Title: INHALATION PARTICLES COMPRISING A SALT OF CARMOTEROL AND A CORTICOSTEROID

Abstract: The present invention relates to crystalline particles wherein each particle comprises a combination of a pharmaceutically acceptable salt of 8-hydroxy-5-[(IR)-1-hydroxy-2-[[[(IR)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(IH)-quinolinone (carmoterol), and a corticosteroid in a pre-determined and constant ratio. The invention also relates to a method for preparing them and to inhalation compositions thereof.
INHALATION PARTICLES COMPRISING A SALT OF CARMOTEROL AND A CORTICOSTEROID

FIELD OF INVENTION

The present invention relates to crystalline particles wherein each particle comprises a combination of a pharmaceutically acceptable salt of 8-hydroxy-5-[(lR)-l-hydroxy-2-[[lR]-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]-2(lH)-quinolinone (carmoterol), and a corticosteroid in a pre-determined and constant ratio.

The invention also relates to a method for preparing them and to inhalation compositions thereof.

The inhalation particles of the invention are particularly useful in the treatment of respiratory diseases such as asthma and COPD.

BACKGROUND OF THE INVENTION

The administration of pharmacologically active ingredients by inhalation to the airways is a widely used technique especially for the prevention and/or treatment of broncho-pulmonary diseases.

The most widely used systems for the administration of drugs to the airways are the dry powder inhalers (DPIs) comprising micronised drug particles as dry powder usually admixed with coarser excipient articles of pharmacologically inert materials such as lactose, and the pressurized metered-dose inhalers (pMDIs) which may comprise a suspension of micronised drug particles in a propellant gas.

Drugs commonly delivered by inhalation for treating broncho-pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD) include long-acting beta_2-agonists (LABA) such as formoterol and salmeterol, and inhaled corticosteroids (ICS) such as
beclometasone dipropionate (BDP), budesonide, mometasone furoate, ciclesonide, and fluticasone propionate.

To improve the compliance of the patients, formulations have been developed comprising a combination of LABA and ICS, thereby reducing the number of inhalers that the patients would normally require.

On the other hand, said formulations usually combine the LABA and ICS only as far as creating a physical mixture of the two separate drugs with or without excipients.

When these combinations are used in said kind of formulations, the method of mechanically mixing the two different drugs has certain drawbacks.

For example, the consistency of drug proportion in each dose cannot be easily controlled. The ratio of drugs in each dose significantly depends on the forces existing between the drugs, and between each drug and the excipients.

In this respect, it is well known that the manufacturing methods currently used, such as conventional milling processes, produce very cohesive particles.

Another factor that jeopardizes the possibility of maintaining the ratio of the drugs in each dose constant is the size of the drug particles. Said parameter indeed cannot easily be controlled, and hence it is difficult obtain drugs having the same particle size.

The inconsistency of the dose could cause serious problems as it could give rise to a risk of an over or under dosage.

In particular, ensuring a good constancy of the drugs ratio, it very critical for combination with very low-dosage strength LABA drugs which are present in the formulation in a very low concentration.

In fact, the lesser the LABA concentration, the greater the ratio between said drug and the ICS in the formulation, and hence more difficult is maintaining the constancy of the ratio.
For example, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[1(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone (hereinafter indicated as carmoterol), is a very low-dosage strength LABA which is to be administered by inhalation at a very low daily therapeutical dose ranging from 1 to 4 µg. It is currently under development in the form of a pharmaceutically acceptable salt in combination with budesonide in ratios in which the corticosteroid is the overwhelming part.

These facts, together with other properties such as its high adhesiveness degree, leads to problems in the manufacturing of compositions comprising carmoterol in combination with a ICS wherein the two drugs are present in a constant ratio in each delivered dose.

Moreover it would be highly preferable to provide formulations wherein both active ingredients are in crystalline form, especially with regard to suspension based-pMDI and DPI formulations. As matter of fact, the presence of amorphous material may lead to batch-to-batch variation in the performance during product’s lifespan in addition to physical and chemical stability problems.

The object of the invention is to provide crystalline particles comprising a combination of a pharmaceutically acceptable salt of carmoterol, and a corticosteroid in a predetermined and constant ratio. Said particles allow preparing formulations for inhalation with improved properties in terms of dosing compliance.

Since said particles allows achieving a co-deposition at the target cell of the lungs of the combination of the active drug substances, the relevant formulations could also give rise to superior therapeutic benefit due to the enhanced synergistic action.

**SUMMARY OF THE INVENTION**

The present invention is directed to crystalline particles for use in
pharmaceutical formulations for inhalation, wherein each particle comprises a combination of a pharmaceutically acceptable salt of 8-hydroxy-5-[(lR)-1-hydroxy-2-[(lR)-2-(4-methoxyphenyl)]-1-methyl] amino]ethyl]-2(IH)-quinolinone (carmoterol), and a corticosteroid in a ratio of no more than 1:50.

The present invention also provides a process for preparing crystalline particles wherein each particle comprises a combination of a pharmaceutically acceptable salt of carmoterol, and a corticosteroid in a ratio of no more than 1:50, said process comprising the steps of: a) preparing solution of the two different active ingredients in a pre-determined ratio in a suitable solvent; b) generating an aerosol from the solution of said two active ingredients; c) collecting the aerosol droplets in a vessel containing an anti-solvent for both active ingredients; d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and e) isolating and collecting the produced particles.

Preferably the solvent is a mixture of dichloromethane and methanol in a ratio comprised between 90:10 and 99:1 v/v, and the anti-solvent is n-heptane.

The invention provides a further process, for preparing crystalline particles wherein each particle comprises a combination of a pharmaceutically acceptable salt of carmoterol, and a corticosteroid in a ratio of no more than 1:50, said process comprising the steps of:

a) preparing solution of the two active ingredients in a pre-determined ratio in a suitable solvent; b) generating an aerosol from the solution of said two active ingredients and drying the atomized droplets to yield unstable part-amorphous or fully amorphous particles; c) collecting the particles in a vessel containing an anti-solvent for both active ingredients; d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and e) isolating and collecting the produced
Moreover, the present invention is directed to crystalline particles for use in pharmaceutical formulations for inhalation, wherein each particle comprises a combination of a pharmaceutically acceptable salt of 8-hydroxy-5-[(IR)-1-hydroxy-2-[(IR)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone (carmoterol), and a corticosteroid in a ratio of no more than 1:50, said particles obtainable by a process comprising the steps of: a) preparing solution of the two different active ingredients in a pre-determined ratio in a suitable solvent; b) generating an aerosol from the solution of said two active ingredients in a vessel containing an anti-solvent for both active ingredients; d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and e) isolating and collecting the produced particles.

Alternatively, the aforementioned crystalline particles are obtainable by a process comprising the step of: a) preparing solution of the two active ingredients in a pre-determined ratio in a suitable solvent; b) generating an aerosol from the solution of said two active ingredients and drying the atomized droplets to yield unstable part-amorphous or fully amorphous particles; c) collecting the particles in a vessel containing an anti-solvent for both active ingredients; d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and e) isolating and collecting the produced particles.

In a further aspect, the present invention provides a formulation for administration by inhalation comprising the aforementioned particles, optionally together with one or more pharmaceutically acceptable excipients.

Preferably, the formulation is provided in the form of dry inhalation powder to be used with dry powder inhaler (DPI) devices or in the form of a
suspension of the particles in a propellant gas to be used with pressurized metered-dose inhaler (pMDI) devices.

Therefore the invention is also directed to a device which may be a single- or multi-dose dry powder inhaler, or a pressurized metered dose inhaler, respectively, filled with the aforementioned formulations.

In yet another aspect, the present invention comprises the use of the crystalline particles of the invention as a medicament.

Finally, the invention concerns the use of the aforementioned particles for the prevention and/or treatment of an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD).

In a still further aspect, the present invention comprises a method of preventing and/or treating an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD), which comprises administration by inhalation of an effective amount of the crystalline particles of the invention.

**DEFINITIONS**

The terms "drug", "active ingredient", "active agent" and "active substance" are used as synonyms.

The term "solvent" is used to mean the medium in which the active ingredient is dissolved and "anti-solvent" to mean the medium in which its crystallization takes place.

The term "very low-dosage strength", refers to active ingredients endowed with particularly high potency which are present in the powder formulation in a very low concentration. Said active ingredients are commonly administered at a daily therapeutic dose lower than 6 µg.

"Daily therapeutically effective dose" refers to the quantity of active ingredient administered in one day by inhalation.

Said daily dose may be delivered in one or more administrations per day
and in one or more actuations of the inhaler per administration.

For "actuation" it is meant the release of active ingredient from the device by a single activation (e.g. mechanical or breath).

The daily dose may be reached by a single or double administration.

The daily dose may be reached by a single administration and delivered in one actuation of the inhaler or, alternatively, in more actuations of the inhaler, preferably two.

In a further embodiment the daily dose may be reached by a double administration and delivered in one actuation of the inhaler or, alternatively, delivered in more actuations of the inhaler, preferably two.

The expression "each particle comprises a combination of a pharmaceutically acceptable salt of carmoterol and a corticosteroid" means that a single unagglomerated particle, whose size is in the range of microns, comprises a crystalline corticosteroid in which carmoterol, being present in a low amount, is incorporated as "an impurity". This phenomenon, known as "crystal doping" is demonstrated by the depression of the melting point of the crystalline corticosteroid.

The expression 'good constancy of the drug ratio' means that the two active ingredients, after delivery of a single therapeutic dose, maintain substantially the same ratio as the pre-determined ratio of said two active ingredient in the formulation, i.e. that the relative standard deviation (RSD) of the ratio of the amounts of drugs measured in an vitro apparatus such as the Andersen Cascade Impactor (ACI) is less is less than 15%, preferably less than 10%.

Generally, the particle size is quantified by measuring a characteristic equivalent sphere diameter, known as volume diameter, by laser diffraction.

The particle size may also be quantified by measuring the mass diameter by means of suitable instrument well known to the skilled person.
such as, for instance the sieve analyser.

The volume diameter (VD) is related to the mass diameter (MD) by the density of the particles (assuming a size independent density for the particles).

In the present application, the particle size is expressed in terms of mass diameter and the particle size distribution is expressed in terms of: i) the volume median diameter (MVD) which corresponds to the diameter of 50 percent by weight or volume respectively, of the particles \([d(v,0.5)]\), and ii) the MD in micron of 10% and 90% of the particles, respectively \([d(v,0.1)]\) and \([d(v,0.9)]\).

Upon aerosolisation, the particle size is expressed as mass aerodynamic diameter (MAD) which indicates the capability of the particles of being transported and suspended in an air stream. The term MMAD stands for median mass aerodynamic diameter.

The expression "good homogeneity" refers to a formulation wherein, upon mixing, the content uniformity of the active ingredient, expressed as relative standard deviation (RSD), is less than 5%, preferably less than 3%.

The expression "respirable fraction" refers to an index of the percentage of active particles which would reach the deep lungs in a patient.

The respirable fraction, also termed fine particle fraction, is evaluated using a suitable in vitro apparata such as the Andersen Cascade Impactor (ACI) or the Multi Stage Liquid Impinger (MLSI) according to procedures reported in common Pharmacopoeias. It is calculated by the ratio between the respirable dose and the delivered dose. The delivered dose is calculated from the cumulative deposition in the apparatus, while the respirable dose (fine particle dose) is calculated from the deposition on Stages 3 (S3) to filter (AF) corresponding to particles \(< 5.0\) micron.

A respirable fraction higher than 30% is an index of good inhalatory performances.
The term "synergistic" means that the activity of the two active ingredients is more than would be expected by summing their respective individual activities in a given assay.

The term "interactive or ordered mixture" refers to powder formulation for inhalation comprising a pharmacologically-inert physiologically acceptable carrier substance, to which the micronised 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 term 'relatively highly fissured surface' means a surface on which there are clefts and valleys and other recessed regions, referred to herein collectively as fissures. Said surface of the coarse excipient particles may be defined in terms of fissure index or rugosity coefficients as disclosed in WO 01/78695 and WO 01/78693 and they can be characterized according to the description therein reported.

FIGURES

Figure 1 - SEM image of particles consisting of carmoterol hydrochloride and budesonide in a ratio 1:100 w/w.

Figure 2 - SEM images of carmoterol hydrochloride (left) and budesonide (right) raw materials.

Figure 3 - X-ray powder diffraction pattern of particles consisting of carmoterol hydrochloride and budesonide in a ratio 1:100 w/w.

Figure 4 - Thermogram of particles consisting of carmoterol hydrochloride and budesonide in a ratio 1:100 w/w (solid line) in comparison to pure crystalline budesonide (dash line) and pure crystalline carmoterol hydrochloride (dash-dot line).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides crystalline particles for use in pharmaceutical formulations for inhalation, each particles comprising a
combination of a pharmaceutically acceptable salt of 8-hydroxy-5-[(lR)-l-
hydroxy-2-[[lR]-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]-2(lH)-
quinolinone (carmoterol), and a corticosteroid in a constant ratio.

Upon inhalation, the particles of the invention provide more controlled
delivery of the combination of carmoterol with a corticosteroid, since they
allow keeping the ratio of the drugs constant upon each actuation.

The particles of the invention are in a substantially crystalline form and
show a reduced tendency of moisture adsorption as demonstrated in Example
3, contributing to increase their physical and chemical stability.

Said particles also exhibit excellent dispersion properties allowing to
easily obtaining homogenous formulations, in particular when the particles are
formulated as dry powders for inhalation.

By scanning electron microscopy (SEM), it can be clearly observed that
said particles are significantly distinct when compared to the SEM image of
the starting materials (Figures 1 and 2).

It can also be appreciated that the particles of the invention exhibit a
more uniform and regular spherical shape and do not appear to be as fractured
and irregular as the starting materials.

The difference in the surface morphology contributes to lower the
tendency of aggregation of the particles, and hence explain their excellent
dispersion properties.

Examples of pharmaceutically acceptable salt of carmoterol include
hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate,
citrate, benzoate, mesylate, ascorbate, salicylate, acetate, succinate, lactate,
glutarate or gluconate.

The hydrochloride salt is preferred.

Advantageously, the corticosteroid is any corticosteroid insoluble or
poorly-soluble in water according to the definition of solubility given in the
European Pharmacopoeia Ed. 4th, 2002, which can be utilised by inhalation for the prevention and/or treatment of respiratory diseases, and having a single therapeutical dose higher than 50 microg, preferably equal to or higher than 80 microg, more preferably equal to higher than 100 microg.

Preferably, the corticosteroid is selected from the group consisting of beclometasone dipropionate (BDP), budesonide, ciclesonide, mometasone and esters thereof, e.g. furoate, fluticasone and esters thereof, e.g. propionate and furoate.

The corticosteroid is preferably budesonide.

The predetermined and constant ratio of carmoterol to the corticosteroid in the particles of the invention is at least of 1:50 expressed as w/w. Depending on the choice of the corticosteroid, it is advantageously comprised between 1:50 and 1:800, preferably between 1:80 and 1:400.

For example, when budesonide is used, the w/w ratio may be comprised between 1:50 to 1:400, preferably between 1:180 and 1:320. In one of the preferred embodiments of the invention the w/w ratio is preferably 1:100, while in another preferred embodiment the w/w ratio is 1:160.

Another corticosteroid that can be advantageously used in the combination is mometasone furoate and in this case the w/w ratio will range from 1:100 to 1:400.

The particles of the invention should have a narrow particle size distribution in a range suitable for their administration by inhalation.

Advantageously the particles of the invention have a particle size distribution lower than 15 micron, and more advantageously at least 90% of the particles have a diameter equal to or lower than 12 micron as determined by measuring the characteristic equivalent sphere diameter, known as volume diameter, by laser diffraction as described above, preferably using a Malvern or an equivalent apparatus.
Preferably no more than 10% of said particles have a volume diameter $[d(v,0.1)]$ lower than 0.8 micron, no more than 50% of have a volume diameter $[d(v,0.5)]$ lower than 2.0 micron, and at least 90% have a volume diameter equal to or lower than 11 micron.

The particles of the invention are substantially in a crystalline form.

Advantageously the degree of crystallinity, expressed as weight % of the crystalline particle with respect to the total weight of the particle, is higher than 90%, preferably higher than 93%, even more preferably equal to or higher than 95%.

The degree of crystallinity of the particle may be determined using X-ray powder diffraction or other known techniques such as microcalorimetry.

The active ingredients in the particles of the invention are substantially in a pure form, e.g. both at least of 95% w/w, preferably 98% or 99% w/w or greater.

The chemical purity may be determined according to methods known to the skilled person such as high-performance liquid chromatography (HPLC).

The particles of the invention may be prepared according to processes disclosed in WO 2004/073827 and WO 2010/00447.

Therefore, in an aspect, and following the teaching of WO 2004/073827 the present invention provides a process for the production of the particles of the invention comprising the steps of:

a) preparing solution of the two active ingredients (the salt of cromoterol and the corticosteroid) in a pre-determined ratio in a suitable solvent;

b) generating an aerosol from the solution of said two active ingredients;

c) collecting the particles in a vessel containing an anti-solvent for both active ingredients;
d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and

e) isolating and collecting the produced particles.

In another aspect and following the teaching of WO 2010/00447 the present invention provides a process for the production of the particles of the invention comprising the steps of:

a) preparing solution of the two active ingredients (the salt of carmoterol and the corticosteroid) in a pre-determined ratio in a suitable solvent;

b) generating an aerosol from the solution of said two active ingredients and drying the atomized droplets to yield unstable part-amorphous or fully amorphous particles;

c) collecting the particles in a vessel containing an anti-solvent for both active ingredients;

d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and

e) isolating and collecting the produced particles.

As far as the step a) is concerned, the choice of the solvent is critical as, besides having a high solubilising capacity for both active ingredients, it should have a suitable degree of volatility and diffusion characteristics within the atomized droplets. These properties indeed significantly affect (i) the particle size distribution of the intermediate part-amorphous or fully amorphous particles; (ii) condition of the particles for subsequent treatment as stated in step d); (iii) the particle size distribution of the final isolated crystalline particles.

When the particles are prepared according to the teaching of WO 2004/073827, it has been found that a mixture of dichloromethane and methanol in a ratio comprised between 90:10 and 99:1 v/v is particularly
suitable, as it gives rise to satisfactory results in terms of crystallinity degree, morphology and particle size distribution.

Preferably mixtures of dichloromethane and methanol in ratios from 97:3 to 95:5 v/v are used.

Instead, when the particles are prepared according to the teaching of WO 2010/00447, methanol turned out to be particularly suitable.

A change in the concentration of the active ingredients in the solution prepared in step a) of the process of the invention also affects the resultant particle size distribution.

For the particles of the invention it has been found that is preferable to utilise an overall concentration of two active ingredients comprised between 0.8 and 5.0% w/v, preferably comprised between 1.0 and 3.0% w/v, more preferably between 1.5 and 2.0% w/v.

For step b), when the particles are prepared according to WO 2004/073827, any aerosol based atomisation system may be used for generation of the aerosol. Various systems for generating aerosols are well-known. The aerosol may, for example, be generated from the desired substance dissolved in a suitable solvent by electrohydrodynamic spraying, high air pressure atomiser or other aerosol generators including pneumatic systems, rotary (spinning-top) systems, spray nozzles, nebulizers, propellant evaporation systems, piezoelectric transducers and ultrasonic transducers.

For example, the aerosol may be generated using the electrohydrodynamic spraying system or the high-pressure atomization system.

On the other hand, when the particles are prepared according to WO 2010/00447, the solution is preferably atomized by spray-drying.

Controlling the conditions of the aerosol generation such as the temperature of the solution, the solution flow rate and the pressure of the
carrier gas allows furthering controlling the particle size distribution of the particles.

Said conditions shall be properly adjusted by the person skilled in the art in relation with the desired particle size distribution and the size of the batch.

In step c) n-heptane is preferably used as anti-solvent.

When the particles are prepared according to the teaching of WO 2010/00447, other anti-solvents such as cyclohexane, 2-propanol and fluorinated hydrocarbons, such as perfluorodecalin may be used. In particular perfluorodecalin is another preferred solvent.

The collection vessel is preferably a temperature-controlled collection vessel.

Advantageously, when the particles are prepared according to WO 2004/073827, the temperature of the anti-solvent is maintained below 10°C, preferably between 5 and 8°C, more preferably at 5°C.

Instead, when the particles are prepared according to WO 2010/00447, the temperature of the anti-solvent may be maintained between 25° and 80°C, preferably between 55° and 75°C.

The volume of the anti-solvent is generally in at least a slightly larger excess than that of the solvent and their ratio is advantageously comprised between 1.5:1 and 10:1 v/v, preferably from 5:1 to 2:1.

In step d) ultrasonic energy is applied to induce nucleation and subsequent crystallisation and thus generating the crystalline particles of the invention.

The ultrasonic energy may be applied continuously or in a discontinuous manner such as by pulsed application. Any suitable source of ultrasonic vibration may be used. An ultrasonic probe may, for example, be inserted into the collection vessel, an ultrasonic emitter may be contained in
the collection vessel or the collection vessel may be housed in an ultrasonic bath.

The amplitude and frequency of the ultrasound waves affects the rate of nucleation and crystal growth. The frequency of the ultrasound waves may for example be from 10 kHz to 1 MHz, preferably from 10-500 kHz, more preferably from 10 - 100 kHz such as at 10, at 20, 40, 60, 80, or 100 kHz or at any frequency therein between, such as, 30 kHz or 50 kHz.

The ultrasonic irradiation is employed at amplitude that is appropriate for the formation of crystals of the desired size.

For laboratory probe systems with an emitting face of, for example 80 cm², the amplitude selected may be from about 1 - 30 µm, typically from 3 to 20 µm, preferably from 5 to 10 µm.

Probes having a probe face surface area of 8 cm² and a power requirement of from 5-80 W, provide a power density of from 0.6 - 12.5 W/cm² using an amplitude of 2-15 mm. In larger systems, comprising transducers bonded onto the flow cell, for example a 6 litre flow cell, the power density for the transducers employed may be from 10 - 100 W/L, preferably from 30-80 W/L, and more preferably from 50-75 W/L, for example 60 W/L or 70 W/L.

In some embodiments of the invention, an ultrasonic probe operating at the frequency of 20 kHz and at a power of 20-40 W was advantageously used.

In step e), the particles obtained at the end of the crystallisation stage may be isolated from the resulting slurry and collected according to well known methods.

Advantageously the particles of the invention may be isolated by supercritical carbon dioxide extraction or by spray-drying, preferably by spray-drying.

It has indeed been found that the particles obtained after isolation by
spray-drying exhibit better flow properties.

In another aspect the present invention provides a formulation for administration by inhalation comprising the particles of the invention. The particles may be formulated together with one or more pharmaceutically acceptable excipients, additives, diluents or carriers.

For example, the formulation is provided in the form of suspension in a propellant as aerosol carrier to be administered by pressurized metered dose inhalers (pMDI).

The pMDI comprises a canister wherein the formulation is filled and a metering valve for delivering a daily therapeutically effective dose of the formulation.

In certain embodiments the aerosol carrier may consist of a non-chlorofluorocarbon-based propellant such as hydrofluoralkane (HFA). In particular the propellants HFA 134a, and HFA 227 or mixtures thereof may be advantageously used.

The suspension formulation may comprise additional excipients such as surfactants, and wetting agents.

In a preferred embodiment, the formulation is provided in the form of dry powder for inhalation, more preferably in the form of an interactive or ordered mixture, by diluting the particles of the invention in a pharmacologically inert physiologically acceptable excipient consisting of coarser particles.

Advantageously, said powder formulation for inhalation may comprise the particles according to the invention and coarse particles of a physiologically acceptable excipient, e.g. particles having a MMD higher than 90 micron and preferably the MD comprised between 50 micron and 500 micron, more preferably between 150 and 400 micron, even more preferably between 210 and 355 micron. In another embodiment, the coarse
particles have a MD comprised between 90 and 150 micron.

In one of the preferred embodiment, when their MD is comprised between 210 and 355 micron, the coarse excipient particles have preferably a relatively highly fissured surface.

Preferably the relevant powder formulation may further comprise a fraction of pharmacologically-inert microparticles having a MMD lower than 35 micron composed of particles of a physiologically acceptable excipient and an additive material selected from the class of the anti-adherents such as the amino acids leucine and isoleucine or of the lubricants such as magnesium stearate; sodium stearyl fumarate, stearyl alcohol, stearic acid and sucrose monopalmitate.

More preferably, said powder formulation comprises a fraction of said pharmacologically-inert microparticles having a MMD lower than 15 micron, preferably lower than 10 micron, composed of particles of a physiologically acceptable excipient and particles of magnesium stearate according to EP 1274406.

In another preferred embodiment of the invention, when their MD is comprised between 90 and 150 micron, the coarse carrier particles have preferably a surface rugosity expressed as the fractal dimension of less than or equal to 1.1, determined according EP 1196146. More preferably the surface of said particles is coated with magnesium stearate.

Magnesium stearate is added to the formulations herein described with the aim of improving the respirable fraction of the active substance.

The physiologically acceptable excipient may be any amorphous or crystalline physiologically acceptable pharmacologically-inert material of animal or vegetal source or combination thereof. Preferred materials are crystalline sugars and for example monosaccharides such as glucose or arabinose, or disaccharides such as maltose, saccharose, dextrose or lactose.
Polyalcohols such as mannitol, sorbitol, maltitol, lactitol may also be used. The most preferred material is α-lactose monohydrate.

Examples of commercial lactose are Capsulac™ and Pharmatose™. An example of commercial mannitol is Pearlitol™.

In a preferred embodiment, the fraction of microparticles is composed of 98% by weight of α-lactose monohydrate and 2% by weight of magnesium stearate and the ratio between the fraction of microparticles and the fraction of coarse particles made of α-lactose monohydrate particles is 10:90% by weight, respectively.

The amount of magnesium stearate in the final formulation is advantageously comprised between 0.02% and 1.0% by weight on the total weight of the formulation, preferably between 0.05 and 0.5% by weight, more preferably between 0.1 and 0.4 % by weight, even more preferably between 0.2 and 0.3% by weight.

The powder formulation for inhalation comprising the powder particles according to the invention is characterized by a high degree of homogeneity. After the mixing, the content uniformity of the active ingredient, expressed as relative standard deviation (RSD), is less than 5%, preferably equal to or less than 3.5%, more preferably equal to or less than 1.5%.

Said powder formulation may be administered by inhalation with any type of known DPIs.

DPIs can be divided into two basic types: i) single dose inhalers, for the administration of pre-subdivided single doses of the active compound; ii) multidose dry powder inhalers (MDPIs), either with pre-subdivided single doses or pre-loaded with quantities of active ingredient sufficient for multiple doses. On the basis of the required inspiratory flow rates (1/min) which in turn are strictly depending on their design and mechanical features, DPIs are divided in: i) low-resistance devices (> 90 1/min); ii) medium-resistance
devices (about 60 l/min); iii) high-resistance devices (about 30 l/min).

The particles of the invention are indicated for the prevention and/or treatment of inflammatory or obstructive airways diseases such as asthma and chronic obstructive pulmonary disease (COPD). Other respiratory disorders characterised by obstruction of the peripheral airways as a result of inflammation and/or presence of mucus such as chronic obstructive bronchiolitis, bronchiectasies, and cystic fibrosis may also benefit by their use.

The invention is further illustrated by the following examples.

**EXAMPLES**

Example 1 - Preparation of crystalline particles of carmoterol hydrochloride and budesonide in a ratio 1:100 according to the teaching of WO 2004/073827

The high pressure atomisation system described in WO 2004/073827 was used to generate the aerosol.

A 1.5% w/v solution was prepared by dissolving 8.19 g of carmoterol hydrochloride and budesonide in a ratio 1:100 w/w in a dichloromethane: methanol 95:4.5 v/v mixture.

Said solution, maintained at room temperature, was sprayed through a 0.7 mm diameter orifice with a supporting nitrogen flow rate of 11.5 ml/min. The flow rate of the solvent is controlled by a syringe pump and was set at 2 ml/min. The aerosol droplets were collected in 500 ml of n-heptane maintained at 5°C via a conical shaped crystallisation vessel. The distance between the atomiser orifice and the collection vessel was pre-set at well-defined separation distances. A typical separation distance was around 15 cm. The whole system was hermetically sealed. Nucleation of the droplets collected in the crystallisation vessel was induced via ultrasonic energy by inserting an ultrasonic probe operating at the frequency of 20 kHz and at a
power of 40 W.

The crystalline particles were isolated from the resulting slurry by supercritical carbon dioxide extraction, collected by filtration, washed with n-heptane, and subsequently dried.

The yield is 1.53 g (18.6%).

**Example 2 - Characterisation of the particles of Example 1**

Figure 1 shows a SEM image of the particles obtained in Example 1.

It can be clearly observed that said particles are significantly distinct when compared to the SEM image of the two starting raw materials reported in Figure 2, i.e. carmoterol hydrochloride and budesonide.

The obtained particles were characterised by X-ray powder diffractometry and differential scanning calorimetry (DSC).

The X-ray powder diffraction (XPRD) pattern, reported in Figure 3, shows characteristic sharp diffraction peaks associated with highly crystalline material consistent with budesonide. Unsurprisingly, no evidence for diffraction peaks corresponding to carmoterol hydrochloride could be observed due to its low amount.

The thermogram, reported in Figure 4, shows the characteristic endothermic transition at approximately 260°C, which corresponds to the melting point of budesonide.

The melting point is indeed slightly lower than that of pure crystalline budesonide (about 262°C). Said melting point depression is indicative of the incorporation of another component, wherein the low amount of carmoterol hydrochloride acts as an impurity.

The obtained particles were also characterised in terms of particle size distribution. The particle size was determined by laser diffraction using a Mastersize X apparatus. The parameters taken into consideration are the volume diameters (VD) in micron of 10%, 50% and 90% of the particles
expressed as d(v, 0.1), d(v, 0.5) and d(v, 0.9), respectively, which correspond to the mass diameter assuming a size independent density for the particles. The mean values of eight samples are reported in Table 1. The standard deviation (S.D.) turns out to be less than ± 0.2.

**Table 1 - Particle size distribution**

<table>
<thead>
<tr>
<th>Particle size (µm)</th>
<th>Particles of Example 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>d(v, 0.1)</td>
<td>1.48</td>
</tr>
<tr>
<td>d(v, 0.5)</td>
<td>4.67</td>
</tr>
<tr>
<td>d(v, 0.9)</td>
<td>10.57</td>
</tr>
</tbody>
</table>

**Example 3 - Moisture uptake experiments**

Dynamic vapour sorption (DVS) studies were performed on the particles of Example 1 with a DVS-I Instrument (Surface Measurement Systems Ltd, London UK). Approximately 50 mg of material was weighed into the sample pan of the DVS and exposed to one 0-90% relative humidity (RH) cycle (10% RH increments).

The moisture sorption isotherms of the sample indicate a maximum water uptake at 90% RH of 0.35% w/w. The desorption isotherm shows that the sample has retained 0.07% w/w water which is indicative of a good stability profile on prolonged storage.

**Example 4 - "Interactive ordered mixture" formulation comprising the particles of Example 1**

The particles as obtained in Example 1 were added to a carrier prepared according to EP 1274406 and reported hereafter.

a) Preparation of the fraction of the pharmacologically-inert microparticles.

α-lactose monohydrate SpheroLac™ 100 with a starting mass diameter of 50 to 400 micron (MMD of about 170 micron) and magnesium stearate particles in the ratio 98:2 percent by weight were co-milled in a jet mill
apparatus until the MMD of the whole mixture is less than 15 micron.

b) Addition of the fraction of microparticles to the fraction of coarse particles.

90 percent by weight of $\alpha$-lactose monohydrate CapsuLac™ (212 - 355 micron) was placed in a 240 ml stainless steel container, then 10 percent by weight of the fraction of pharmacologically-inert microparticles was added. The blend was mixed in a Turbula mixer for 2 hours at 42 r.p.m. to obtain the carrier.

c) Addition of the particles of Example 1 to the carrier.

The particles were added to the carrier in a suitable amount in order to obtain a ratio of $1+100 \, \mu g$ of carmoterol hydrochloride+budesonide to 10 mg of final formulation. The resulting blend was mixed in a Turbula mixer for 30 min at 46 r.p.m.

**Example 5 - Characterisation of the powder formulation of Example 4**

The powder formulation of Example 4 was characterised in terms of the uniformity of distribution of the active ingredient and aerosol performances after loading it in the multidose dry powder inhaler Pulvinal™.

The uniformity of distribution of the active ingredients was evaluated by withdrawing six samples from different parts of the blend and evaluated by HPLC.

The evaluation of the aerosol performance was carried out using the Andersen Cascade Impactor (Apparatus D) according to the conditions reported in the European Pharmacopeia 6th Ed 2008, par 2.9.18, pages 293-295.

After aerosolization of 10 doses, the ACI apparatus was disassembled and the amounts of drug deposited in the stages were recovered by washing with a solvent mixture and then quantified by High-Performance Liquid
Chromatography (HPLC). The following parameters, were calculated: i) the delivered dose which is the amount of drug delivered from the device recovered in the impactor; ii) the fine particle dose (FPD) which is the amount of delivered dose recovered in the S3-AF stages having a particle size equal to or lower than 5.0 micron; iii) the fine particle fraction (FPF) which is the percentage of the fine particle dose; iv) the MMAD.

The results in terms of uniformity of distribution and aerosol performances (mean value ± S.D) are reported in Table 2.

Table 2 - Uniformity of distribution of the active ingredients (.a.i.) and aerosol performances

<table>
<thead>
<tr>
<th>Uniformity of distribution of the a.i. (µg)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- carmoterol hydrochloride</td>
<td>1.25 ± 0.02</td>
</tr>
<tr>
<td>- budesonide</td>
<td>101.12 ± 1.91</td>
</tr>
<tr>
<td>Delivered dose (µg)</td>
<td></td>
</tr>
<tr>
<td>- carmoterol hydrochloride</td>
<td>1.26 ± 0.01</td>
</tr>
<tr>
<td>- budesonide</td>
<td>103.06 ± 0.42</td>
</tr>
<tr>
<td>Fine particle dose (FPD, µg)</td>
<td></td>
</tr>
<tr>
<td>- carmoterol hydrochloride</td>
<td>0.29 ± 0.05</td>
</tr>
<tr>
<td>- budesonide</td>
<td>34.80 ± 2.86</td>
</tr>
<tr>
<td>Fine particle fraction (FPF, %)</td>
<td></td>
</tr>
<tr>
<td>- carmoterol hydrochloride</td>
<td>42.39 ± 1.00</td>
</tr>
<tr>
<td>- budesonide</td>
<td>35.14 ± 1.55</td>
</tr>
<tr>
<td>MMAD (µm)</td>
<td></td>
</tr>
<tr>
<td>- carmoterol hydrochloride</td>
<td>2.77 ± 0.13</td>
</tr>
<tr>
<td>- budesonide</td>
<td>3.66 ± 0.10</td>
</tr>
</tbody>
</table>

The formulation prepared using the particles of Example 1 shows an
excellent uniformity of distribution of the active ingredients.

In fact, the content uniformity of both active ingredients, expressed as relative standard deviation (RSD), is less than 2%.

From the delivered dose values, it can also be appreciated that the formulation provides a controlled delivery of the combination of carmoterol with budesonide, as the ratio of the drugs in each dose is substantially the same as that present in the particles before delivery.

Finally, the formulation shows good aerosol performances in terms of respirable fraction with more than 30% of FPF for both active ingredients.

**Example 6 - Preparation of crystalline particles of carmoterol hydrochloride and budesonide in a ratio 1:100 according to WO 2010/007447 (PXI)**

A 2.5% w/v solution was prepared by dissolving carmoterol hydrochloride and budesonide in a ratio 1:100 w/w in methanol.

The solution was atomized and droplets subsequently dried using a Büchi laboratory-scale spray-drier.

The typical process consisted of atomizing the methanol solution using: (i) the 100% aspirator setting (which equates to approximately 35-40 m³/hr gas flow-rate); (ii) the 30% pump setting (which equates to 9-10 mL/min) and (iii) an inlet temperature approximately 20°C greater than the boiling point of selected system. An atomization pressure of 3-3.5 bar was used for the pressure with the gas flow rate of typically 10 L/min.

The generated unstable particles were collected in an ultrasonic chamber filled with n-heptane maintained at 25°C.

Nucleation of the unstable particles collected in the ultrasonic chamber was induced via ultrasonic energy by using ultrasonic probe operating at the frequency of 20 kHz and at a power of 20 W.

The final crystalline particles were isolated by supercritical carbon
dioxide extraction, collected by filtration, washed with n-heptane, and subsequently dried.

The yield was 0.7 g.

**Example 7 - Preparation of crystalline particles of carmoterol hydrochloride and budesonide in a ratio 1:100 according to WO 2010/007447 (PX2)**

A 2.5% w/v solution was prepared by dissolving carmoterol hydrochloride and budesonide in a ratio 1:100 w/w in methanol.

The solution was atomized using a Buchi laboratory-scale spray-drier. The typical process consisted of atomizing the methanol solution using: (i) the 100% aspirator setting (which equates to approximately 35-40 m³/hr gas flow-rate); (ii) the 30% pump setting (which equates to 9-10 mL/min) and (iii) an inlet temperature approximately 20°C greater than the boiling point of selected system. An atomization pressure of 3-3.5 bar was used for the pressure with the gas flow rate of typically 10 L/min.

The generated unstable particles were collected in an ultrasonic chamber filled with n-heptane maintained at 55°C.

Nucleation of the unstable particles collected in the ultrasonic chamber was induced via ultrasonic energy by using ultrasonic probe operating at the frequency of 20 kHz and at a power of 20 W.

The crystalline particles were isolated by spray-drying and subsequently dried.

The yield was 1.0 g.

**Example 8 - Preparation of crystalline particles of carmoterol hydrochloride and budesonide in a ratio 1:100 according to WO 2010/007447 (PX3)**

The particles were prepared as described in Example 7 but using perfluorodecalin as anti-solvent maintained at 75°C. The yield is 1. The
crystalline particles were isolated by filtration. The yield is 1.0 g.

Example 9 - Preparation of crystalline particles of carmoterol hydrochloride and budesonide in a ratio 1:50 according to WO 2010/007447 (PX4)

The particles were prepared as described in Example 7 but using a ratio of carmoterol hydrochloride and budesonide of 1:50 w/w.

The yield is 1.1 g.

Example 10 - Characterisation of the particles of Examples 6, 7, 8 and 9

The content of the two active ingredients in each sample is determined by HPLC. The results are reported in Table 3.

Table 3 - Content % (± S.D.) of the two active ingredients in the samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>% of both a.i.</th>
<th>Carmoterol HCl (%)</th>
<th>Budesonide (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PX 1</td>
<td>99.33</td>
<td>1.04 ± 0.01</td>
<td>98.29 ± 0.35</td>
</tr>
<tr>
<td>PX 2</td>
<td>97.61</td>
<td>0.90 ± 0.09</td>
<td>96.71 ± 0.18</td>
</tr>
<tr>
<td>PX3</td>
<td>97.43</td>
<td>0.94 ± 0.02</td>
<td>96.50 ± 0.42</td>
</tr>
<tr>
<td>PX 4</td>
<td>97.60</td>
<td>1.94 ± 0.06</td>
<td>95.66 ± 0.57</td>
</tr>
</tbody>
</table>

The samples were also characterised by differential scanning calorimetry (DSC) as reported in Example 2.

The thermogram of all the particles shows a melting point slightly lower than that of pure crystalline budesonide which is indicative of the incorporation of carmoterol hydrochloride.

It can be appreciated that the content of the active ingredients corresponds to the expected ratio, i.e. 1:100 for PX1, PX2, PX3 and 50:1 for PX4.
The particle size distribution was determined as reported in Example 2. The values are reported in Table 4

**Table 4 - Particle size distribution**

<table>
<thead>
<tr>
<th>Sample</th>
<th>$d_{v0.1}$ (µm)</th>
<th>$d_{v0.5}$ (µm)</th>
<th>$d_{v0.9}$ (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PX 1</td>
<td>0.83</td>
<td>1.77</td>
<td>3.07</td>
</tr>
<tr>
<td>PX 2</td>
<td>0.85</td>
<td>2.03</td>
<td>2.78</td>
</tr>
<tr>
<td>PX 3</td>
<td>0.85</td>
<td>1.42</td>
<td>1.93</td>
</tr>
<tr>
<td>PX 4</td>
<td>1.91</td>
<td>3.37</td>
<td>6.13</td>
</tr>
</tbody>
</table>

**Example 11 - Characterisation of powder formulations comprising the particles of Examples 6, 7, 8 and 9**

The powder formulations were prepared as reported in Example 4 and characterised in terms of the uniformity of distribution of the active ingredient and aerosol performances as reported in Example 5.

The results are reported in Table 5.

**Table 5 - Uniformity of distribution of the active ingredients (a.i.) and aerosol performances**

<table>
<thead>
<tr>
<th></th>
<th>PX1</th>
<th>PX2</th>
<th>PX3</th>
<th>PX4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uniformity of distribution of the a.i. (µg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- carmoterol hydrochloride</td>
<td>1.13 ± 0.03</td>
<td>1.04 ± 0.03</td>
<td>1.03 ± 0.07</td>
<td>2.04 ± 0.07</td>
</tr>
<tr>
<td>- budesonide</td>
<td>101.7 ± 2.0</td>
<td>102.4 ± 1.3</td>
<td>104.3 ± 2.3</td>
<td>100.8 ± 2.9</td>
</tr>
<tr>
<td><strong>Delivered dose (µg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- carmoterol hydrochloride</td>
<td>1.22 ± 0.03</td>
<td>1.01 ± 0.06</td>
<td>1.08 ± 0.09</td>
<td>2.07 ± 0.25</td>
</tr>
<tr>
<td>- budesonide</td>
<td>109.8 ± 3.0</td>
<td>108.2 ± 7.8</td>
<td>111.98 ± 6.2</td>
<td>102.3 ± 12.2</td>
</tr>
<tr>
<td><strong>Fine particle dose (FPD, µg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>MMAD (µm)</td>
<td>MMAD (µm)</td>
<td>MMAD (µm)</td>
<td>MMAD (µm)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Carmoterol hydrochloride</td>
<td>0.87 ± 0.03</td>
<td>0.48 ± 0.01</td>
<td>0.82 ± 0.05</td>
<td>0.74 ± 0.11</td>
</tr>
<tr>
<td>Budesonide</td>
<td>78.96 ± 4.75</td>
<td>44.62 ± 0.63</td>
<td>79.27 ± 1.2</td>
<td>28.17 ± 2.59</td>
</tr>
</tbody>
</table>

Fine particle fraction (FPF, %)

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>FPF</th>
<th>FPF</th>
<th>FPF</th>
<th>FPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmoterol hydrochloride</td>
<td>78.93 ± 2.04</td>
<td>49.98 ± 4.02</td>
<td>85.53 ± 1.5</td>
<td>43.27 ± 0.48</td>
</tr>
<tr>
<td>Budesonide</td>
<td>77.18 ± 1.40</td>
<td>44.62 ± 0.63</td>
<td>82.48 ± 5.3</td>
<td>36.53 ± 1.05</td>
</tr>
</tbody>
</table>

From the delivered dose values, it can also be appreciated that all formulation provide a controlled delivery of the combination of carmoterol with budesonide, as the ratio of the drugs in each dose is substantially the same as that present in the particles before delivery.

Moreover, all formulations show good aerosol performances in terms of respirable fraction with more than 30% of FPF for both active ingredients.

Finally, after storage under long-term conditions (25°C, 60% r.h.) for three months, both active ingredients in the formulations turned out to be chemically stable and no significant change in the respirable fraction was observed.
CLAIMS

1. Crystalline particles for use in pharmaceutical formulations for inhalation, wherein each particle comprises a combination of a pharmaceutically acceptable salt of 8-hydroxy-5-[(IR)-l-hydroxy-2-[(IR)-2-(4-methoxyphenyl)-l-methylethyl]amino]ethyl]-2(lH)-quinolinone (carmoterol) and a corticosteroid in a ratio of no more than 1:50.
2. The crystalline particles according to claim 1, wherein the corticosteroid is selected from the group consisting of beclometasone dipropionate (BDP), budesonide, ciclesonide, mometasone and esters thereof, and fluticasone and esters thereof.
3. The crystalline particles according to claim 2, wherein the beclometasone dipropionate (BDP), budesonide, ciclesonide, mometasone ester is the furoate.
4. The crystalline particles according to claim 2, wherein the fluticasone esters are the propionate and furoate.
5. The crystalline particles according to claims 1 or 2, wherein the ratio is comprised between 1:50 and 1:800.
6. The crystalline particles according to claim 5, wherein the ratio is comprised between 1:80 and 1:400.
7. The crystalline particles according to claim 6, wherein the corticosteroid is budesonide.
8. A process for preparing the crystalline particles of claim 1 comprising the steps of:
   a) preparing solution of the two different active ingredients in a pre-determined ratio in a suitable solvent;
   b) generating an aerosol from the solution of said two active ingredients;
   c) collecting the aerosol droplets in a vessel containing an anti-solvent
for both active ingredients;

d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and

e) isolating and collecting the produced particles.

9. A process for preparing the crystalline particles of claim 1 comprising the steps of:

a) preparing solution of the two active ingredients in a pre-determined ratio in a suitable solvent;

b) generating an aerosol from the solution of said two active ingredients and drying the atomized droplets to yield unstable part-amorphous or fully amorphous particles;

c) collecting the particles in a vessel containing an anti-solvent for both active ingredients;

a) preparing solution of the two active ingredients in a pre-determined ratio in a suitable solvent;

b) generating an aerosol from the solution of said two active ingredients and drying the atomized droplets to yield unstable part-amorphous or fully amorphous particles;

c) collecting the particles in a vessel containing an anti-solvent for both active ingredients;

d) applying high intensity ultrasound to induce crystallisation of said two active ingredients into an individual particle; and

e) isolating and collecting the produced particles.

10. The process according to claim 8 or 9, wherein the particles of step e) are isolated by spray-drying.

11. A pharmaceutical formulation for administration by inhalation comprising the particles according to any one of claim 1 to 7, optionally together with one or more pharmaceutically acceptable excipients.

12. The formulation according to claim 11 in the form of dry inhalation powder.

13. A dry powder inhaler filled with the dry powder formulation according to claim 12.

14. The formulation according to claim 11 in the form of a suspension of the particles in a propellant.

15. A pressurized metered dose inhaler comprising a canister filled with the
formulation of claim 14 and a metering valve for delivering a daily therapeutically effective dose of the formulation.

16. Use of the crystalline particles of any one of claims 1 to 7 as a medicament.

17. Use of the crystalline particles of any one of claims 1 to 7 for the prevention and/or treatment of an inflammatory or obstructive airways disease.

18. The use according to claim 17, wherein the disease is asthma or chronic obstructive pulmonary disease (COPD).
Figure 1

Figure 2

SUBSTITUTE SHEET (RULE 26)
Figure 3

Figure 4

SUBSTITUTE SHEET (RULE 26)
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/EP2010/001089

**A CLASSIFICATION OF SUBJECT MATTER**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A61K31/167</td>
<td>A61K9/14</td>
<td></td>
</tr>
<tr>
<td>A61K31/58</td>
<td>A61K9/16</td>
<td></td>
</tr>
<tr>
<td>A61K9/00</td>
<td>A61K9/00</td>
<td></td>
</tr>
</tbody>
</table>

**B. RELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical search terms used)

EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data, CHEM A3S Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation</th>
<th>Relevant to claim No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>EP 1 452 179 A (CHIESI FARMA SPA [IT]) 1 September 2004 (2004-09-01) example 4</td>
<td>1-13</td>
</tr>
</tbody>
</table>

**Date of the actual completion of the international search**

19 May 2010

**Date of mailing of the international search report**

27/05/2010

Name and mailing address of the ISA

European Patent Office, P & B 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Fax (+31-70) 340-3016

Authorized officer

Laffargue-Haak, T
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| Y        | US 2003/180227 A1 (STANI FORTH JOHN NICHOLAS [IT] ET AL)  
cited in the application  
examples 11,1 | 1-13 |
| Y        | WO 02/00199 A (GLAXO GROUP LTD [GB]; LANCASTER ROBERT WILLIAM [GB]; SINGH HARDEV [GB]) 3 January 2002 (2002-01-03)  
cited in the application  
examples 1-16; example 1 | 1-18 |
| A        | LUQUE DE CASTRO ET AL: "Ultrasound-assisted crystallization (sonocrystallization)"  
ULTRASONICS: SONOCHEMISTRY, BUTTERWORTH-HEINEMANN, GB,  
v01.14, no. 6, 24 May 2007 (2007-05-24),  
pages 717-724, XP022095538  
ISSN: 1350-4177  
abstract | 1-18 |
| X        | WO 2004/073827 A1 (UNIV BATH [GB]; PRICE ROBERT [GB]; KAERGER JOERG SEBASTIAN [DE])  
2 September 2004 (2004-09-02)  
cited in the application  
abstract  
page 12, last paragraph; examples 2, 4 | 8-10 |
| X        | WO 2010/007447 A1 (PROSONIX LTD [GB]; RUECROFT GRAHAM [GB]; PARIKH DIPESH [GB]; HIPKISS D) 21 January 2010 (2010-01-21)  
cited in the application  
abstract  
claims 1-25; examples 1-7 | 8-10 |
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP 14521 79</td>
<td>01-09-2004</td>
<td>AT 401887 T</td>
<td>15-08-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2004216472 A</td>
<td>10-09-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR PI0408047 A</td>
<td>14-02-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2517321 Al</td>
<td>10-09-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1753678 A</td>
<td>29-03-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101244063 A</td>
<td>20-08-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 1603585 T3</td>
<td>10-11-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DO 2253825 A</td>
<td>22-09-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 230503 T3</td>
<td>16-12-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HK 1087009 Al</td>
<td>25-07-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 20050726 A2</td>
<td>28-02-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 20065 19204 T</td>
<td>24-08-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 200501 04367 A</td>
<td>02-11-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MA 27630 Al</td>
<td>01-11-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA0509007 A</td>
<td>18-10-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 541997 A</td>
<td>24-12-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT 1603565 E</td>
<td>06-10-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UA 8221 7 C2</td>
<td>25-03-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2007020190 Al</td>
<td>25-01-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200506820 A</td>
<td>29-11-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 377416 T</td>
<td>15-11-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 399195 T</td>
<td>15-10-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 784719 B2</td>
<td>01-06-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 4858101 A</td>
<td>30-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 485950 1 A</td>
<td>30-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 583430 1 A</td>
<td>30-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0110139 A</td>
<td>31-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0110141 A</td>
<td>28-01-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 011030 1 A</td>
<td>30-12-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2405767 Al</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 24061 19 Al</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2406201 Al</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1424909 A</td>
<td>18-06-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 20023437 A3</td>
<td>12-02-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60123031 T2</td>
<td>08-03-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60125344 T2</td>
<td>19-07-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60131265 T2</td>
<td>06-03-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 1276472 T3</td>
<td>16-04-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK 1274406 T3</td>
<td>22-01-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 200200593 A</td>
<td>15-04-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WD 01178693 A2</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1276472 A2</td>
<td>22-01-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1276473 A2</td>
<td>22-01-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1274406 A2</td>
<td>15-01-2003</td>
</tr>
<tr>
<td>US 2003180227</td>
<td></td>
<td>EP 1719505 A2</td>
<td>08-11-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1829533 A2</td>
<td>05-09-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2275669 T3</td>
<td>16-06-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2292576 T3</td>
<td>16-03-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2272473 T3</td>
<td>01-05-2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WD 01178694 A2</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WD 01178695 A2</td>
<td>25-10-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 2363987 A</td>
<td>16-01-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 2363988 A</td>
<td>16-01-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0300490 A2</td>
<td>28-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0300499 A2</td>
<td>28-07-2003</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
<td>Publication date</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
<td>-------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>HU 0300593 A2</td>
<td>29-09-2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JP 2003530425 T</td>
<td>14-10-2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA 26892 A1</td>
<td>20-12-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX PA02010212 A</td>
<td>29-06-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX PA02010213 A</td>
<td>01-07-2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX PA02010218 A</td>
<td>23-05-2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO 20024971 A</td>
<td>17-12-2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO 20024973 A</td>
<td>16-12-2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO 20024980 A</td>
<td>17-12-2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ 521887 A</td>
<td>25-06-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL 358640 A1</td>
<td>09-08-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL 358875 A1</td>
<td>23-08-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL 359289 A1</td>
<td>23-08-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 0200199 A</td>
<td>03-01-2002</td>
<td>AT 306252 T</td>
<td>15-10-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 6621901 A</td>
<td>08-01-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60114002 D1</td>
<td>17-11-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60114002 T2</td>
<td>06-07-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1294360 A1</td>
<td>26-03-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2248348 T3</td>
<td>16-03-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2004500984 T</td>
<td>15-01-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004045805 A1</td>
<td>11-03-2004</td>
</tr>
<tr>
<td>WO 2004073827 A1</td>
<td>02-09-2004</td>
<td>CA 2516733 A1</td>
<td>02-09-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1610878 A1</td>
<td>04-01-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2006519780 T</td>
<td>31-08-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2007065372 A1</td>
<td>22-03-2007</td>
</tr>
</tbody>
</table>