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(54) Titre : SUCCINATE DE SOLIFENACINE CRISTALLIN
(54) Title: CRYSTALLINE SOLIFENACIN SUCCINATE

(57) Abrégé/Abstract:
Crystalline solifenacin succinate, the solifenacin succinate having an average axial ratio of 5:1 or less, preferably an average axial ratio of 5:1 to 1:1, more preferably an average axial ratio of 1:1, and having at least one of the following properties: a) a particle size d 0.9 < 200 μm; b) an average particle size of approximately 2 to 40 μm; and c) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8° 2θ ± 0.2° 2θ.

Abstract

Crystalline solifenacin succinate, the solifenacin succinate having an average axial ratio of 5:1 or less, preferably an average axial ratio of 5:1 to 1:1, more preferably an average axial ratio of 1:1, and having at least one of the following properties: a) a particle size d 0.9 < 200 μm; b) an average particle size of approximately 2 to 40 μm; and c) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8° 2θ ± 0.2° 2θ.

Crystalline solifenacin succinate

The present invention relates to crystalline solifenacin succinate, its use, a method for manufacturing solifenacin succinate, a solifenacin succinate that can be manufactured by that method, and its use.

Background of the invention

Solifenacin is a medicinal agent from the pharmacotherapeutic group of urological spasmolytic agents for the treatment of symptoms of a hyperactive bladder and is described in the international patent application WO 96/020194. Solifenacin is used pharmaceutically as solifenacin succinate, which is also known as butane dioic acid: (I S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H) - isoquinoline carboxylate (1 : 1). Solifenacin is licensed for the symptomatic treatment of urge incontinence or pollakiuria and imperative urge micturition, which can occur in patients with hyperactive bladder syndrome. Solifenacin is a competitive, specific, cholinergic receptor antagonist.

The mechanism of action of solifenacin is based on the fact that the bladder is innervated by parasympathetic, cholinergic nerves. Acetyl choline acts via muscarine receptors, mainly via subtype M3, causing a contraction of the smooth muscle of the Musculus detrusor. Solifenacin inhibits the subtype M3 muscarine receptor competitively and specifically, since it only exhibits low or no affinity for various other receptors and ion channels.

Solifenacin succinate is slightly soluble in water and moderately soluble in organic solvents. A crystalline modification of solifenacin succinate and amorphous solifenacin succinate are known in the state of the art. The amorphous substance is chemically unstable and easily forms decomposition products.

The crystalline modification of solifenacin succinate was first described in the European patent application EP 1 832 288 A1. Solifenacin succinate is known to crystallise from organic solvents and mixtures of solvents. In EP 1 832 288 A1, for example, mixtures of solvents such as ethyl acetate/EtOH were used. In all the published solvents and mixtures of solvents such as ethyl acetate/ethanol or ethyl acetate/acetone solifenacin succinate crystallises in the form of long needles. This acicular solifenacin succinate tends to agglutinate, which gives rise to a number of technological problems in the production of pharmaceutical compositions and formulations. These technological problems are ultimately also due to the poor flow properties of the acicular crystallised solifenacin succinate resulting from the agglutination. Specifically, this leads, for example, to an uneven content of solifenacin succinate in a pharmaceutical composition or formulation or to the delamination and spalling of tablets containing acicular solifenacin succinate of this kind, i.e. tablets of this kind tend to separate into layers.

WO 2009/139002 A2 describes methods for preparing solifenacin succinate. The solifenacin succinate obtained is crystallised from ethyl acetate and/or acetone. In the process, however, the product is obtained in the form of long needles, but these are disadvantageous because of their poor flow and processing properties.

US 2008/0242697 A1 describes methods for synthesising solifenacin succinate. The solifenacin succinate obtained is crystallised from acetone, methanol or a mixture of methanol and acetone. In the process, however, the product is obtained in the form of long needles, but these are disadvantageous because of their poor flow and processing properties.

EP 2 088 148 A2 describes methods for preparing solifenacin and its salts, such as solifenacin succinate. The solifenacin succinate obtained is crystallised from a mixture of ethanol and ethyl acetate. In the process, however, the product is obtained in the form of long needles, but these are disadvantageous because of their poor flow and processing properties.

US 2008/0114028 A1 describes methods for preparing polymorphous forms of solifenacin succinate, the solifenacin succinate being crystallised from solvents and

mixtures of solvents, such as mixtures of methanol and acetone. In the process, however, the product is obtained in the form of long needles, but these are disadvantageous because of their poor flow and processing properties. Action is taken against this problem in US 2008/0114028 A1 by adding glidants, such as silicate, talcum, starch or calcium phosphate, though this is disadvantageous for economic reasons, *inter alia*, which limits the possible uses of the product.

US 2009/0099365 A1 describes methods for preparing solifenacin succinate, which is crystallised from solvents and mixtures of solvents, such as ethyl acetate or acetone. In the process, however, the product is obtained in the form of long needles, but these are disadvantageous because of their poor flow and processing properties.

The solifenacin succinate crystals prepared using the methods described above which are known from the state of the art are thus obtained in the form of long needles, which correspond to the crystals shown in Figures 10 and 11 and have an average axial ratio of > 10 : 1. The methods known from the state of the art for preparing solifenacin succinate thus lead to products which possess the disadvantageous product and processing properties described above.

It is recognised by the experts working in the field that these technological problems either make further technical measures necessary, such as adding microcrystalline cellulose in order to avoid the spalling or delamination of such tablets, or entail a limitation of the pharmaceutical compositions containing this form of solifenacin succinate. One example of a limitation is that no pharmaceutical formulations containing solifenacin succinate of this kind are manufactured in which it is necessary to maintain a uniform content of solifenacin succinate within narrow tolerances.

Problem of the invention

The present invention is therefore based on the problem of providing a form of solifenacin succinate which possesses better flow properties than the acicular crystalline solifenacin succinate known in the state of the art.

Description of the invention

This and other problems are solved by the subject matter of the attached independent claims. Preferred embodiments can be gathered from the dependent claims which are likewise attached.

In particular, these and further problems are solved by the aspects and embodiments of the present invention described below.

In a first aspect, the problems are solved in accordance with the invention by a crystalline solifenacin succinate wherein the solifenacin succinate has an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1 and at least one of the following properties:

a) a particle size d 0.9 $\leq$ 200 µm;

b) an average particle size of about 2 to 40 µm; and

c) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

This is also a first embodiment of the first aspect.

In a second embodiment of the first aspect, which is also an embodiment of the first embodiment of the first aspect, it is contemplated that the solifenacin succinate has

a) an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1;

b) a particle size d 0.9 $\leq$ 200 µm; and

c) an average particle size of about 2 to 40 µm.

In a third embodiment of the first aspect, which is also an embodiment of the first embodiment of the first aspect, it is contemplated that the solifenacin succinate has

a) an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1;

b) a particle size d 0.9 $\leq$ 200 µm; and

c) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

In a fourth embodiment of the first aspect, which is also an embodiment of the first embodiment of the first aspect, it is contemplated that the solifenacin succinate has

a) an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1;

b) an average particle size of about 2 to 40 µm; and

c) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

In a fifth embodiment of the first aspect, which is also an embodiment of the first embodiment of the first aspect, it is contemplated that the solifenacin succinate has the following properties:

a) an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1;

b) a particle size d 0.9 ≤ 200 µm;

c) an average particle size of about 2 to 40 µm; and

d) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

In a further preferred embodiment of the first aspect, which is also an embodiment of the first embodiment of the first aspect, it is contemplated that the solifenacin succinate has the following properties:

(a) an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1 and

(b) an average particle size of about 2 to 40 µm, preferably 5 to 30 µm.

In a second aspect, the problems are solved in accordance with the invention by a crystalline solifenacin succinate wherein the solifenacin succinate has an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1. This is also a first embodiment of the second aspect.

In a third aspect, the problems are solved in accordance with the invention by a crystalline solifenacin succinate wherein the solifenacin succinate has a particle size d 0.9 ≤ 200 µm, preferably d 0.9 ≤ 150 µm and particularly preferably d 0.9 ≤ 100 µm. This is also a first embodiment of the third aspect.

In a fourth aspect, the problems are solved in accordance with the invention by a crystalline solifenacin succinate wherein the solifenacin succinate has an average particle size of about 2 to 40 µm, preferably 5 to 30 µm. This is also a first embodiment of the fourth aspect.

In a fifth aspect, the problems are solved in accordance with the invention by a crystalline solifenacin succinate wherein the solifenacin succinate has peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ. This is also a first embodiment of the fifth aspect.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the particle size is determined by means of laser diffraction.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that d 0.9 is ≤ 150 µm and preferably d 0.9 is ≤ 100 µm.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the average particle size is about 5 to 30 µm.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the average particle size is determined by means of laser diffraction.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it

is contemplated that the the X-ray powder diffractogram is produced in Bragg-Brentano geometry over a range of angles of 3 - 45° and a copper cathode.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the X-ray powder diffractogram is substantially the X-ray powder diffractogram shown in Fig. 1.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the crystalline solifenacin succinate includes more than 10 % by weight of solifenacin succinate with an X-ray powder diffractogram wherein the X-ray powder diffractogram has peaks at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the crystalline solifenacin succinate is a micronised solifenacin succinate.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the crystalline solifenacin succinate of the invention is intended and/or is suitable for the production of a medicament, wherein it is contemplated in a further embodiment that the medicament is a solid dosage form. In an even more preferred embodiment, it is contemplated that the solid dosage form is a tablet, preferably a divisible tablet. The medicament can be used in its various embodiments or is suitable for use in the treatment and/or prevention of a disease or condition, wherein the disease and/or the condition is selected from the group comprising symptoms of a hyperactive bladder, urge incontinence, pollakiuria and imperative urge micturition.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the solifenacin succinate of the invention is suitable for or is

used for the production of a medicament, wherein the medicament is or can be a solid dosage form in its various forms described herein or known to experts in the field. In these embodiments for their part, it is contemplated that the dosage form has a content of ≤ 5 mg solifenacin succinate, preferably ≤ 2.5 mg solifenacin succinate and particularly preferably ≤ 1 mg solifenacin succinate.

In an embodiment of the first, second, third, fourth and fifth aspects, which is also an embodiment of any embodiment of the first, second, third, fourth and fifth aspects, it is contemplated that the crystalline solifenacin succinate is used or is suitable for use in a method for the treatment of a living creature, preferably a human being, wherein the method comprises administering a pharmaceutically effective amount of the crystalline solifenacin succinate to the living creature.

In a sixth aspect, the problems are solved in accordance with the invention by the use of the crystalline solifenacin succinate of the present invention and especially in accordance with any embodiment of the first, second, third, fourth and fifth aspects for the production of a medicament. This is also a first embodiment of the first aspect.

In a second embodiment of the sixth aspect, it is contemplated that the medicament is suitable for use or is used in the treatment and/or prevention of a disease or condition, wherein the disease and/or the condition is selected from the group comprising symptoms of a hyperactive bladder, urge incontinence, pollakiuria and imperative urge micturition.

In a seventh aspect, the problems are solved in accordance with the invention by a method for the production of crystalline solifenacin succinate, wherein it is contemplated that crystalline solifenacin succinate is used as the starting material, wherein the solifenacin succinate used as the starting material is a crystalline solifenacin succinate which is different from the crystalline solifenacin succinate according to any embodiment of the first, second, third, fourth and fifth aspects of the present invention, and that the starting material is subjected to a comminution step, wherein the particle size and/or the average particle size and/or the axial ratio of the starting

material is reduced in the comminution step. This is also a first embodiment of the seventh aspect.

In a second embodiment of the seventh aspect, which is also an embodiment of the first embodiment of the seventh aspect, it is contemplated that the comminution step comprises a measure selected from the group comprising sublimation, grinding, micronising and wet micronising.

In a third embodiment of the seventh aspect, which is also an embodiment of the first and second embodiments of the seventh aspect, it is contemplated that the solifenacin succinate to be produced is a crystalline solifenacin succinate according to any embodiment of the first, second, third, fourth, fifth and sixth aspects of the present invention.

In a fourth embodiment of the seventh aspect, which is also an embodiment of the first, second and third embodiments of the seventh aspect, it is contemplated that the crystalline solifenacin succinate used as the starting material has peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

In a fifth embodiment of the seventh aspect, which is also an embodiment of the first, second, third and fourth embodiments of the seventh aspect, it is contemplated that the comminution step is performed to the extent that or until the average axial ratio of the solifenacin succinate is 5 : 1 or less, preferably the average axial ratio of the solifenacin succinate is from 5 : 1 to 1 : 1 and particularly preferably the average axial ratio is 1 : 1.

In an eighth aspect, the problems are solved in accordance with the invention by a crystalline solifenacin succinate which is obtainable by a method according to the seventh aspect of the present invention and its various embodiments. This is also a first embodiment of the eighth aspect.

In a second embodiment of the eighth aspect, which is also an embodiment of the first embodiment of the eighth aspect, it is contemplated that the crystalline solifenacin succinate is intended or suitable for use as described herein in connection with

the first, second, third, fourth, fifth and sixth aspects of the present invention and its various embodiments.

The form of solifenacin succinate and especially crystalline solifenacin succinate described in the context of the present invention is also referred to herein as solifenacin succinate in accordance with the invention or the solifenacin succinate of the invention.

The present inventor has surprisingly found a new form of solifenacin succinate, which possesses at least one of the following four properties:

a) an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1;
b) a particle size d 0.9 ≤ 100 µm;
c) an average particle size of about 2 to 40 µm; and
d) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21;8 °2 Θ ± 8 ° 0;2° 2Θ.

This new form of solifenacin succinate is also referred to herein as solifenacin succinate in accordance with the invention or the solifenacin succinate of the invention.

In addition, the present inventor has surprisingly found that this new form of solifenacin succinate exhibits very good flow properties with the axial ratio and/or small particle size specified. Without wishing to be committed to this in the following, the reason for this property of the solifenacin of the invention appears to be that the acicular shape of the solifenacin is less pronounced than in the prior-art solifenacin. This property preferably finds expression in a comparatively low axial ratio, or an axial ratio which is lower than that of the prior-art solifenacin. The technical teaching provided in the context of the present invention is therefore diametrically different from the technical teaching of the state of the art in this respect, and the technical effect achieved with the technical teaching of the present invention is surprising in that the opposite route was proposed and adopted in the state of the art in order to increase the flowability of solifenacin succinate. According to Nagakawa S. et al. ("The abstract of Lectures at the Memorial Symposium for the Foundation of the

Japan Process Chemistry Association (held on July 4 to July 5, 2002), pp. 85-86", as cited in EP 1 726 304 A1), the fluidity of solifenacin succinate can be improved by increasing the particle size and especially also by means of a comparatively large axial ratio. According to Nagakawa et al., crystals with a size of 50 - 100 µm exhibit poor fluidity; crystals with a size of several hundred µm, however, exhibit considerably improved fluidity.

Without wishing to be committed to this in the following, the inventors presume that the advantageous properties of the crystalline solifenacin in accordance with the present invention and especially of the crystalline solifenacin succinate in accordance with the present invention are due to the fact that the axial ratio of the crystalline solifenacin in accordance with the present invention is reduced compared to the axial ratio of solifenacin succinate according to the state of the art. Such a reduction in the axial ratio of crystalline solifenacin succinate can be achieved by, for example, subliming, grinding, micronising and wet micronising a suitable starting material. It is preferable to use as the starting material a crystalline solifenacin succinate whose peaks in the X-ray powder diffractogram correspond to those of the crystalline solifenacin succinate in accordance with the present invention. In a preferred embodiment, the peaks in the X-ray powder diffractogram are at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

In addition, it has also been surprisingly found in the present context that the combination of the axial ratio of the invention with the particle size in accordance with the invention leads to a particularly advantageous flow behaviour and to particularly good processing properties of the solifenacin succinate. A further reduction of the particle size of the solifenacin succinate to d 0.9 < 10 µm and/or of the average particle size to < 5 µm, especially < 2 µm, led once again to a deterioration of the flow behaviour despite the average axial ratio in accordance with the invention. It is therefore preferable that the solifenacin succinate of the invention should have an axial ratio as described herein, and also a particle size distribution of d 0.1 > 5 µm, d 0.5 of < 150 µm and d 0.9 < 200 µm and/or an average particle size of >2 µm, preferably >5 µm.

This form of crystalline solifenacin succinate overcomes the disadvantages of acicular crystalline solifenacin succinate described in the state of the art. The solifenacin succinate according to the present invention is characterised, especially with regard to its handling properties, by the fact that, compared to the acicular crystalline form of solifenacin succinate, it has better flow properties. Better flow properties of this kind find expression in, among other things, improved aggregative properties and a reduced tendency to agglomerate, and also greater fluidity. In addition, the solifenacin succinate of the invention exhibits greater bulk density.

The axial ratio, referred to herein as the average axial ratio, is determined by measuring the solifenacin succinate crystals in their axial and longitudinal directions using light-optical microscope images. For this purpose, a large number of solifenacin succinate crystals, which are selected at random from a sample, are measured using light-optical microscope images, and their extension in the axial and longitudinal directions is determined. The extension in the longitudinal direction in this context corresponds to the maximum distance between two opposing points of a solifenacin succinate crystal, while the extension in the axial direction corresponds to the minimum distance between two opposing points transversely to the longitudinal direction, measured at the centre point of the longitudinal axis. In order to arrive at a meaningful statement, the average axial ratio is determined by means of the average of the results obtained from at least 10 crystals selected at random.

The properties of the solifenacin succinate of the invention mean that it can advantageously be used especially in the production of tablets and specifically in the production of tablets by means of direct compression, which is one of the most important, economical and elegant methods for producing tablets. The flowability of the powder mixtures is a precondition for direct compression, which is also known as direct tabletting, because it is essential for the powder to flow evenly and in a controlled manner into the tabletting machines for controlled processing of the tablets in the tablet presses. If, as when solifenacin succinate particles according to the state of the art are used, the mixture to be compressed into tablets does not flow smoothly, tablets which are too light may be formed. In addition, the components can separate. Non-uniform mixtures lead to fluctuations in the content of active agent. This means that with the solifenacin succinate according to the invention, a form of solifenacin

succinate is provided which is suitable for the production of pharmaceutical compositions and can be used for that purpose, the pharmaceutical compositions being in particular ones which have a small content of solifenacin succinate, which contain an amount of solifenacin succinate where the amount may only fluctuate within narrow tolerances between the individual compositions and especially between the individual tablets, or which must exhibit a uniform distribution of the active agent, i.e. the solifenacin succinate, within the individual composition and especially within a single tablet.

Pharmaceutical dosage forms in which the solifenacin succinate of the invention can be used in a particularly advantageous manner are divisible tablets and scored tablets, which are known to those skilled in the art and which can be produced by the latter in the light of the technical teaching provided herein, using the solifenacin succinate of the present invention. Dosage forms of this kind are described *inter alia* in Bauer / Frömming / Führer "Lehrbuch der pharmazeutischen Technologie" (Textbook of pharmaceutical technology), chapter on "Tablets", or the European Pharmacopoeia 6.1 in the chapter "Tablets".

How the particle size is determined is known to those skilled in the art and is described by way of example in the example section herein and in the European Pharmacopoeia 6.1, Chap. 2.9.31 "Particle size analysis by laser light diffraction". Typically, the particle size is determined by means of laser diffraction in silicone oil. It is typical in this context to use a Malvern Mastersizer 2000 to determine the particle size. In order to analyse the individual particles and not the agglomerates, the suspension of solifenacin succinate and silicone oil is treated for one minute in an ultrasonic bath.

As those skilled in the art will know, the d(0.5) or d 0.5 value is the value at which 50 % of the particles are below a size stated after it. The d(0.9) or d 0.9 value is the value at which the 90 % of the particles are below a size stated after it.

How the average particle size is determined is known to those skilled in the art and is described by way of example in the example section herein.

How an X-ray powder diffractogram is produced is known to those skilled in the art and is described by way of example in the European Pharmacopoeia 6.1, Chap. 2.9.33 "Characterisation of crystalline and partially crystalline solids by X-ray powder diffraction" and briefly in the example section herein.

It will be appreciated by those skilled in the art that the parameters which characterise the solifenacin succinate of the invention are determined or can be determined, where not otherwise specified, using the various corresponding methods described or disclosed herein.

Description of the Figures and Examples

The present invention will now be illustrated in more detail with reference to the following Figures and Examples, from which further features, embodiments and advantages of the invention can be seen, though without limiting the subject matter of the present invention. There,

Fig. 1 shows the X-ray powder diffractogram of the solifenacin succinate of the invention;

Fig. 2 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with Example 1 (10-fold magnification in paraffin oil);

Fig. 3 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with Example 2 (40-fold magnification in paraffin oil);

Fig. 4 shows a diagram representing the particle size distribution of solifenacin succinate in accordance with Example 2, as measured by laser diffraction;

Fig. 5 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with Example 3;

Fig. 6 shows a diagram representing the particle size distribution of solifenacin succinate in accordance with Example 3, as measured by laser diffraction;

Fig. 7 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with Example 4;

Fig. 8 shows a diagram representing the particle size distribution of solifenacin succinate in accordance with Example 4, as measured by means of laser diffraction;

Fig. 9 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with the technical teaching of EP 1 714 956 A1;

Fig. 10 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with Comparative Example 2 after recrystallisation in ethyl acetate (10-fold magnification); and

Fig. 11 shows a light-optical microscope image of solifenacin succinate crystals as obtained in accordance with Comparative Example 3 after recrystallisation in a mixture of ethyl acetate and acetone.

The axial ratio of the solifenacin succinate crystals was determined by measuring 10 crystals selected at random, using the microscope images shown in the Figures.

<u>Example 1</u>: Production of solifenacin succinate in accordance with the invention

0.56 g crystalline solifenacin succinate with Bragg peaks at 3.7; 11.1; 18.6; 21.8 ° 2 Θ ± 0.2° 2Θ were dissolved in 2.3 ml ethyl acetate and 0.8 ml ethanol in a round-bottomed flask. After that, the round-bottomed flask containing the solution was shock-chilled to 0° C in an ice water bath in a freezer. A solid cake formed in the round-bottomed flask. The cake was evacuated in the flask at 90° C and 20 mbar in a vacuum drying cabinet. The cake was still solid and was easy to scrape out of the flask. The crystals had good flow properties.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 2. The axial ratio found was approx. 2.5 : 1.

An X-ray powder diffractogram of the crystalline solifenacin succinate obtained in this way was produced, which is shown as Fig. 1.

Example 2: Production of solifenacin succinate in accordance with the invention

Acicular crystalline solifenacin succinate with Bragg peaks at 3.7; 11.1; 18.6; 21.8 ° 2 Θ ± 0.2° 2Θ was placed in a hand-held mortar and ground with a pestle for approx. 1 minute. The ground substance had good flow properties and did not form lumps.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 3. The axial ratio found was approx. 1 : 1.

The particle size distribution of the crystalline solifenacin succinate obtained in this way was determined by laser diffraction. The result is shown in Fig. 4.

Example 3: Production of solifenacin succinate in accordance with the invention

Crystalline solifenacin succinate with Bragg peaks at 3.7; 11.1; 18.6; 21.8 ° 2 Θ ± 0.2° 2Θ was placed in a type MM 301 Retsch vibration grinding mill and ground with a ball for approx. 2 minutes at 10 Hz in a metal container intended for that apparatus.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 5. The axial ratio found was approx. 1.5 : 1.

The particle size distribution of the crystalline solifenacin succinate obtained in this way was determined by laser diffraction. The result is shown in Fig. 6.

Example 4: Production of solifenacin succinate in accordance with the invention

Crystalline solifenacin succinate with Bragg peaks at 3.7; 11.1; 18.6; 21.8 ° 2 was placed in a type MM 301 Retsch vibration grinding mill and ground with a ball for approx. 10 minutes at 15 Hz in a metal container intended for that apparatus.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 7. The axial ratio found was approx. 1 : 1.

The particle size distribution of the crystalline solifenacin succinate obtained in this way was determined by laser diffraction. The result is shown in Fig. 8.

Comparative Example 1: Production of solifenacin succinate in accordance with EP 1 714 965 A1

The crystalline solifenacin succinate was produced in accordance with Example 1 of EP 1 714 965 A1, though because of the laboratory scale, the following amounts of solvents were used in the context of the recrystallisation, which were reduced proportionately to the amounts specified in the Example:

0.24 g solifenacin succinate were dissolved in 2.3 ml ethyl acetate and 0.45 ml ethanol and cooled to 0° C. The crystals had poor flow properties and had a pronounced tendency to agglomerate.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 9. The axial ratio found was approx. 6 : 1.

Comparative Example 2: Production of crystalline solifenacin succinate

100 mg crystalline solifenacin succinate with Bragg peaks at 3.7; 11.1; 18.6; 21.8 ° 2 Θ ± 0.2° 2Θ (manufacturer: Medichem S.A.) were heated in 8 ml ethyl acetate on a

water bath with backflow. The solution was chilled rapidly in an ice water bath, and the crystals were filtered off. The crystals had poor flow properties and had a pronounced tendency to agglomerate.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 10. The axial ratio found was approx. 45 1.

Comparative Example 3: Production of crystalline solifenacin succinate

250 mg crystalline solifenacin succinate with Bragg peaks at 3.7; 11.1; 18.6; 21.8 ° 2 Θ ± 0.2° 2Θ (manufacturer Medichem S.A.) were heated in 8 ml ethyl acetate / acetone (1 : 1) on a water bath with backflow. The solution was chilled rapidly in an ice water bath in an ultrasonic bath. The crystals were filtered off. The crystals had poor flow properties.

The crystalline solifenacin succinate obtained in this way was examined under a light-optical microscope; the light-optical microscopic image is shown as Fig. 11. The axial ratio found was approx. 10 : 1.

Example 5: Production of a tablet containing solifenacin succinate in accordance with the invention

A tablet with an active-agent content of 5 mg solifenacin succinate in accordance with the invention was produced as follows and had the following composition.

Production:

2.5 kg solifenacin succinate in accordance with the present invention were prepared with 7.75 kg starch 1500, 25 kg Granulac 230 and 1.25 kg HPMC 606 in a fluidised-bed granulator (e.g. Glatt GPCG 30). 0.625 kg of the HPMC were sprayed on in 15 1 water (2.0 %). After the granules were dried, they were passed though a 1 mm screen. 375 g magnesium stearate was passed though a 0.5 mm screen and added to the granules. The mixture was mixed in a barrel mixer for 10 minutes at 10 rpm. The

tablet was compressed in a rotary press (e.g. ex Fette). The tablet was film-coated with an aqueous suspension of 1.2475 kg Opadry 11 and 2.5 g iron oxide yellow in a Glatt Coater 750. (Amount of water: 13.75 l)

Composition of the tablets:

solifenacin succinate	5.0 mg
starch 1500	15.5 mg
Granulac 230	50.0 mg
HPMC 606	3.75 mg
Mg stearate	0.75 mg
Opadry 11	2.495 mg
iron oxide yellow	0.005 mg

<u>Example 6:</u> Methods for characterising solifenacin succinate

The following methods were employed to characterise the solifenacin succinate of the kind which is the subject of the Examples and Comparative Examples described herein, unless any statements are made to the contrary. These methods can also be employed to determine the parameters, or the corresponding values, characterising the solifenacin succinate of the invention.

Production of X-ray powder diffractograms

The X-ray powder diffractograms were produced on a Panalytical X'Pert Pro Series (manufacturer: Panalytical). The equipment settings were as follows:

geometry: Bragg Brentano
copper cathode
range of angles 3 - 45° 2 Θ.

The samples were measured by means of backloading methods or on zero-background holders. The measurements were performed with a Soller collimator 0.02 rad using a nickel filter.

Particle size analysis

In order to analyse particle sizes, 50 mg substance were typically moistened with 5 drops of silicone oil in a test tube and suspended on a vortexer. 6 ml silicone oil were added and again suspended on a vortexer. The suspension was exposed to ultrasonic waves for 1 minute in an ultrasonic bath. After that a homogeneous suspension was produced on the vortexer. Homogenisation was quite quickly successful by drawing the suspension into a pipette and emptying it again. After that, enough suspension was placed in the sample holding unit of a Mastersizer, using the pipette, until a shading of 10 - 25 % was obtained. The measurement was performed without any prior waiting time.

Light-optical microscopy

The microscope images were obtained on a Leica DMLB transmitted light microscope. For this purpose, a spatula tip of substance was placed on a specimen slide, and 1-2 drops of paraffin oil were dripped onto it. Using a cover slip, a uniform suspension was produced on the specimen slide.

Determining the axial ratio

The average axial ratio was determined using the light-optical microscope images by establishing the extension in the longitudinal direction and the extension in the transverse direction, as described herein, wherein the value given corresponds to the average of the values measured for at least 10 crystals selected at random.

The features of the invention disclosed in the above description, claims and drawings can be essential to implementing the invention in its various embodiments both individually and in any combinations.

Claims

1. Crystalline solifenacin succinate, wherein the solifenacin succinate has an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1, and possesses at least one of the following properties:

a) a particle size d 0.9 ≤ 200 µm;

b) an average particle size of about 2 to 40 µm; and

c) peaks in the X-ray powder diffractogram at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

wherein the average axial ratio is determined by measuring the solifenacin succinate crystals in their axial and longitudinal directions using light-optical microscope images.

2. Crystalline solifenacin succinate as claimed in claim 1, wherein d 0.9 ≤ 150 µm and preferably d 0.9 ≤ 100 µm.

3. Crystalline solifenacin succinate as claimed in any of claims 1 to 2, wherein the average particle size is about 5 to 30 µm.

4. Crystalline solifenacin succinate as claimed in any of claims 1 to 3, wherein the crystalline solifenacin succinate has more than 10 % by weight of solifenacin succinate with an X-ray powder diffractogram wherein the X-ray powder diffractogram has peaks at 3.7; 11.1; 18.6; 21.8 °2 Θ ± 0.2° 2Θ.

5. Crystalline solifenacin succinate as claimed in any of claims 1 to 4, wherein the crystalline solifenacin succinate is a micronised solifenacin succinate.

6. Crystalline solifenacin succinate as claimed in any of claims 1 to 5, wherein the solifenacin succinate has an average axial ratio of 5 : 1 or less, preferably an average axial ratio of 5 : 1 to 1 : 1, particularly preferably an average axial ratio of 1 : 1, and an average particle size of about 2 to 40 µm, preferably 5 to 30 µm.

7. Crystalline solifenacin succinate as claimed in any of claims 1 to 6 for the production of a medicament.

8. Crystalline solifenacin succinate as claimed in claim 7, wherein the medicament is a solid dosage form, preferably a tablet, particularly preferably a divisible tablet.

9. Crystalline solifenacin succinate as claimed in any of claims 7 or 8, wherein the dosage form has a content of $\leq$ 5 mg solifenacin succinate, preferably $\leq$ 2.5 mg solifenacin succinate and particularly preferably $\leq$ 1 mg solifenacin succinate.

10. Crystalline solifenacin succinate as claimed in any of claims 1 to 6 for or suitable for use in a method for the treatment of a living creature, preferably a human being, wherein the method comprises administering a pharmaceutically effective amount of the crystalline solifenacin succinate to the living creature.

11. Use of crystalline solifenacin succinate as claimed in any of claims 1 to 6 for the production of a medicament.

12. Crystalline solifenacin succinate as claimed in any of claims 7 to 10 and use as claimed in claim 11, wherein the medicament is for the treatment and/or prevention of a disease or condition, wherein the disease and/or the condition is selected from the group comprising symptoms of hyperactive bladder, urge incontinence, pollakiuria and imperative urge micturition.

13. Method for the production of crystalline solifenacin succinate as claimed in any of claims 1 to 6, characterised in that crystalline solifenacin succinate is used as the starting material, wherein the solifenacin succinate used as the starting material is a crystalline solifenacin succinate which is different from the crystalline solifenacin succinate as claimed in any of claims 1 to 6, and that the starting material is subjected to a comminution step, wherein the particle size and/or the average particle size and/or the axial ratio of the starting material is reduced in the comminution step.

14. Crystalline solifenacin succinate obtainable by a method as claimed in claim 13.

15. Crystalline solifenacin succinate as claimed in claim 14, for use as defined in any of claims 7 to 12.

Application number / numéro de demande: EP20110699 69

Figures: Fig. 2, 3, 5, 7, 9

Pages:

Unscannable items
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(Request original documents in File Prep. Section on the 10th floor)

Documents reçu avec cette demande ne pouvant être balayés
(Commander les documents originaux dans la section de préparation des dossiers au 10ème étage)

Impulse Standard 3-45 20mm 0.008 60 sec solifenacin succinate SLF-07L87 Sample ROH

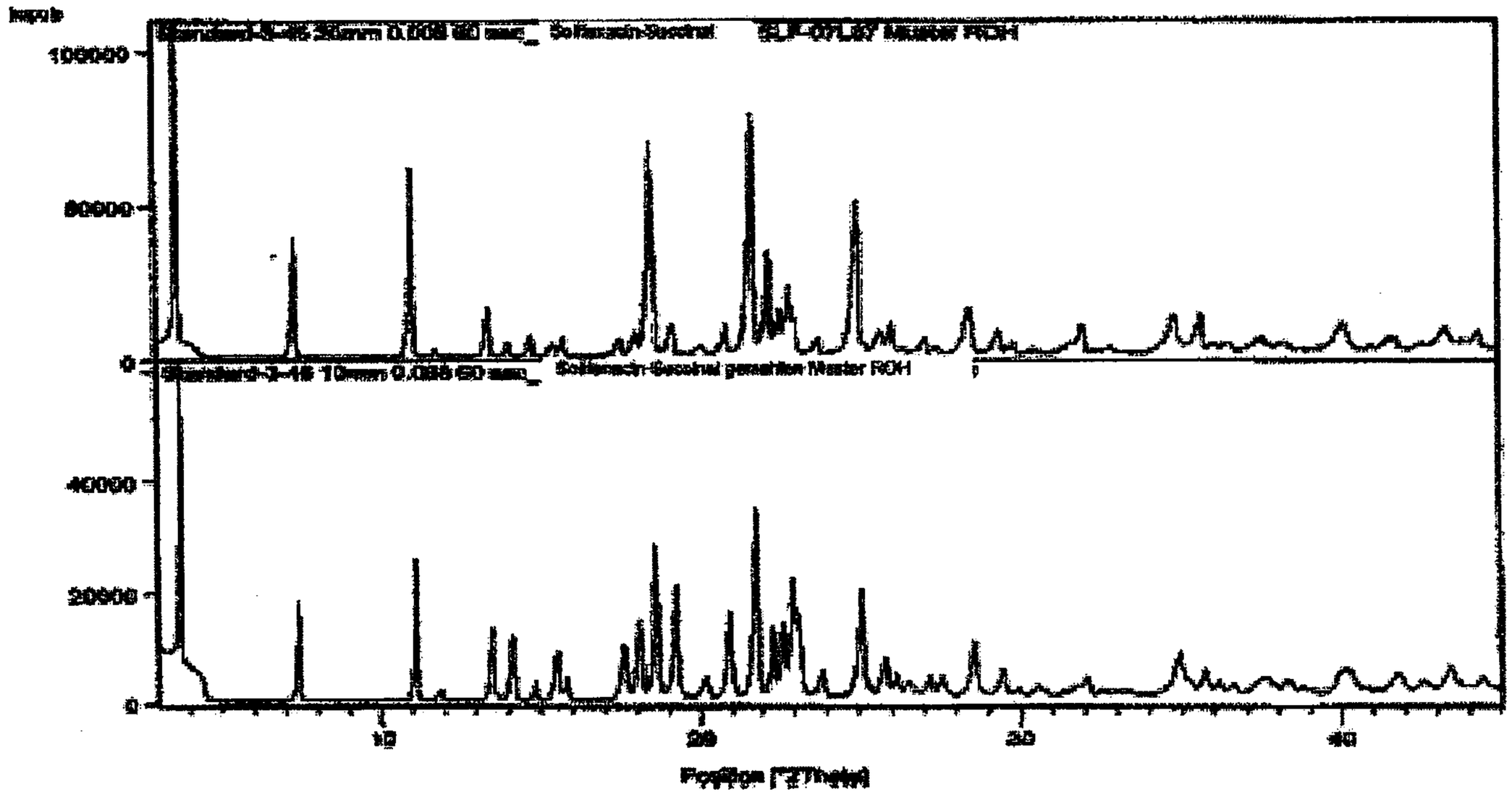
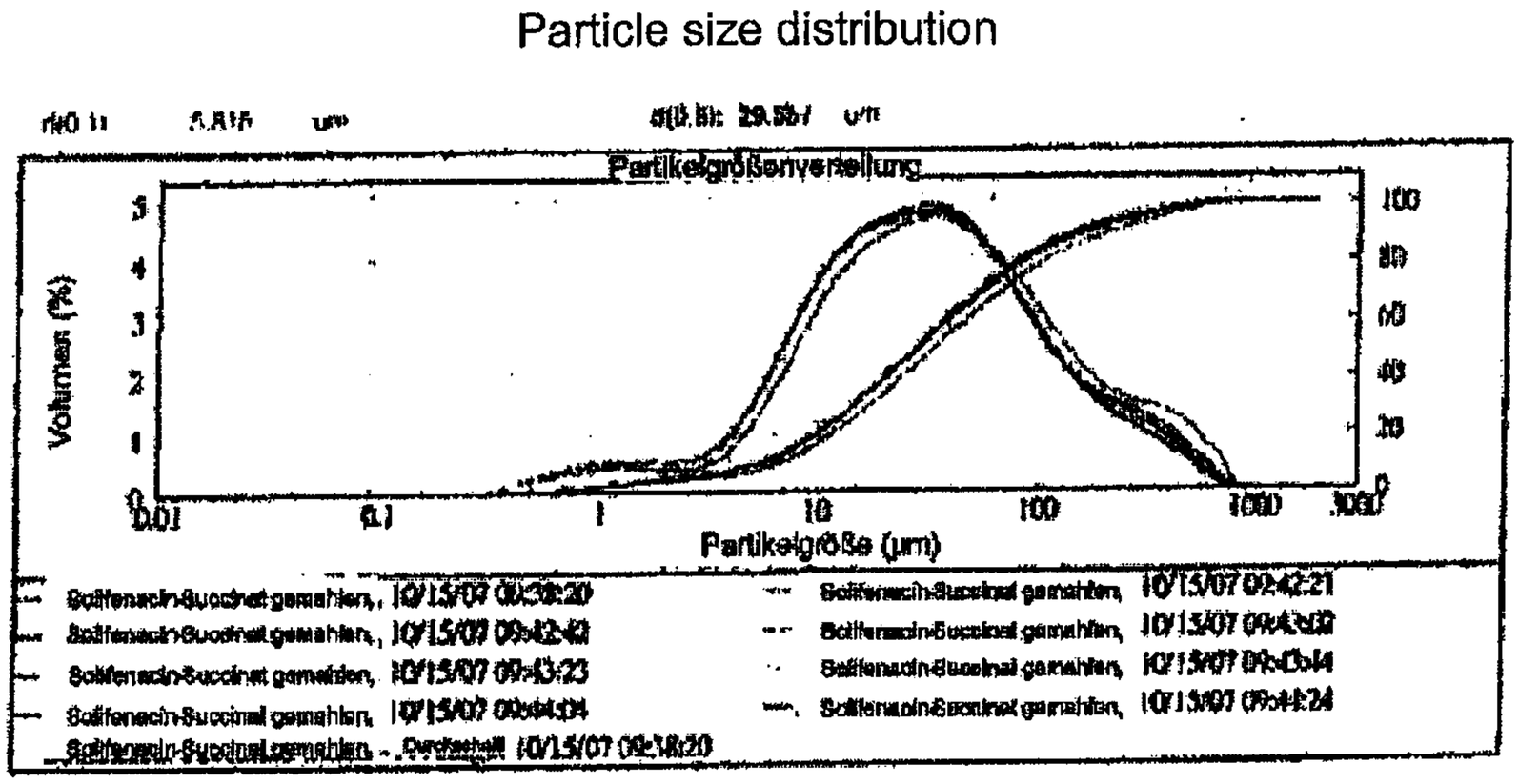


Fig. 1 Standard 3-45 10mm 0.008 60 sec solifenacin succinate ground Sample ROH

Fig. 4



Solifenacin succinate ground

Average

Fig. 6

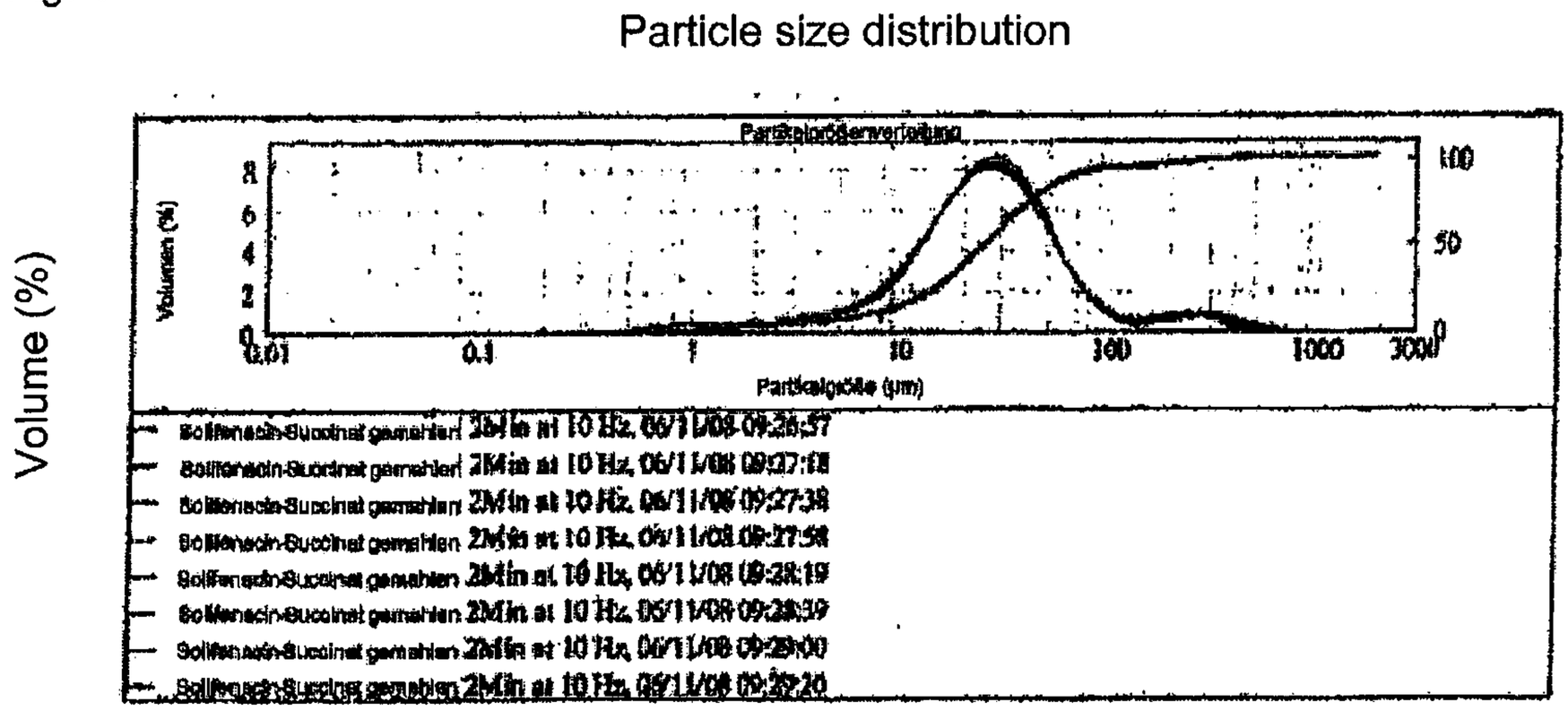
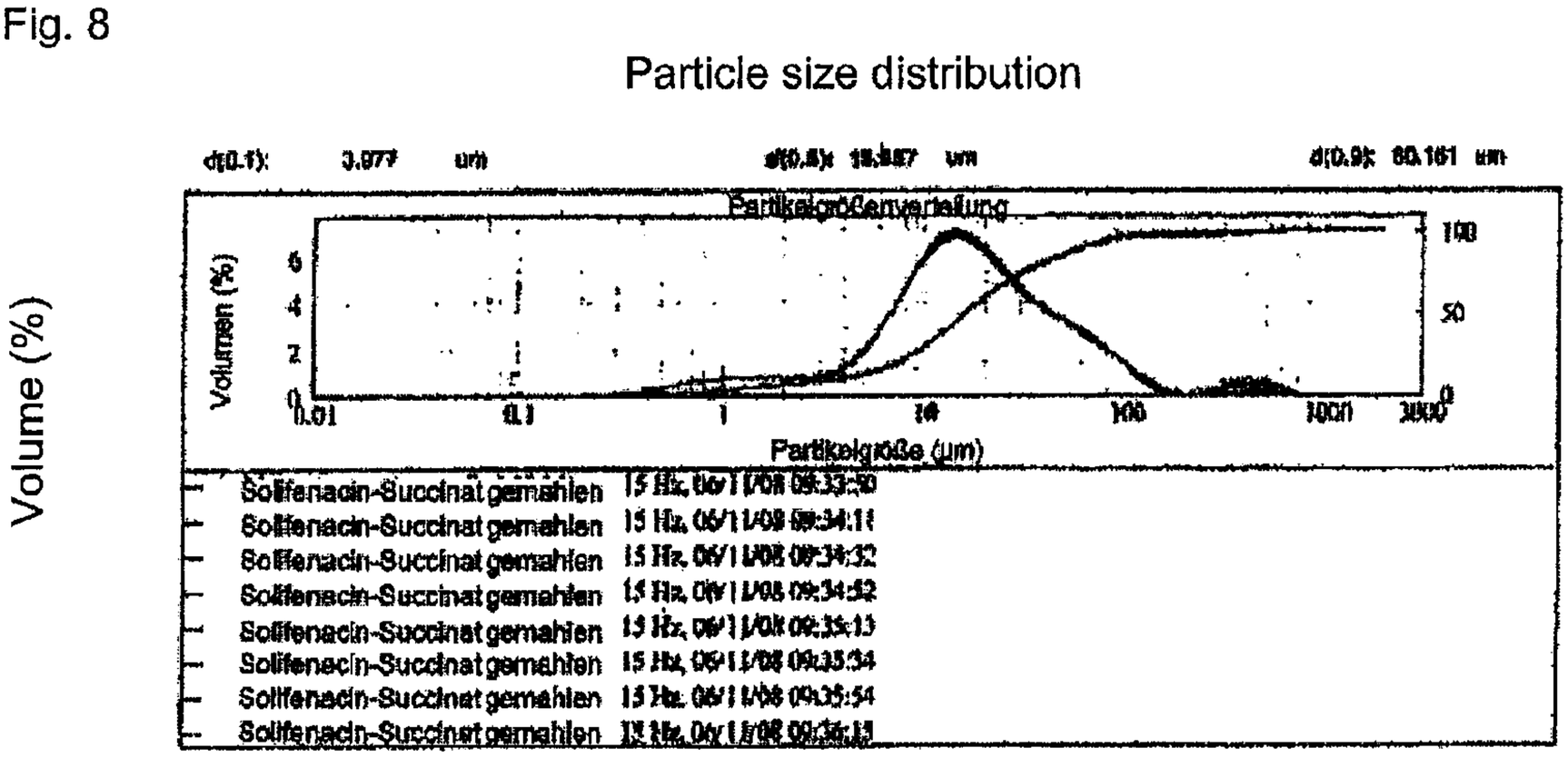

Particle size distribution
Volume (%)
Particle size (µm)
Solifenacin succinate ground

Fig. 8



Solifenacin succinate ground

Fig. 10

Fig. 11