(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
12. Dezember 2002 (12.12.2002)

PCT

(10) Internationale Veröffentlichungsnummer
WO 02/098874 A3

(51) Internationale Patentklassifikation[7]: A61K 9/00, 31/46, 31/585, C07D 451/10

(21) Internationales Aktenzeichen: PCT/EP02/05600

(22) Internationales Anmeldedatum:
27. Mai 2002 (27.05.2002)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
101 26 924.2 1. Juni 2001 (01.06.2001) DE

(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(72) Erfinder; und

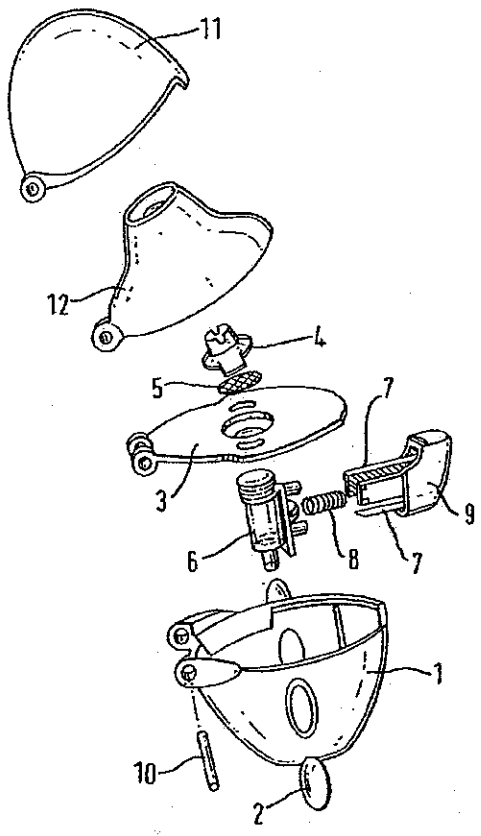
(75) Erfinder/Anmelder *(nur für US)*: **HOCHRAINER, Dieter** [AT/DE]; Vor der Hardt 16, 57392 Oberkirchen (DE). **BECHTOLD-PETERS, Karoline** [DE/DE]; Ulmenweg 12, 88400 Biberach/Rissegg (DE). **WALZ, Michael** [DE/DE]; Prizrenstraße 22, 55411 Bingen (DE). **TRUNK, Michael** [DE/DE]; Selztalstrasse 44, 55218 Ingelheim (DE).

(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,

[Fortsetzung auf der nächsten Seite]

(54) Title: INHALATION CAPSULES

(54) Bezeichnung: INHALATIONSKAPSELN



(57) Abstract: The invention relates to inhalation capsules (Inhalettes) made from specific capsule material with reduced moisture content, containing the active agent tiotropium in the form of a powder preparation and characterised by an improved stability.

(57) Zusammenfassung: Die Erfindung betrifft Inhalationskapseln (Inhaletten) aus spezifischen Kapselmaterialien mit reduziertem Feuchtegehalt, die den Wirkstoff Tiotropium in Form pulverförmiger Zubereitungen enthalten und durch eine erhöhte Stabilität gekennzeichnet sind.

WO 02/098874 A3

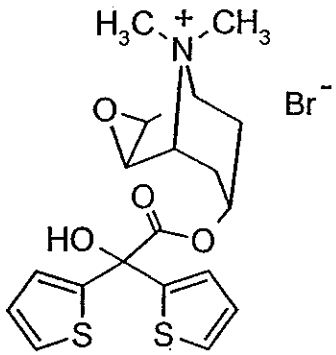
78188pct.209

Capsules for inhalation

The invention relates to capsules for inhalation (inhalettes) consisting of specific capsule materials with a reduced moisture content, which contain the active substance tiotropium in the form of powdered preparations and are characterised by increased stability.

Background to the invention

Tiotropium bromide is known from European Patent Application EP 418 716 A1 and has the following chemical structure:



Tiotropium bromide is a highly effective anticholinergic with a long-lasting effect, which may be used to treat respiratory complaints, particularly COPD (chronic obstructive pulmonary disease) and asthma. By tiotropium is meant the free ammonium cation.

When treating the above diseases it is convenient to administer the active substance by inhalation. In addition to the administration by inhalation of broncholytically active compounds in the form of metered aerosols and solutions these medicaments may also be administered in the form of inhalable powders containing active substance.

In the case of active substances with a particularly high efficacy, only small amounts of the active substance are needed per single dose to achieve the therapeutically desired effect. In such cases the active substance has to be diluted with suitable excipients to prepare the inhalable powder. In the case of active substances characterised by a particularly high efficacy it is particularly important, in order to ensure that the content administered remains reproducibly constant, to prepare the pharmaceutical composition in a form which is characterised by a high degree of stability. If this high degree of stability is not achieved, uniform dosage of the active substance cannot be guaranteed.

One embodiment of the invention is to prepare capsule for inhalation containing an inhalable powder which contains tiotropium, which guarantees sufficient stability of the active substance.

A further embodiment of the invention is to prepare a capsule for inhalation which by virtue of its stability ensures that the active substance is released with a high metering accuracy (with regard to the amount of active substance and powder mixture packed into each capsule by the manufacturer and also the quantity of active substance released by each capsule in the inhalation process and delivered to the lungs).

The present invention may also relate to another embodiment to prepare a capsule for inhalation which enables the active substance to be administered while emptying the capsule completely.

A further embodiment of the invention is to prepare capsules for inhalation which have good perforation qualities with good stability and low brittleness and which can therefore be used without any problems in inhalers designed for the administration of inhalettes.

Detailed description of the invention

Surprisingly, it has now been found that the problems set out above are solved by the capsules for inhalation (inhalettes) according to the invention described hereinafter.

The capsules for inhalation according to a first aspect the invention contain as the inhalable powder tiotropium, in admixture with a physiologically acceptable excipient, characterised in that the capsule material has a reduced moisture content as a TEWS or halogen drier moisture content of less than 15%.

According to a second aspect of the present invention, there is provided a use of capsules for inhalation according to the first aspect and an inhaler for preparing a medicament for inhalation.

According to a third aspect of the present invention, there is provided a use of empty capsules which are characterised by a TEWS or halogen drier moisture content of less than 15%, for preparing tiotropium-containing capsules for inhalation according to the first aspect.

The term TEWS moisture level within the scope of the present invention means the moisture level which can be determined using the MW 2200 moisture measuring apparatus made by TEWS. The method of measurement used is an indirect one. The activities derived from the water content (microwave absorption by the water contained in the product) are measured and indicated as a microwave value. In order to determine the water content in percent by weight, the apparatus has to be

calibrated using calibration samples. The resulting calibration curve is used by the apparatus in subsequent measurements for calculations. The moisture level is given in % and stored in the memory.

A halogen drier, for example, may be used to calibrate the TEWS apparatus within the scope of the present invention. Because the TEWS apparatus is calibrated using a halogen drier within the scope of the present invention the concept of the TEWS moisture level is to be regarded as equivalent to the concept of the halogen drier moisture content. For example, within the scope of the present invention, a 15% TEWS moisture level corresponds to a halogen drier moisture content of 15%. Whereas the TEWS apparatus represents a relative method of measuring water content, by virtue of its mode of operation, the halogen drier gives absolute values for the capsule moisture content. The water content is determined by weight loss in the halogen drier. The capsules are heated, whereupon the water escapes. The capsules are dried until a constant weight is achieved and then the results are read off. The difference in mass between the starting weight and final weight (in grams) represents the water content of the capsules and can be converted into percent by weight. When measuring the water content the TEWS apparatus merely compares the measurement curves of the actual capsules with internal calibration curves. These calibration curves are recorded using capsules with a defined water content whose absolute water content has been determined beforehand using the halogen drier method. In this way, the correlation with absolute water contents is established for the TEWS relative method with the aid of the halogen drier method.

Preferred capsules for inhalation according to the invention have a TEWS or halogen drier moisture content of less than 12%, particularly preferably ≤ 10%.

By capsule material is meant, within the scope of the present invention, the material from which the shell of the capsule for inhalation is made. The capsule material is according to the invention selected from among gelatine, cellulose derivatives, starch, starch derivatives, chitosan and synthetic plastics.

If gelatine is used as the capsule material, it may be used in admixture with other additives selected from among polyethyleneglycol (PEG), preferably PEG 3350, glycerol, sorbitol, propyleneglycol, PEO-PPO block copolymers and other polyalcohols and polyethers. Within the scope of the present invention gelatine is used particularly preferably in admixture with PEG, preferably PEG 3350. A gelatine capsule according to the invention preferably contains PEG in an amount of 1-10% (wt.-%), preferably 3-8 %. Particularly preferred gelatine capsules contain PEG in an

amount of 4-6%, a PEG content of about 5% being most preferred according to the invention.

In the case of gelatine-containing capsule materials, the capsules according to the invention preferably have a TEWS or halogen drier moisture content of less than 12%, particularly preferably ≤ 10%.

If cellulose derivatives are used as the capsule material, it is preferable to use hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose and hydroxyethylcellulose. In this case, hydroxypropylmethylcellulose (HPMC), particularly preferably HPMC 2910 is used as the capsule material. When cellulose derivatives are used as capsule materials the level of the TEWS or halogen drier moisture content is preferably less than 8%, particularly preferably less than 5%. Most preferably, capsules for inhalation consisting of cellulose derivatives are dried to a TEWS or halogen drier moisture content of less than 4 %, particularly preferably less than 2%, before being filled with the inhalable powder containing tiotropium.

If synthetic plastics are used as the capsule material, these are preferably selected according to the invention from among polyethylene, polycarbonate, polyester, polypropylene and polyethylene terephthalate. Particularly preferred synthetic plastics for the capsules for inhalation according to the invention are polyethylene, polycarbonate or polyethylene terephthalate. If polyethylene is used as one of the particularly preferred capsule materials according to the invention, polyethylene with a density of between 900 and 1000 kg/m^3, preferably from 940 - 980 kg/m^3, particularly preferably 960 kg/m^3 (high-density polyethylene) is preferably used. When synthetic plastics are used as the capsule materials the level of the TEWS or halogen drier moisture content is optionally less than 3%, optionally less than 1%.

After the empty capsules have been prepared in one of the embodiments mentioned hereinbefore, the capsules for inhalation according to the invention are filled with inhalable powder containing tiotropium. This may be done using methods known from the art. The empty capsules for inhalation to be used for filling may also be prepared using methods known from the prior art. For example, possible production methods include the dipping method, the blast pressure method, injection moulding, extrusion and deep drawing, all of which are known in the art.

When producing the capsules for inhalation according to the invention it is essential that, if the capsule material does not already have a suitably reduced moisture

content as a result of its storage or production before being filled with the inhalable powder containing the active substance, the empty capsules are dried. This drying is carried out until a moisture level is reached which corresponds to the specification of not more than 15% TEWS or halogen drier moisture content according to the invention.

Within the scope of the present invention the term capsule for inhalation is to be regarded as synonymous with the word Inhalette.

One embodiment of the present invention may relate to the use of capsules which are characterized by a TEWS or halogen drier moisture content of less than 15% and may consist of the abovementioned capsule materials, for preparing inhalettes (capsules for inhalation) which contain tiotropium-containing inhalable powder. Within the scope of the present invention the term capsule is to be taken as a reference to empty capsules for inhalation, i.e. ones which do not yet contain any inhalable powder.

According to the invention, capsules for inhalation which contain inhalable powder with a tiotropium content of 0.001 to 2 % are preferred . Capsules for inhalation which contain inhalable powder with a tiotropium content of 0.04 to 0.8%, preferably 0.08 to 0.64%, particularly preferably 0.16 to 0.4% are particularly preferred. The percentages specified with regard to the content of tiotropium within the scope of the present invention correspond to percent by weight, based on the total quantity of inhalable powder.

By tiotropium is meant the free ammonium cation. The counter-ion (anion) may be chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate. Of these anions, the bromide is preferred. Accordingly, the present invention preferably relates to inhalettes containing inhalable powders which are characterised by a tiotropium bromide content of 0.0012 – 2.41%.

According to the invention, it is particularly advantageous to use inhalable powders which contain between 0.048 and 0.96%, preferably 0.096 to 0.77%, particularly preferably 0.19 to 0.48% tiotropium bromide.

The inhalable powders contained in the inhalettes according to the invention may contain the tiotropium bromide preferably contained therein in the form of its hydrates. Crystalline tiotropium bromide monohydrate is most preferably used. Accordingly the present invention relates to inhalettes which contain powders for

If a mixture of coarser and finer excipient fractions is used as the excipient, these may also consist of chemically identical or chemically different substances, while inhalable powders in which the coarser excipient fraction and the finer excipient fraction consist of the same chemical compound are preferred.

Examples of physiologically acceptable excipients which may be used to prepare the inhalable powders used in the inhalettes according to the invention include, for example, monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

The capsules for inhalation according to the invention may, for example, be administered using inhalers as described in WO 94/28958. A particularly preferred inhaler for using the inhalettes according to the invention is shown in exploded view in Figure 1.

This inhaler (Handihaler) for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is connected to the capsule chamber 6, on which is provided a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, and a mouthpiece 12 which is connected to the housing 1, the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut. The capsule chamber is closed off by a filter 5. The filter is carried by a filter holder fixed to the mouthpiece 12.

The capsules for inhalation according to the invention may contain amounts of from 2 to 50mg, preferably 4 to 25mg of inhalable powder per capsule for inhalation. They then contain between 1.2 and 80µg of tiotropium. If each capsule for inhalation contains the particularly preferred amount of 4 to 6 mg of inhalable powder, each one contains between 1.6 and 48µg, preferably between 3.2 and 38.4µg, particularly preferably between 6.4 and 24µg of tiotropium. A tiotropium content of 18µg for example corresponds to a tiotropium bromide content of about 21.7µg.

Consequently, capsules for inhalation containing 3 to 10mg of inhalable powder according to the invention preferably contain between 1.4 and 96.3µg of tiotropium bromide. With a preferred content of 4 to 6 mg of inhalable powder in each capsule for inhalation, the content of tiotropium bromide in each capsule is between 1.9 and 57.8µg, preferably between 3.9 and 46.2µg, particularly preferably between 7.7 and 28.9µg. A tiotropium bromide content of 21.7µg of tiotropium bromide, for example, corresponds to a tiotropium bromide monohydrate content of about 22.5µg.

Consequently, capsules for inhalation containing 3 to 10mg of inhalable powder preferably contain between 1.5 and 100µg of tiotropium bromide-monohydrate. With a preferred content of 4 to 6 mg of inhalable powder in each capsule for inhalation, the tiotropium bromide monohydrate content of each capsule is between 2 and 60µg, preferably between 4 and 48µg, particularly preferably between 8 and 30µg.

The capsules for inhalation according to the invention are characterised in accordance with the objective of the present invention by a high degree of homogeneity in terms of the accuracy of single doses. This accuracy is in the region of < 8% , preferably < 6% , particularly preferably < 4%.

The inhalable powders preferably used to fill the capsules for inhalation according to the invention may be obtained by the method described below.

After the starting materials have been weighed out, the next step is to prepare the mixture of excipients, in those cases where the excipient used is a mixture of coarser and finer fractions. If the excipient used is a uniform fraction in terms of its average particle size (e.g. 15 - 80µm), this first step can be omitted.
The inhalable powder is then prepared from the excipient, possibly the mixture of excipients, and the active substance. The capsules for inhalation according to the invention are dried before filling with the tiotropium-containing inhalable powder until the maximum permissible level of TEWS or halogen drier moisture content according to the invention is reached. Then the powder-filled capsules for inhalation are produced using methods known in the art.

In the preparation processes described hereinafter, the abovementioned components are used in the amounts by weight described in the abovementioned compositions of the inhalable powders.

If mixtures of coarser and finer excipient fractions are used as the excipient, the

coarser and finer excipient fractions are placed in a suitable mixing container. The two components are preferably added using a granulating sieve with a mesh size of 0.1 to 2 mm, preferably 0.3 to 1 mm, most preferably 0.3 to 0.6 mm. Preferably, the coarser excipient is put in first and then the finer excipient fraction is added to the mixing container. During this mixing process the two components are preferably added in batches, with some of the coarser excipient being put in first and then finer and coarser excipient being added alternately. It is particularly preferred when producing the excipient mixture to sieve in the two components in alternate layers. The two components are preferably sieved in alternately in 15 to 45, most preferably 20 to 40 layers each. The mixing of the two excipients may take place while the two components are still being added. Preferably, however, mixing is only done once the two components have been sieved in layer by layer.

This step is, of course, omitted if an excipient fraction of uniform particle size is used (e.g. average particle size of 15-80µm).

Then the excipient, optionally the excipient mixture and the active substance are placed in a suitable mixing container. The active substance used has an average particle size of 0.5 to 10 µm, preferably 1 to 6 µm, most preferably 2 to 5 µm. The two components are preferably added using a granulating sieve with a mesh size of 0.1 to 2 mm, preferably 0.3 to 1 mm, most preferably 0.3 to 0.6 mm. Preferably, the excipient mixture is put in first and then the active substance is added to the mixing container. During this mixing process the two components are preferably added in batches. It is particularly preferred when producing the excipient mixture to sieve in the two components in alternate layers. The two components are preferably sieved in alternately in 25 to 65, most preferably 30 to 60 layers. The mixing of the excipient mixture with the active substance may take place while the two components are still being added. Preferably, however, mixing is only done once the two components have been sieved in layer by layer.

The powder mixture thus obtained may optionally be added once or repeatedly using a granulating sieve and then subjected to another mixing process.

In another preferred embodiment of the invention, the capsules for inhalation are filled with the inhalable powder containing tiotropium bromide obtained by the above process and then subjected to the dryness process described as follows.

The filled capsules are subjected in a first phase (drying phase) for a period of 0.5 - 10 hours, preferably 1.5 - 7 hours, preferably 2 – 5.5 hours, particularly preferably about 2.5 – 4.5 hours at a temperature of about 10 - 50°C, preferably 20 - 40 °C,

particularly preferably about 25 - 35°C to a relative humidity of not more than 30% r.h., preferably not more than 20% r.h., particularly preferably about 5 - 15% r.h.. By relative humidity (r.h.) is meant, within the scope of the present invention, the quotient of the partial steam pressure and the steam pressure at the temperature in question. In a subsequent second phase (equilibrium phase) the capsules are exposed to a relative humidity of not more than 35% r.h., preferably not more than 25% r.h., particularly preferably about 10 - 20% r.h. for a period of 0.5 - 10 hours, preferably 1.5 - 7 hours, preferably 2 – 5.5 hours, particularly preferably about 2.5 – 4.5 hours at a temperature of about 10 - 50°C, preferably 20 - 40 °C, particularly preferably about 25 - 35°C. This is optionally followed by a cooling phase if the temperature in the preceding steps was adjusted to levels above ambient temperature (i.e. 23°C). During this cooling phase the capsules are exposed to a relative humidity of at most 35% r.h., preferably at most 25% r.h., particularly preferably about 10 - 20% r.h. for a period of 0.1 - 6 hours, preferably 0.5 - 4 hours, preferably 0.75 – 2.5 hours, particularly preferably about 1 - 2 hours at a temperature of about 23°C. In a particularly preferred embodiment the values set for the relative humidity in the equilibrium phase and cooling phase are identical.

When the term active substance is used within the scope of the present invention, this is intended as a reference to tiotropium. According to the invention, any reference to tiotropium, which is the free ammonium cation, corresponds to a reference to tiotropium in the form of a salt (tiotropium salt) which contains an anion as the counter-ion. Tiotropium salts which may be used within the scope of the present invention are those compounds which contain chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate, in addition to tiotropium as counter-ion (anion). Within the scope of the present invention, tiotropium bromide is preferred of all the tiotropium salts. References to tiotropium bromide within the scope of the present invention should always be taken as references to all possible amorphous and crystalline modifications of tiotropium bromide. These may, for example, include molecules of solvent in their crystalline structure. Of all the crystalline modifications of tiotropium bromide, those which also include water (hydrates) are preferred according to the invention. It is particularly preferable to use tiotropium bromide monohydrate within the scope of the present invention, which may be obtained using the procedure described in detail hereinafter.

In order to prepare the capsules for inhalation containing tiotropium according to the invention, first of all tiotropium has to be prepared in a form which can be used for pharmaceutical purposes. For this, tiotropium bromide, which may be prepared as disclosed in EP 418 716 A1, is preferably subjected to another crystallisation step.

Depending on the reaction conditions and solvent used, different crystal modifications are obtained. For the purposes of preparing the capsules for inhalation according to the invention it has proved particularly suitable to use crystalline tiotropium bromide monohydrate.

The following Examples serve to illustrate the present invention in more detail without restricting the scope of the invention to the embodiments described hereinafter by way of example.

Starting materials

In the Examples which follow, lactose-monohydrate (200M) is used as the excipient. It may be obtained, for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

In the Examples which follow, lactose-monohydrate (200M) is also used as the coarser excipient when excipient mixtures are used. It may be obtained, for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

In the Examples which follow, when excipient mixtures are used, lactose-monohydrate (5µm) is used as the finer excipient. It may be obtained from lactose-monohydrate 200M by conventional methods (micronising). Lactose-monohydrate 200M may be obtained, for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

Preparation of crystalline tiotropium bromide monohydrate:

15.0 kg of tiotropium bromide are added to 25.7 kg of water in a suitable reaction vessel. The mixture is heated to 80-90°C and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80-90°C and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70°C . The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled by 3-5°C every 20 minutes to a temperature of 20-25°C. The apparatus is further cooled to 10-15°C using cold water and crystallisation is completed by stirring for at least one hour. The crystals are isolated using a suction drier, the crystal slurry isolated is washed with 9

litres of cold water (10-15°C) and cold acetone (10-15°C). The crystals obtained are dried in a nitrogen current at 25°C over 2 hours.
Yield : 13.4 kg of tiotropium bromide monohydrate (86 % of theory)

The crystalline tiotropium bromide monohydrate obtainable using the method described above was investigated by DSC (Differential Scanning Calorimetry). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50-120°C can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at 230 ± 5°C can be put down to the melting of the substance. This data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

The crystalline tiotropium bromide monohydrate according to the invention was characterised by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5µmol of tiotropium bromide monohydrate in 300 mg of KBr.

The following Table shows some of the essential bands of the IR spectrum.

Wave number (cm^{-1})	Attribution	Type of oscillation
3570, 410	O-H	elongated oscillation
3105	Aryl C–H	elongated oscillation
1730	C=O	elongated oscillation
1260	Epoxide C-O	elongated oscillation
1035	Ester C-OC	elongated oscillation
720	Thiophene	cyclic oscillation

The crystalline tiotropium bromide monohydrate obtainable by the above process has, according to single crystal X-ray structural analysis, a simple monoclinic cell with the following dimensions: a = 18.0774 Å, b = 11.9711 Å, c = 9.9321 Å, β =

102.691°, V = 2096.96 Å^3. These data were collected on an AFC7R- 4-circuit diffractometer (Rigaku) using monochromatic copper K_α radiation. The structural solution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program).

The crystalline tiotropium bromide monohydrate thus obtained is micronised by known methods to prepare the active substance in the form of the average particle size corresponding to the specifications according to the invention.

The method of determining the average particle size of the various ingredients of the formulation according to the invention is described as follows.

A) Determining the particle size of finely divided lactose:

Measuring equipment and settings:
The equipment is operated according to the manufacturer's instructions.

Measuring equipment:	HELOS Laser-diffraction spectrometer, (SympaTec)
Dispersing unit:	RODOS dry disperser with suction funnel, (SympaTec)
Sample quantity:	from 100 mg
Product feed:	Vibri Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel:	40 rising to 100 %
Duration of sample feed:	1 to 15 sec. (in the case of 100 mg)
Focal length:	100 mm (measuring range: 0.9 - 175 µm)
Measuring time:	about 15 s (in the case of 100 mg)
Cycle time:	20 ms
Start/stop at:	1 % on channel 28
Dispersing gas:	compressed air
Pressure:	3 bar
Vacuum:	maximum
Evaluation method:	HRLD

Sample preparation /product feed:
At least 100 mg of the test substance are weighed onto a piece of card. Using another piece of card all the larger lumps are broken up. The powder is then sprinkled finely over the front half of the vibrating channel (starting about 1 cm from the front edge). After the start of the measurement the frequency of the vibrating

channel is varied from about 40 % up to 100 % (towards the end of the measurement). The time taken to feed in the entire sample is 10 to 15 sec.

B) Determining the particle size of micronised tiotropium bromide monohydrate:

Measuring equipment and settings:

The equipment is operated according to the manufacturer's instructions.

Measuring equipment:	Laser diffraction spectrometer (HELOS), Sympatec
Dispersing unit:	RODOS dry disperser with suction funnel, Sympatec
Sample quantity:	50 mg - 400 mg
Product feed:	Vibri Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel:	40 rising to 100 %
Duration of sample feed:	15 to 25 sec. (in the case of 200 mg)
Focal length:	100 mm (measuring range: 0.9 - 175 µm)
Measuring time:	about 15 s (in the case of 200 mg)
Cycle time:	20 ms
Start/stop at:	1 % on channel 28
Dispersing gas:	compressed air
Pressure:	3 bar
Vacuum:	maximum
Evaluation method:	HRLD

Sample preparation /product feed:

About 200 mg of the test substance are weighed onto a piece of card. Using another piece of card all the larger lumps are broken up. The powder is then sprinkled finely over the front half of the vibrating channel (starting about 1 cm from the front edge). After the start of the measurement the frequency of the vibrating channel is varied from about 40 % up to 100 % (towards the end of the measurement). The sample should be fed in as continuously as possible. However, the amount of product should not be so great that adequate dispersion cannot be achieved. The time over which the entire sample is fed in is about 15 to 25 seconds for 200 mg, for example.

C) Determining the particle size of lactose 200M :

Measuring equipment and settings:

The equipment is operated according to the manufacturer's instructions.

Measuring equipment:	Laser diffraction spectrometer (HELOS), Sympatec
Dispersing unit:	RODOS dry disperser with suction funnel, Sympatec
Sample quantity:	500 mg
Product feed:	VIBRI Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel:	18 rising to 100 %
Focal length (1):	200 mm (measuring range: 1.8 - 350 µm)
Focal length (2):	500 mm (measuring range: 4.5 - 875 µm)
Measuring time:	10 s
Cycle time:	10 ms
Start/stop at:	1 % on channel 19
Pressure:	3 bar
Vacuum:	maximum
Evaluation method:	HRLD

Sample preparation /product feed:

About 500 mg of the test substance are weighed onto a piece of card. Using another piece of card all the larger lumps are broken up. The powder is then transferred into the funnel of the vibrating channel. A gap of 1.2 to 1.4 mm is set between the vibrating channel and funnel. After the start of the measurement the amplitude setting of the vibrating channel is increased from 0 to 40 % until a continuous flow of product is obtained. Then it is reduced to an amplitude of about 18%. Towards the end of the measurement the amplitude is increased to 100%.

Apparatus

The following machines and equipment, for example, may be used to prepare the inhalable powders:

Mixing container or powder mixer: Gyrowheel mixer 200 L; type: DFW80N-4; made by: Messrs Engelsmann, D-67059 Ludwigshafen.

Granulating sieve: Quadro Comil; type: 197-S; made by: Messrs Joisten & Kettenbaum, D-51429 Bergisch-Gladbach.

To determine the TEWS moisture level the following apparatus is used in accordance with the manufacturer's instructions.

Apparatus for determining the TEWS moisture level:
Manufacturer: Messrs TEWS Elektronik, Hamburg
Type: MW 2200
Measuring range: 1 to 85% moisture
Accuracy of measurement: 1 % of the final value of the measuring range chosen.
Mains connection: 220 V +/- 10%, 50 – 60 Hz

In order to determine the halogen drier moisture content as well as to adapt the TEWS apparatus, the following apparatus is used in accordance with the manufacturer's instructions.

Apparatus for determining the halogen drier moisture level:
Mettler halogen drier HR 73; manufacturer: Messrs Mettler-Toledo, D-35396 Gießen;

The following apparatus is used to fill the empty capsules with powder for inhalation containing tiotropium.

Capsule filling machine:
MG2, Type G100, manufacturer: MG2 S.r.l, I-40065 Pian di Macina di Pianoro (BO), Italy.

Example 1:

1.1: Excipient mixture:
31.82 kg of lactose monohydrate for inhalation (200M) are used as the coarser excipient component. 1.68 kg of lactose monohydrate (5µm) are used as the finer excipient component. In the resulting 33.5 kg of excipient mixture the proportion of the finer excipient component is 5%.

About 0.8 to 1.2 kg of lactose monohydrate for inhalation (200M) are added to a suitable mixing container through a suitable granulating sieve with a mesh size of 0.5 mm. Then alternate layers of lactose monohydrate (5µm) in batches of about 0.05 to 0.07 kg and lactose monohydrate for inhalation (200M) in batches of 0.8 to 1.2 kg

are sieved in. Lactose monohydrate for inhalation (200M) and lactose monohydrate (5µm) are added in 31 and 30 layers, respectively (tolerance: ±6 layers).

The ingredients sieved in are then mixed together (mixing at 900 rpm).

1.2: Final mixture:

To prepare the final mixture, 32.87 kg of the excipient mixture (1.1) and 0.13 kg of micronised tiotropium bromide monohydrate are used. The content of active substance in the resulting 33.0 kg of inhalable powder is 0.4%.

The same procedure is followed using only 32.87 kg of lactose monohydrate (200 M) if an excipient fraction of uniform average particle size is used as the excipient. In this case, step 1.1 is naturally omitted.

About 1.1 to 1.7 kg of excipient or excipient mixture (1.1) are added to a suitable mixing container through a suitable granulating sieve with a mesh size of 0.5 mm. Then alternate layers of tiotropium bromide monohydrate in batches of about 0.003 kg and excipient or excipient mixture (1.1) in batches of 0.6 to 0.8 kg are sieved in. The excipient or excipient mixture and the active substance are added in 47 or 45 layers, respectively (tolerance: ±9 layers).

The ingredients sieved in are then mixed together (mixing at 900 rpm). The final mixture is passed through a granulating sieve twice more and then mixed (mixing at 900 rpm).

Example 2:

Inhalation capsules (inhalettes) having the following composition were produced using the mixture obtained according to Example 1:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 µm):	0.2750 mg
hard gelatine capsule (5% PEG 3350; 9% TEWS moisture):	49.0 mg
Total:	54.5 mg

Example 3:

Inhalation capsules:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	4.9275 mg
lactose monohydrate (5 µm):	0.5500 mg
hard gelatine capsule (5% PEG 3350; 9% TEWS moisture):	49.0 mg
Total:	54.5 mg

The inhalable powder needed to prepare the capsules was obtained analogously to Example 1.

Example 4:

Inhalation capsules:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 µm):	0.2750 mg
HPMC (<2% TEWS moisture):	49.0 mg
Total:	54.5 mg

The inhalable powder needed to prepare the capsules was obtained analogously to Example 1.

Example 5:

Inhalation capsules:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 µm):	0.2750 mg
polyethylene (<1% TEWS moisture):	100.0 mg
Total:	105.5 mg

The inhalable powder needed to prepare the capsules was obtained analogously to Example 1.

Example 6:

Inhalation capsules:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.4775 mg
polyethylene (<1% TEWS moisture):	100.0 mg
Total:	105.5 mg

The inhalable powder needed to prepare the capsules was obtained analogously to Example 1.

Example 7:

Inhalation capsules (inhalettes) having the following composition were produced using the mixture obtained according to Example 1:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 µm):	0.2750 mg
hard gelatine capsule (5% PEG 3350):	49.0 mg
Total:	54.5 mg

These capsules are adjusted to a water content of about 8.7 % (measured with a TEWS microwave moisture measuring apparatus) under suitable climatic conditions in an air-conditioned chamber using the following procedure.
To start with, a drying phase is carried out, followed by a so-called equilibrium phase. Finally, the capsules are subjected to a so-called cooling phase. The capsules thus dried are then packaged directly afterwards in corresponding storable packaging or the like.

Process data

Setting the climatic conditions to the following rated values:

Drying phase:	30 °C
	10 % r.h. (relative humidity)
	3.5 h
Equilibrium phase:	30 °C
	16 % r.h.

		20
		3.5 h
Cooling phase	:	23 °C
		16 % r.h.
		1.5 h

By relative humidity (r.h.) within the scope of the present invention is meant the quotient of the partial steam pressure and the vapour pressure of the water at the temperature in question.

For the purposes of the present invention, the average particle size means the value in µm at which 50% of the particles of the volume distribution have a particle size which is smaller than or the same as the value specified. The laser diffraction/dry dispersion method is used as the method of measuring the total distribution of the particle size distribution.

Patent Claims

1) Capsules for inhalation which contain as the inhalable powder tiotropium in admixture with a physiologically acceptable excipient, characterised in that the capsule material has a reduced moisture content as a TEWS or halogen drier moisture content of less than 15%.

2) Capsules for inhalation according to claim 1, characterised in that the capsule material is selected from among gelatine, cellulose derivatives, starch, starch derivatives, chitosan and synthetic plastics.

3) Capsules for inhalation according to claim 2, characterised in that the capsule material used is gelatine in admixture with other additives selected from among polyethyleneglycol (PEG), preferably PEG 3350, glycerol, sorbitol, propyleneglycol, PEO-PPO block copolymers and other polyalcohols and polyethers.

4) Capsules for inhalation according to claim 3, characterised in that the capsule material contains, in addition to gelatine, PEG in an amount of 1-10 wt.-%, preferably 3-8 %.

5) Capsules for inhalation according to claim 3 or 4, characterised in that the capsule material has a TEWS or halogen drier moisture content of less than 12%, particularly preferably ≤ 10%.

6) Capsules for inhalation according to claim 2, characterised in that the capsule material is selected from the cellulose derivatives hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose and hydroxyethylcellulose.

7) Capsules for inhalation according to claim 6, characterised in that the capsule material has a TEWS or halogen drier moisture content of less than 8%, particularly preferably ≤ 5%.

8) Capsules for inhalation according to claim 2, characterised in that the capsule material is selected from the synthetic plastics polyethylene, polycarbonate, polyester, polypropylene and polyethylene terephthalate.

9) Capsules for inhalation according to claim 8, characterised in that the capsule material is selected from polyethylene, polycarbonate and polyethylene terephthalate.

10) Capsules for inhalation according to claim 8 or 9, characterised in that the capsule material has a TEWS or halogen drier moisture content of less than 3%, particularly preferably ≤ 1%.

11) Capsules for inhalation according to one of claims 1 to 10, characterised in that the inhalable powder contains 0.001 to 2% tiotropium in admixture with a physiologically acceptable excipient.

12) Capsules for inhalation according to claim 11, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of finer excipient in the total quantity of excipient being 1 to 20%.

13) Capsules for inhalation according to claim 12, characterised in that the tiotropium is in the form of its chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methylsulphate.

14) Use of capsules for inhalation according to one of claims 1 to 13 and an inhaler for preparing a medicament for inhalation.

15) Use according to claim 14 for the treatment of asthma or COPD.

16) Use of empty capsules which are characterised by a TEWS or halogen drier moisture content of less than 15%, for preparing tiotropium-containing capsules for inhalation according to one of claims 1 to 13.