurements) shows that magnesium stearate brings about protection against increased temperature and humidity even in the case of the moisture-sensitive active compound salbutamol sulfate, but stabilization of the FPF is only achieved at higher magnesium stearate concentrations than in the case of the formoterol fumarate preparations.

TABLE 5

Formulation	MS [%G/G]	SS [% G/G]	FPF [%] after		
			0 d	5 d	7 d
5-A	0.5	0.5	9.3	14.2	12.0
5-B	0.5	1.0	22.3	17.1	14.9
5-C	0.5	2.5	30.2	25.6	22.3
5-D	1.0	0.5	19.0	18.8	13.5
5-E	1.0	1.0	23.0	20.1	15.8
5-F	1.0	2.5	25.0	22.6	20.8
5-G	2.5	1.0	22.7	23.4	21.5
5-H	2.5	2.5	25.9	26.4	27.4
Comparison:					
5-I	0.00	0.5	13.5	5.3	4.0
5-J	0.00	1.0	19.7	9.5	6.6
5-K	0.00	2.5	25.3	14.8	13.9

EXAMPLE 6

99.2 g of lactose monohydrate having a particle size of <315 μm for 100%, <150 μm for 55–90% and <63 μm for at most 10% of the particles (screen analysis) are screened and mixed with 0.5 g of screened magnesium stearate in a tumble mixer. Following this, 0.34 g of tiotropium bromide and the preliminary mixture are screened and mixed. The mixture obtained is filled after preparation or storage at 40° C./75% r.h. for 7 days into a suitable metering dry powder inhaler. For the determination of the FPD or FPF, an adequate number of doses are released and collected in a multi-stage impinger according to Ph. Eur. and the active compound content of the individual fractions is determined analytically. The samples filled immediately after preparation showed an FPF of 8.0 μg and an FPF of 48.4% (mean values of 2 measurements); for the samples stored for 7 days under moist conditions, an FPD of 6.9 μg and an FPF of 43.0% were obtained (mean values of 4 measurements), i.e. stabilization with 0.5% magnesium stearate produces a sufficiently uniform FPD or FPF even in the case of the moisture-sensitive tiotropium bromide.

EXAMPLE 7

For the investigation of the influence of increased humidity and temperature on formulations according to the invention under conditions near to those in practice, dry powder inhalers of the SkyePharma mDPI type (SkyePharma AG, Switzerland), were filled, according to the disclosure of WO-A-97/20589, with 2 g each of dry powder, freshly prepared according to example 1, consisting of 99.23% by weight of lactose monohydrate, 0.50% by weight of magnesium stearate and 0.27% by weight of micronized formoterol fumarate dihydrate (formulation 1-A). The in-vitro data were determined immediately after filling and after 3, 6 and 12 months' storage of the unpacked inhalers without moisture protection under various temperature and humidity conditions. The doses released and the stroke masses were determined by means of strokes Nos 2–4, 149–152 and 298–300 from three inhalers each, which were released into a Buchner funnel according to the method described by Collins at the Conference Drug Delivery to the Lungs VIII,

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London, December 1998 (meeting reports pages 116–119). The FPD or FPF was determined at 60 l/min by means of a 5-stage liquid impactor according to Ph. Eur. with the aid of strokes Nos 6–15 and 287–296 from three inhalers each. The mean values and relative standard deviations compiled in table 6 show that the formulation according to the invention is barely adversely affected over long periods of time even under comparatively extreme temperature and humidity conditions.

TABLE 6

Storage	Stroke mass [mg]	Released dose [μg]	FPF [%]	FPD [μg]
none	6.0 ($\pm 5.4\%$)	10.2 ($\pm 10.1\%$)	43.5	6.0
25° C./60% r.h.: 3 months	6.1 ($\pm 4.8\%$)	10.5 ($\pm 9.5\%$)	40.8	5.4
6 months	5.9 ($\pm 8.2\%$)	10.9 ($\pm 6.9\%$)	47.8	7.0
12 months	6.1 ($\pm 5.0\%$)	12.1 ($\pm 5.9\%$)	42.2	5.9
30° C./70% r.h.: 3 months	6.1 ($\pm 6.9\%$)	11.0 ($\pm 12.9\%$)	40.1	5.6
6 months	6.2 ($\pm 8.7\%$)	10.6 ($\pm 11.5\%$)	39.9	5.7
12 months	6.3 ($\pm 4.3\%$)	10.7 ($\pm 5.9\%$)	42.0	5.7
40° C./75% r.h.: 3 months	5.8 ($\pm 9.7\%$)	9.9 ($\pm 9.8\%$)	38.1	5.2
6 months	6.0 ($\pm 19.5\%$)	10.3 ($\pm 19.2\%$)	35.1	4.9
12 months	6.7 ($\pm 6.8\%$)	10.7 ($\pm 7.9\%$)	37.9	5.4

EXAMPLE 8

Analogously to example 4, a dry powder consisting of 0.2% by weight of formoterol fumarate dihydrate, 0.5% by weight of glycopyrrolate, 0.5% by weight of magnesium stearate and 98.8% by weight of lactose monohydrate was prepared.

We claim:

1. A dry powder formulation for inhalation in the form of an ordered mixture, comprising

a) a pharmaceutically inactive carrier having particles of noninhalable particle size,

b) a finely divided pharmaceutically active compound having particles of inhalable particle size, said pharmaceutically active compound being selected from the group consisting of formoterol, ipratropium, tiotropium and pharmaceutically acceptable salts thereof, and

c) magnesium stearate adhering to said particles of said pharmaceutically inactive carrier, the magnesium stearate being in an amount of 0.1 to 2% by weight, based on the total weight of the formulation, said amount being sufficient to provide the formulation with an improved resistance to moisture.

2. The formulation of claim 1, wherein the magnesium stearate is present in an amount of 0.25 to 1% by weight, based on the total weight of the formulation.

3. The formulation of claim 1, wherein the magnesium stearate is present in an amount of 0.4 to 0.8% by weight, based on the total weight of the formulation.

4. The formulation of claim 1, wherein the carrier is selected from the group consisting of monosaccharides, disaccharides, sugar alcohols, polylactic acid and cyclodextrin.

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5. The formulation of claim 1, wherein the carrier is selected from the group consisting of glucose, lactose monohydrate and trehalose.

6. The formulation of claim 1, further comprising particles of micronized lactose monohydrate wherein at least 50% of the particles thereof have a maximum particle size of 10 μm .

7. The formulation of claim 1 wherein the pharmaceutically acceptable salt is a member selected from the group consisting of formoterol fumarate, formoterol tartrate, ipratropium bromide and tiotropium bromide.

8. The formulation of claim 7, wherein the magnesium stearate is present in an amount of 0.25 to 1% by weight, based on the total weight of the formulation.

9. The formulation of claim 7, wherein the magnesium stearate is present in an amount of 0.4 to 0.8% by weight, based on the total weight of the formulation.

10. The formulation of claim 7, wherein the carrier is selected from the group consisting of monosaccharides, disaccharides, sugar alcohols, polylactic acid and cyclodextrin.

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11. The formulation of claim 7, wherein the carrier is selected from the group consisting of glucose, lactose monohydrate and trehalose.

12. The formulation of claim 7, wherein the pharmaceutically active compound is formoterol fumarate, the carrier is lactose monohydrate, and the magnesium stearate is present in an amount of 0.4 to 0.8% by weight, based on the total weight of the formulation.

13. The formulation of claim 7, further comprising particles of micronized lactose monohydrate wherein at least 50% of the particles thereof have a maximum particle size of 10 μm .

14. The formulation of claim 7, wherein the pharmaceutically active compound is present in an amount of 0.1 to 5% by weight, based on the total weight of the formulation.

15. The formulation of claim 14 wherein the pharmaceutically active compound is formoterol fumarate, the carrier is lactose monohydrate, and the magnesium stearate is present in an amount of 0.4 to 0.8% by weight, based on the total weight of the formulation.

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United States Patent [19]

Newman et al.

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[45] Date of Patent: May 7, 1985

[54] SOLUBLE SODIUM CROMOGLYCATE
COMPOSITIONS

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[52] U.S. Cl. 514/460

[58] Field of Search 424/283

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[57] ABSTRACT

There is described a mixture of sodium cromoglycate of mass median diameter from 2 to 30 microns with a pharmaceutically acceptable water soluble carrier of sieve size from 200 to 1000 microns, the carrier having a solubility of greater than 1 to 5 by weight in water at 20° C.

The mixture is useful in the treatment of conditions of the gastrointestinal tract.

10 Claims, No Drawings

SOLUBLE SODIUM CROMOGLYCATE COMPOSITIONS

This is a continuation of application Ser. No. 315,958, filed Oct. 28, 1981, now abandoned.

This invention relates to a new pharmaceutical formulation.

Sodium cromoglycate is well-known to be useful, when administered by inhalation, for the treatment of asthma. For this use, a dry powder mixture is sold comprising fine particles of the drug and coarser, (30-80 micron) particles of lactose in a 1:1 weight ratio. This formulation has a slightly bitter taste. The objective in this formulation is to provide a composition in which the particles of drug adhere to the coarse lactose, but are capable of being shaken off the lactose in the airstream which is inhaled by the patient. This formulation is more fully described in British Patent Specification No. 1,242,211. A modification of this powder formulation in which the particle size of the lactose carrier is from 80 to 150 microns in size is disclosed in British Patent Specification No. 1,381,872 and a further modification in which the particle size of the drug is from 2 to 4 microns is disclosed in British Patent Specification No. 1,410,588.

Sodium cromoglycate has also been known for many years, e.g. from British Patent Specification No. 1,423,985, to be useful for the treatment of conditions of the gastro-intestinal tract. Various formulations have been suggested for this use including hard, dense granules of the drug, (as described in British Patent Specification No. 1,549,229), which have been put up in a capsule which is designed to be swallowed. These granules can also be removed from the capsule and dissolved in water. However it has been found that the granules are slow to dissolve, and it has been found necessary to follow the tedious procedure of dissolving them in hot water to ensure complete dissolution, and then to dilute the resulting solution with cold water. Adding sodium cromoglycate powder directly to cold water results in dry, unwetted powder being trapped in a gel of dissolving sodium cromoglycate, and, in consequence, solution time is prolonged because of inadequate wetting/de-aeration. Food allergy is thought to start in the mouth, and the physicochemical properties of sodium cromoglycate, in relation to the anatomy and biochemical conditions of the gastro-intestinal tract, therefore indicate that it should be taken by the patient as a solution for maximum therapeutic benefit. These liquid formulations are prima facie attractive. However multidose liquid formulations inevitably require the inclusion of preservative substances which are undesirable in the treatment of the allergic conditions. Many of the conventionally used preservatives are chemically incompatible with sodium cromoglycate and the limited range of compatible substances have allergenic potential for the group of patients to be treated. On the other hand unit dose liquid forms of drugs are expensive, and are technically very difficult to produce, especially when formulated aseptically without a preservative. Indeed we are unaware of any unpreserved liquid unit dose drug formulation being available commercially. Furthermore liquid dosage forms of all kinds are expensive to transport and store because of their high volume and weight per unit dose.

Tablets containing the drug have been contemplated, but tablet formulations contain excipients, which, as

with the preservatives conventionally used in solutions, tend to be allergenic. Furthermore tablets tend to take a long time to dissolve and are therefore inconvenient to the patient.

As a finely divided powder, which is a primary requisite for rapid dissolution, sodium cromoglycate is cohesive, and in pure form aggregates into a gel-like mass in contact with water, especially in cold drinking water.

We have now found, however, that certain therapeutically acceptable carrier materials, classified into particular sized particles, have the property of forming a uniform surface coating of sodium cromoglycate, even in the absence of binding agents. The resulting mixture is free-flowing with a uniform distribution of the drug and has the particular advantage that it dissolves rapidly and completely in cold water. Furthermore the formulation can be readily filled into unit dose containers, e.g. sachets, whereby it can be protected from the damaging effects of atmospheric moisture.

This product form has the advantage that it is cheap to produce and distribute, it maximises the drug's bioavailability with the minimum of inconvenience to the patient, and by using a non-allergenic excipient it minimises the chance of any allergic response to the formulation itself. A particular advantage of the formulation is that by selecting a sweet-tasting carrier substance, the unpleasant taste of sodium cromoglycate can be masked acceptably without the need for an artificial flavouring agent. This is of particular value in the treatment of food allergic disease in children where the exclusion of artificial flavours in the diet is a pre-requisite of treatment and where, as with all patients, good compliance with the prescribed drug therapy is as difficult to achieve as it is essential.

As can be appreciated from the considerations set out above the pharmaceutical criteria which are applicable to oral and inhalation forms of the drug are entirely different, and indeed the medical conditions treated by the two different forms of the drug are dealt with by quite separate groups of medical specialist.

Thus, according to the invention we provide a mixture of sodium cromoglycate of mass median diameter from 2 to 30 microns with a pharmaceutically acceptable water soluble carrier of sieve size from 200 to 1000 microns, the carrier having a solubility of greater than 1 to 5 by weight of water at 20° C.

The finely divided sodium cromoglycate preferably has a mass median diameter of from 2 to 10 microns, and more preferably from 3 to 6 microns with 90% of the particles being of less than 30 microns diameter. The particle size of the sodium cromoglycate when below 10 microns may be measured by means of a Coulter counter. When above 10 microns the particle size may be measured by sieving.

The water soluble carrier preferably has a particle size of from 200 to 500 microns, e.g. a mean size of from 270 to 370 microns. The particle size of the water soluble carrier may be measured by sieving.

The water soluble carrier is preferably a sugar, for example xylitol and even more preferably sucrose, e.g. beet sucrose. We naturally prefer to avoid sugars which are poorly absorbed and which can, in certain circumstances, cause diarrhoea. We also prefer the sugar to be in a form which will dissolve quickly in water.

The water soluble carrier preferably has a solubility of greater than 1 to 4 more preferably greater than 1 to 2 and most preferably greater than 1 to 1.5, by weight in water at 20° C.

Sucrose is a particularly acceptable excipient for the formulation since it combines in one substance the merits of ready availability in appropriate size grades, cheapness, the desired physical characteristics for coating with the drug, good crystal strength with a rapid aqueous dissolution rate, freedom from allergenic potential, and a degree of sweetness appropriate to mask the taste of sodium cromoglycate in proportions which are pharmaceutically and medically acceptable. In addition it has a low moisture content and with the crystal size selected does not aggregate either in manufacture or storage.

When the formulation is added to cold water the coated carrier, e.g. sucrose particles, remain separate during the dissolution process and this ensures that the individual particles of sodium cromoglycate are uniformly wetted, thus promoting rapid drug dissolution without gelling.

Other sugars may be used in place of sucrose, but many have disadvantages. Thus glucose has a negative heat of solution which militates against ease of dissolution, lactose is insufficiently water soluble nor is it very sweet and, because of its origins, may contain allergic impurities, and xylitol is expensive and is not readily available in the desired particle size.

We prefer the composition to contain an excess, e.g. a 2 to 20 times, and preferably a 4 to 15 times by weight excess, of the water soluble carrier, e.g. sugar, and especially just sufficient sugar to mask the taste of the sodium cromoglycate. The proportion of sugar will thus depend on the particular sugar used. However, we have found that with sucrose a suitable proportion is from 5 to 12, and especially from 7.5 to 10 parts by weight for each part by weight of sodium cromoglycate.

The formulation may be put up into unit dosages, e.g. sachets (which are preferably made of material which will prevent the ingress of water) containing from 50 to 300 mg; e.g. 100 or 200 mg, of sodium cromoglycate and from 1-3 g, e.g. about 2 g, of sugar. The unit doses may be administered from 1 to 6 times a day, preferably before, e.g. about 30 minutes before meals. The composition preferably contains a low proportion of 'heavy metal ions', as we have found that the presence of such ions tends to produce cloudy solutions when the composition is dissolved in water. By the term 'heavy metal ions' we mean ions of metals in groups IIa, Ib, IIb, IIIa, IVa and IVb of the periodic table and of the transition metals. Specific 'metal ions' which are detrimental, in excessive concentrations (i.e. above about 20 ppm) in solutions made up from the compositions of the invention, are Pb^{++} , Ca^{++} , Mg^{++} and in particular Fe^{++} , Fe^{+++} and Zn^{++} ions. We particularly prefer to keep the concentration of Mg^{++} ions as low as possible, e.g. less than about 0.22 p.p.m.

The composition also preferably contains a low proportion of water, e.g. less than 2%, preferably less than 1% and typically about 0.5% by weight. We prefer to carry out the mixing, and forming of the mixture into unit doses, at a relative humidity of less than about 65%, e.g. from about 40 to 65%.

The composition preferably comprises particles of the relatively coarse carrier coated with a layer of the fine sodium cromoglycate. We have surprisingly found that we can achieve the same effect as with the so called 'ordered mixing' with many times larger proportion of fine sodium cromoglycate to carrier than would be expected from theoretical considerations. The composition also desirably is such that there is no caking of the

blend between mixing and formation into unit dosages, e.g. sacheting. The mixture also desirably is such that there is no, or very little, segregation when it is filled, stored and transported.

We prefer the composition to contain no other excipients than the water soluble carrier.

The compositions of the invention can be used in the treatment of a wide variety of conditions, e.g. Crohn's disease (a condition of the small, and sometimes also of the large, intestine), atrophic gastritis (a condition of the stomach), ulcerative colitis (a condition of the rectum), proctitis (a condition of the rectum and lower large intestine), coeliac disease (a condition of the small intestine), regional ileitis (a regional inflammatory condition of the terminal ileum), peptic ulceration (a condition of the stomach and duodenum), gastrointestinal allergy (e.g. milk, gluten, food additive etc. allergy), irritable bowel syndrome and gastrointestinal bleeding induced by administration of an anti-inflammatory, e.g. indomethacin or aspirin.

The composition is particularly useful for the treatment of food allergy in children.

The compositions of the invention may be made by mixing the fine sodium cromoglycate with the coarse carrier e.g. in a planetary or a matrix mixer. Desirably a three (or greater) layer sandwich of the components is placed in the mixer before the mixing commences. The mixing should be carried out for a sufficient time to ensure as uniform a mix as possible. Mixing times of up to 60 minutes, but preferably of less than 15 minutes are generally suitable. The mixer is preferably such as not to change the particle sizes of the ingredients significantly during the mixing process.

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

EXAMPLE 1

	100 mg	200 mg
Sodium cromoglycate (Apex milled mass median diameter 3-6 microns, greater than 90% less than 30 microns. Measured as 'anhydrous' material)		
Sucrose (Caster Sugar sieve cut 90% to greater than 150 microns, 90% less than 450 microns)	1.03 g	2.01 g

A sandwich of sucrose-sodium cromoglycate-sucrose was placed in a matrix mixer (100L Fielder) in which a main rotor, passed through the base of the powder and a side chopper rotor, disrupts the mass movement of the powder. A satisfactory degree of mixing is achieved after a time of from about 2 to 10 minutes of operation of the mixer. The formulations are put up in paper/foil/polyethylene or 'Suriyn' laminate sachets; the individual sachets being 40×75 mm and produced in strips of five 160×75 mm with perforations between each. These strips are cartoned for appropriate treatment periods, e.g. 50's, 60's, 100's etc.

EXAMPLE 2

2 g Of the mixture of Example 1 when poured into 80 ml of tap water at 25° C. ± 3° C. in a 100 ml beaker stirred by a high speed stirrer (1200 rpm) dissolved (visual assessment) in 20-25 seconds. By way of contrast 200 mg of granules of sodium cromoglycate mean size 120 microns took 45-50 seconds to dissolve.

We claim:

1. A water-soluble composition for treatment of a condition of a gastro-intestinal tract comprising:

a particulate water-soluble pharmaceutically acceptable carrier consisting essentially of sucrose and having a particle size of 200-1000 microns; and

particulate sodium cromoglycate having a mass median diameter of 2-30 microns forming a coating on said carrier particles.

the proportion of carrier to sodium cromoglycate in the coated particles being 2-20 parts by weight of carrier to 1 part of sodium cromoglycate.

2. A composition according to claim 1, wherein the sodium cromoglycate has a mass median diameter of from 2 to 10 microns, and the water soluble carrier has a particle size of from 200 to 500 microns.

3. A composition according to claim 1 containing from 5 to 12 parts by weight of sucrose for each part by weight of sodium cromoglycate.

4. A composition according to claim 1 in unit dosage form containing from 50 to 300 mg of sodium cromoglycate.

5. A composition according to claim 4 contained in a sachet made of material which will prevent the ingress of water.

6. A composition according to claim 1 containing less than 2% by weight of water.

7. A composition according to claim 1 containing no other excipient than the water soluble carrier.

8. A method for preparing a sodium cromoglycate composition having an increased rate of dissolution in cold water which comprises depositing particulate sodium cromoglycate having a mass median diameter of 2-30 microns as a surface layer on a particulate water-soluble pharmaceutically acceptable carrier having a particle size of 200-1000 microns and consisting essentially of sucrose, the proportion of carrier to sodium cromoglycate in the coated particles being 2-20 parts of weight of carrier to 1 part of sodium cromoglycate.

9. The method of claim 8 wherein the sodium cromoglycate has a mass median diameter of 2-10 microns, and the water soluble carrier has a particle size of 200-500 microns.

10. The method of claim 8 wherein the proportion of carrier to sodium cromoglycate in the coated particles is 5-12 parts by weight of carrier to 1 part of sodium cromoglycate.

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