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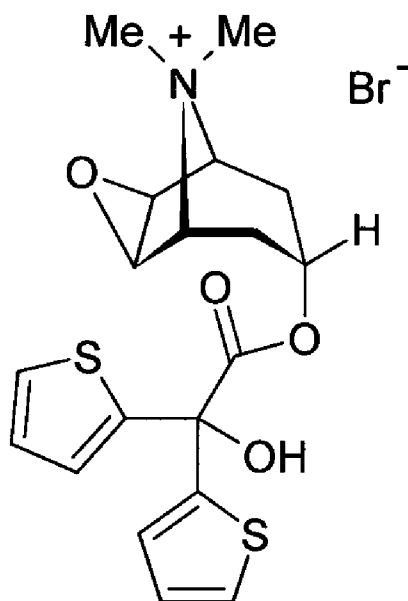
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- (54) **Title:** CRYSTALLINE COMPOUND COMPRISING TIOTROPIUM BROMIDE



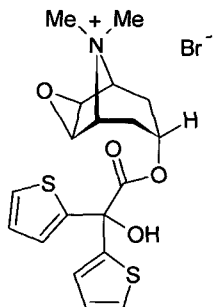
formula I

(57) **Abstract:** The present invention refers to a crystalline compound I comprising Tiotropium bromide (formula I) and water, characterized in that it has an FT-Raman spectrum comprising peaks at wavenumbers (expressed in ± 2 cm^{-1}) of 3070, 3053, 2982, 2967, 1743, 1479, 1429, 1238, 1078, 699, 295 and 121 cm^{-1} and a crystalline compound II comprising Tiotropium bromide (formula I) and CH_2Cl_2 , characterized in that it has an FT-Raman spectrum comprising peaks at wavenumbers (expressed in ± 2 cm^{-1}) of 3109, 3074, 3057, 3023, 2979, 2970, 2955, 2935, 1747, 1479, 1433, 1348, 1324, 1244, 1161, 1071, 1039, 1000, 962, 886, 859, 797, 753, 665, 651, 626, 538, 432, 289, 253, 209 and 173 cm^{-1} or a hydrate thereof, as well as methods of obtaining the same.

CRYSTALLINE COMPOUND COMPRISING TIOTROPIUM BROMIDE

The present invention refers to a crystalline compound comprising Tiotropium bromide and water and to a process for manufacturing the same.

Tiotropium bromide disclosed in EP 0 418 716 A1 has the following chemical structure:



Tiotropium bromide is a highly effective anticholinergic with a long lasting effect. It can be used for treating respiratory complaints and particularly COPD (chronic obstructive pulmonary disease) and asthma.

For treating the abovementioned complaints, Tiotropium bromide is preferably administered by the inhalation route. In addition to the administration of broncholytically active compounds in the form of metered aerosols and inhalable solutions, use of inhalable powders containing active substance is of particular importance.

Tiotropium bromide is preferably administered by the inhalation route. Suitable inhalable powders packed into appropriate capsules (inhalettes) **blisters** may be used. Alternatively, it may be administered by the use of suitable inhalable aerosols. These also include powdered inhalable aerosols which contain, for example, HFA134a, HFA227 or mixtures thereof as propellant gas.

However, since Tiotropium bromide is very effective, only a small amount of the pharmaceutically active substance suffices per single dose to achieve the desired therapeutic effect. Thus, the pharmaceutically active substance has to be diluted in a suitable excipient in order to prepare an inhalable powder. The amount of inhalable composition must be accurately metered in every single dose. Because of the large amount of excipient, the properties of the inhalable powder are significantly influenced by the choice of the excipient. Moreover, the particle size of the pharmaceutically active substance and of the excipient is very important for the emptying characteristics of capsules or blisters when used in an inhaler.

The active substance particles that shall be administered by the inhalation route should optimally meet essential requirements such as appropriate aerodynamic particle size, appropriate particle shape, uniformity of particle size distribution, low aerodynamic dispersion forces, low density, high physical and chemical stability.

Additionally, other physical properties of the pharmaceutically active substance such as the absorption of water and the ease of grinding of the pharmaceutically active substance are of great importance.

The correct manufacture of the abovementioned compositions which are suitable for use for the administration of a pharmaceutically active substance by the inhalation route is based on various parameters which are connected with the nature of the active substance itself. In pharmaceutical compositions which are used like tiotropium bromide in the form of inhalable powders or inhalable aerosols, the crystalline active substance is used in ground (micronised) form for preparing the formulation. Since the pharmaceutical quality of a pharmaceutical formulation requires that the pharmaceutically active substance should always have the same crystalline modification, the stability and properties of the crystalline active substance are subject to stringent requirements from this point of view as well.

WO 03/000265 A1 teaches the manufacture of anhydrous Tiotropium bromide as well as Tiotropium bromide monohydrate. Tiotropium bromide according to EP 418 716 A1 is recrystallized in water and Tiotropium monohydrate is obtained by using 0,4 to 1,5 kg of water ($M_w = 18 \text{ g/mol}$) as solvent per mol Tiotropium bromide ($M_w = 472 \text{ g/mol}$). The molar ratio of Tiotropium bromide to water is at least 1: 22. Since the crystallization is performed in pure water, the water activity a_w is approximately 1.

Subsequently, Tiotropium bromide monohydrate can be converted to anhydrous Tiotropium bromide when it is heated to more than 50 °C, preferably in high-vacuum. However, anhydrous Tiotropium bromide must be stored at a relative humidity of less than 75%. In the case that anhydrous Tiotropium bromide is micronized, it might be necessary storing it at an even lower relative humidity than 75%.

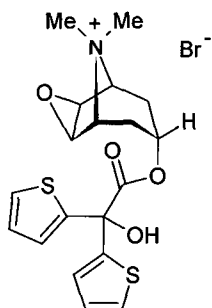
In summary; first, Tiotropium bromide monohydrate is obtained and subsequently the water comprised in said compound is removed to convert it to the pharmaceutically active substance anhydrous Tiotropium bromide. Anhydrous Tiotropium bromide must be stored at a relative

humidity of less than 75 % or at even lower relative humidity when micronized; otherwise it will be detrimentally affected.

Thus, it is an objective of the present invention to provide Tiotropium bromide in form of salt having good chemical and/or physical stability and/or good processability both during its preparation as a pharmaceutically active substance as well as in the preparation of pharmaceutical compositions containing Tiotropium bromide. It is a further objective to provide crystalline salts of Tiotropium bromide that are accessible in a reproducible manner and constant quality in inexpensive and well controlled production processes.

The fact that Tiotropium bromide has therapeutic efficacy as a pharmaceutically active substance even at very low doses indicates the need in the technical field to find a further effective substance for administration in inhalable composition form. Thus, a further technical problem that the present invention relates to is to prepare useful dosage forms of Tiotropium bromide in inhalable composition form.

The technical problem underlying the present invention is solved by a crystalline compound I comprising Tiotropium bromide (formula I)



formula I

and water, characterized in that it has an FT-Raman spectrum comprising peaks at wavenumbers (expressed in $\pm 2 \text{ cm}^{-1}$) of 3070, 3053, 2982, 2967, 1743, 1479, 1429, 1238, 1078, 699, 295 and 121 cm^{-1} .

The term “crystalline compound comprising Tiotropium bromide (formula I) and water” signifies that these two substances are in the same crystalline matrix or different crystalline/amorphous matrices.

The crystalline compound I of the present invention can be admixed with suitable excipients in order to obtain an inhalable composition. The crystalline compound can be ground in order to

adjust the particle size very accurately. Moreover, an inhalable composition comprising the crystalline compound of the present invention can be stored without losing effectiveness.

Preferably, the crystalline compound I has an XRPD pattern with at least one characteristic peak (expressed in $2\theta \pm 0,1^\circ 2\theta$ (CuK α radiation)) at 14.9° , 17.0° , 21.7° , 23.8° and 29.9° .

As regards the process for obtaining the aforementioned crystalline compound I, a further crystalline compound II is very useful, namely a crystalline compound comprising Tiotropium bromide (formula I) and CH_2Cl_2 , or a hydrate thereof characterized in that it has an FT-Raman spectrum comprising peaks at wavenumbers (expressed in $\pm 2 \text{ cm}^{-1}$) of 3109, 3074, 3057, 3023, 2979, 2970, 2955, 2935, 1747, 1479, 1433, 1348, 1324, 1244, 1161, 1071, 1039, 1000, 962, 886, 859, 797, 753, 665, 651, 626, 538, 432, 289, 253, 209 and 173 cm^{-1} or a hydrate thereof.

Preferably, the crystalline compound II has an XRPD pattern with at least one characteristic peak (expressed in $2\theta \pm 0,1^\circ 2\theta$ (CuK α radiation)) at 18.0° , 19.9° , 21.0° , 21.5° , 23.8° , 25.0° , 26.0° , 26.9° , 27.1° , 30.0° , 30.2° , 30.3° , 30.6° , 31.0° and 31.8° .

In a preferred embodiment of the invention, the molar ratio of the compound of formula I and CH_2Cl_2 is in the range of from 1: 0,3 to 1: 0,7, more preferably of from 1:0,4 to 1:0,6 and most preferably 1:0,5.

The term “crystalline compound comprising Tiotropium bromide (formula I) and CH_2Cl_2 or a hydrate thereof” signifies that these two substances are in the same crystalline matrix or different crystalline/amorphous matrices.

Preferably, the crystalline compound II of the present invention can be admixed with suitable excipients in order to obtain an inhalable composition. The crystalline compound can be ground in order to adjust the particle size very accurately. Moreover, an inhalable composition comprising the crystalline compound of the present invention can be stored without losing effectiveness.

Said compound II is also very useful as intermediate for obtaining the crystalline compound I. Compound II can be obtained by a process comprising the steps of:

- a) providing Tiotropium bromide (formula I)
- b) adding CH_2Cl_2 to the composition of step a)

- c) optionally concentrating the composition of step b)
- d) crystallizing
- e) optionally equilibrating the obtained suspension of step d)
- f) isolating the obtained precipitate.

Preferably, in step d) and/or e) seed crystals are added.

Subsequently, crystalline compound II can be used as starting material for obtaining the crystalline compound I of the present invention.

A further aspect of the present invention is a process for obtaining the crystalline compound I comprising the steps of:

- a) providing Tiotropium bromide (formula I) in a suitable solvent or mixture of solvents or providing the crystalline compound II in a suitable solvent or mixture of solvents, wherein the water activity of the composition is adjusted to have a value of from 0,1 to 0,6
- b) optionally concentrating the composition of step a)
- c) crystallizing
- d) optionally equilibrating the obtained suspension of step c)
- e) isolating the obtained precipitate and
- f) drying the obtained precipitate under a water activity of 0.1 to 0.6, preferably at a water activity of 0.1 to 0.5.

Preferably, in step a) a carboxylic acid like L-lactic acid may be added to the composition.

The water activity is a thermodynamic measure for the effective water concentration in a given system. It is defined as $a_w = p/p_0$, where p and p_0 are the partial pressures of water over a given solvent or solvent mixture and over pure water.

Water activity is a function of the composition but is also a function of the temperature. For typical ambient conditions (room temperature) it essentially corresponds to the relative humidity in % divided by 100.

When manufactured, the tiotropium bromide monohydrate requires a high water activity of 1, whereas the tiotropium bromide anhydrate according to the state of the art requires a water activity of zero (waterfree environment). Contrary thereto, the crystalline compound I of the

present invention is obtained wherein the water activity of the composition of step a) is adjusted to have a value of from 0,1 to 0,6.

Preferably, in step a) and/or step f) the crystalline compound I of the present invention is prepared at water activities of from 0,2 to 0,5 and more preferably from 0,3 to 0,5.

The water activity in a suspension of Tiotropium bromide in an organic solvent is adjusted by addition of the correct amount of water to the system. The amount of water to be added depends on the solvent used for the suspension experiment. The necessary data can be obtained from the literature, for instance, D.R. Lide, CRC Handbook of Thermophysical and Thermochemical Data (1994).

An example for acetone is given in the following table:

Molar fraction of water in acetone at 30°C	Water activity a_w
0	0
0.1	0.43
0.3	0.72
0.5	0.81
0.7	0.86

A possible way to adjust the water activity for drying the crystalline compound I is the proportional mixing of two equal flows of air, nitrogen or any other inert-gas in a defined ratio. One gas-flow is dry gas, thus having a water activity of 0; and the other gas flow is previously saturated with water, thus exhibiting a water activity of 1.0.

For preparation of the crystalline compound I, the preferred solvents are organic solvents that preferably do not form solvates or preferably form only very metastable solvated forms. These are acetone or other ketones such as methyl ethyl ketone or 2-pentanone; other acetates such as ethyl acetate, or isopropyl acetate and butyl acetate; TBME, acetonitrile, DMSO or mixtures thereof.

Generally, it is possible to suspend the compound of formula I (tiotropium bromide) or crystalline compound II in an organic solvent or solvent mixture and adjust the water activity by addition of required amount of water. Suitable solvents are, for instance, ethyl acetate, acetone, or other ketones such as methyl ethyl ketone, or 2-pentanone or other acetates such as isopropyl acetate and butyl acetate, TBME, acetonitrile, DMSO or mixtures thereof.

Alternatively, the compound of formula I (tiotropium bromide) or the crystalline compound II can be dissolved in an organic solvent or solvent mixture in which the water activity is adjusted by addition of the required amount of water. Suitable solvents are, for instance, ethyl acetate, acetone, or other ketones such as methyl ethyl ketone, or 2-pentanone or other acetates such as isopropyl acetate and butyl acetate, TBME, acetonitrile, DMSO or mixtures thereof.

Examples

Instrumental Parameters and Measurement Procedures

Powder X-ray diffraction (XRPD)

The measurements were carried out with a Bruker D8 Advance powder X-ray diffractometer using Cu K α radiation in the Bragg-Brentano reflection geometry. Generally, the 2θ values are accurate within an error of ± 0.1 - 0.2° . The relative peak intensities can vary considerably for different samples of the same crystalline form because of different preferred orientations of the crystals. The samples were prepared without any special treatment other than the application of slight pressure to get a flat surface. Silicon single crystal sample holders of either 1.0, 0.5 mm or 0.1 mm depth and 12 mm cavity diameter were used. The tube voltage and current were 40 kV and 40 mA, respectively. The X-ray diffractometer is equipped with a LynxEye detector. A variable divergence slit was used with a 3° window. The step size was $0.02^\circ 2\theta$ with a step time of 37 seconds. The samples were rotated at 0.5 rps during the measurement.

Thermogravimetry coupled with Fourier Transform Infrared Spectroscopy (TG-FTIR)

TG-FTIR was performed on a Netzsch Thermo-Microbalance TG 209 which is coupled to a Bruker FT-IR Spectrometer Vector 22. The measurements were carried out with aluminum crucibles with a micro pinhole under a nitrogen atmosphere and at a heating rate of $10^\circ\text{C}/\text{min}$ over the range 25 - 250°C .

FT-Raman spectroscopy

Raman spectra were recorded using a Bruker RFS100 Raman spectrometer equipped with a germanium detector and a Nd:YAG laser with an excitation wavelength of 1064 nm. A few milligrams of material were pressed into aluminum sample holders. Spectra in the range of 50-

3500 cm^{-1} and with a resolution of 2 cm^{-1} were measured with a laser power of 300 mW. 64 scans were accumulated.

HPLC

HPLC was carried out on a TSP HPLC chromatograph (UV3000, AS3000, P4000, SCM1000 software version 4.1). The column type used was a Waters XTerra MS C18, 100 x 4.6 mm, 5 μm (CC01C). Mobile phase A was H_2O / ACN 95:5 + 0.1 % TFA and mobile phase B was H_2O / ACN 5:95 + 0.1 % TFA. The applied flow rate was 1.0 mL per minute, the injection volume was 10 microliter and the detection wavelength was 240 nm. The gradient was at 0 min 100% mobile phase A, at 20 min 100% mobile phase B, from 20 to 30 minutes pure mobile phase A.

^1H -NMR

The ^1H -NMR spectra were recorded using a Bruker DPX300 instrument. Generally, DMSO-d_6 was used as the solvent.

Example 1: Preparation of seed crystals of the crystalline compound I with the known orthorhombic anhydrate as starting material.

100 mg of orthorhombic tiotropium bromide anhydrate according to example 1 of WO 2006/117299 A1 and 19 mg of L-lactic acid are co-milled in a Retsch MM200 ball mill at 30 Hz 3x10 min with 10 min breaks. The obtained sticky sample is suspended in 1.0 ml of ethyl acetate (dried over 4Å molecular sieve) and placed on a standard laboratory shaker. Shaking is carried out at 400 rpm for one day and simultaneously temperature cycles are run according to the following cycle program one hour at 25°C, heating in one hour to 50°C, 1 hour 50°C, cooling to 25°C in 1 hour. After one day of temperature cycling, the mixture is kept at room temperature for 15 days. Thereafter, the mixture is sonicated for one minute and stirred for 7 days and room temperature. The suspension is filtered and the obtained solid dried in air at room temperature at a water activity of 0.2 to 0.3 for a few minutes. The product is investigated by FT-Raman spectroscopy, powder X-ray diffraction, TG-FTIR, and dynamic water vapour sorption. A new and characteristic Raman spectrum as displayed in Figure 3 and Figure 4 is obtained for which a peak list is provided in Table 2. Similarly, the obtained crystalline form I exhibits a characteristic XRPD pattern as shown in Figure 1 which exhibits

X-ray diffraction reflexions as listed in Table 1. TG-FTIR reveals a mass loss of 2.3% which is attributable to loss of water.

Table 1: Powder X-ray diffraction peaks for the crystalline compound I

Pos. [2θ .]	d-spacing [$\text{\AA}$]	Qualitative Intensity
9.1	9.7	m
11.5	7.7	w
12.0	7.4	s
12.6	7.0	m
13.7	6.4	s
14.1	6.3	m
14.9	5.92	s
15.8	5.60	s
17.0	5.22	vs
17.6	5.03	s
18.4	4.81	s
18.9	4.70	s
19.4	4.57	m
19.9	4.46	s
20.3	4.38	s
21.0	4.23	m
21.7	4.10	s
22.3	3.99	m
23.1	3.85	m
23.8	3.74	vs
24.0	3.70	s
24.3	3.66	s
24.7	3.60	s
24.9	3.57	s
25.3	3.52	vs
25.5	3.49	s
26.1	3.42	s
27.0	3.30	s
27.6	3.23	m
28.1	3.17	m
28.2	3.16	s
29.2	3.06	s
29.4	3.04	s

Pos. [2θ .]	d-spacing [$\text{\AA}$]	Qualitative Intensity
29.9	2.98	s
30.5	2.93	s
31.6	2.83	s
32.2	2.78	m
32.8	2.73	m
33.1	2.70	m
34.2	2.62	m
35.7	2.51	m
36.5	2.46	m
37.2	2.42	m
38.1	2.36	m
39.0	2.31	m
39.3	2.29	m

Table 2: Raman peaklist for the crystalline compound I

Wavenumbers [cm^{-1}]	Relative intensity
3098	0.07
3070	0.05
3053	0.18
2982	0.03
2967	0.30
2948	0.02
2931	0.03
2881	0.02
1743	0.03
1528	0.02
1479	0.02
1429	0.44
1347	0.07
1238	0.03
1204	0.04
1163	0.03
1078	0.10
960	0.02
865	0.02
856	0.09
699	0.15

Wavenumbers [cm-1]	Relative intensity
652	0.08
295	0.08
160	0.03
121	0.06

Example 2: Preparation of the crystalline compound I in presence of L-lactic acid.

17.9 mg of L-lactic acid is dissolved in 1.0 ml ethyl acetate and 101 mg of crystalline compound II of example 4 are suspended in this solution. The resulting suspension is seeded with a few crystals of the crystalline compound I according to example 1, sonicated for one minute and stirred overnight at room temperature. Then 10 microliter of water is added to the mixture to adjust the water activity a_w in the composition to be 0,5, again sonication is applied for one minute and stirring is continued for another 20 hours. The solid is separated by filtration and the obtained crystalline product is dried in air at a water activity of 0.2 to 0.3 and a Raman spectrum of the solid is measured. FT-Raman spectroscopy confirms that the crystalline compound I is obtained as the Raman spectrum corresponds to the Raman spectrum as shown in figure 3 and figure 4.

Example 3: Preparation of new hydrate by conversion of the crystalline compound II

106 mg of crystalline compound II prepared according to example 4 are suspended in 1.0 ml ethyl acetate. The suspension is seeded with the new hydrate according to example 1, and 10 microliter of water is added to adjust the water activity a_w in the composition to be 0,5. This mixture is sonicated for about one minute and stirred at room temperature overnight. A crystalline solid sample is recovered by filtration and after a few minutes of drying in air at room temperature is investigated by FT-Raman spectroscopy, which shows that crystalline compound I is obtained.

Example 4: Preparation of the crystalline compound II

To 40 mg of amorphous tiotropium bromide, 2.0 ml of dichloromethane is added and the resulting suspension is stirred at room temperature. After overnight stirring, the suspension is filtered and the obtained solid dried under vacuum for about one hour. Investigation by powder X-ray diffraction shows that a crystalline sample with a characteristic XRPD pattern is

obtained as shown in Figure 2 with peaks as listed in Table 3. Thermogravimetry coupled with FT-IR spectroscopy indicates a mass loss of about 9.3% which is essentially attributable to loss of dichloromethane. This suggests a dichloromethane hemisolvate because the theoretical dichloromethane content for a dichloromethane hemisolvate is 8.2%. ¹H-NMR spectroscopy confirms the structural integrity of tiotropium bromide and consistently shows presence of about 0.5 equivalents of dichloromethane. Characterization by FT Raman spectroscopy shows that crystalline compound II has a characteristic Raman spectrum as depicted in Figure 5 and Figure 6 with peaks as listed in Table 4.

Reference Example: Preparation of tiotropium bromide monohydrate according to EP 1 326 862 B1.

165 mg of crystalline tiotropium bromide anhydrate according to EP 1 401 445 A1 is suspended in 2.0 ml of water and the resulting suspension is stirred at room temperature for one day. The water activity of the suspension is 1 since water is used as solvent. Thereafter the suspension is filtered and the obtained crystalline form is dried in air at a relative humidity of about 80% for about one hour and investigated by powder X-ray diffraction and FT- Raman spectroscopy. The simulation of the powder pattern using the single crystal data provided in EP 1 326 862 B1, and comparison of the calculated pattern with the experimental pattern obtained from the produced crystalline form are in good agreement, which confirms that the known tiotropium bromide monohydrate is obtained. An FT-Raman spectrum of the monohydrate is provided in Figure 7. An exemplary overlay plot in a region where characteristic differences can be found of the Raman spectra of crystalline compound I according to example 1 and tiotropium bromide monohydrate according to the reference example is shown in figure 8.

Table 3: Powder X-ray diffraction peaks for the crystalline compound II (M417)

Pos. [°2 θ .]	d-spacing [Å]	Qualitative Intensity
9.9	8.9	w
11.1	8.0	w
13.4	6.6	m
13.5	6.5	m
15.2	5.81	s
15.4	5.75	m
16.1	5.50	w
16.3	5.44	m

Pos. [$^{\circ}2\theta$.]	d-spacing [$\text{\AA}$]	Qualitative Intensity
17.8	4.97	m
18.0	4.92	vs
19.9	4.46	vs
21.0	4.22	s
21.5	4.13	vs
23.1	3.85	m
23.6	3.77	s
23.8	3.73	s
24.5	3.63	m
24.6	3.61	s
25.0	3.56	s
26.0	3.43	s
26.1	3.41	m
26.2	3.39	m
26.7	3.34	m
26.9	3.31	m
27.1	3.29	s
27.3	3.27	m
27.7	3.21	s
28.0	3.19	m
29.3	3.05	m
29.6	3.02	m
29.8	3.00	s
30.0	2.97	s
30.2	2.96	s
30.3	2.94	s
30.6	2.92	m
31.0	2.88	m
31.8	2.81	s
32.6	2.75	m

Table 4: Raman peaklist for the crystalline compound II

Wavenumbers [cm^{-1}]	Relative intensity
3109	0.04
3074	0.09
3057	0.03
3023	0.03

Wavenumbers [cm-1]	Relative intensity
2979	0.01
2970	0.03
2955	0.22
2935	0.01
1747	0.03
1479	0.02
1433	0.37
1348	0.06
1324	0.02
1244	0.04
1161	0.03
1071	0.10
1039	0.04
1000	0.04
962	0.02
886	0.03
859	0.07
797	0.02
753	0.05
665	0.03
651	0.07
626	0.02
538	0.03
432	0.03
289	0.07
253	0.02
209	0.04
173	0.02

The pharmaceutical compositions comprising pharmaceutically acceptable, nontoxic and a therapeutically effective amount of the crystalline compound I or crystalline compound II of the present invention and also preparation methods thereof are the characteristic features of the present invention.

The pharmaceutical compositions comprising the crystalline compound I or crystalline compound II of the present invention are in dry powder form or pressurized metered dose inhalation composition form, preferably in dry powder inhalation composition form.

During preparation process of dry powder inhalation compositions, two methods are commonly implemented in order to transmit effective amount of the medicament to the target area. One of them is based on controlled agglomeration of undiluted medicament; the other one is based on adhesion of micronized medicament particles to the surface of an inert carrier having large particle size. The pharmaceutical compositions of the present invention are preferably prepared by implementing the both methods, preferably by implementing the second method. When the second method is implemented, the pharmaceutical composition comprises at least one pharmaceutically acceptable inert carrier and optionally at least one pharmaceutically acceptable excipient different from the carrier(s) along with the active substance.

The term ‘‘micronized medicament particles’’ refers to propionic acid solvate of tiotropium bromide. The solvate of tiotropium bromide of the present invention is characterized by having an average particle size in the range of 1-10 μ m, preferably in the range of 1-5 μ m. The pharmaceutical compositions of the present invention are characterized by comprising propionic acid solvate of tiotropium bromide of the present invention in the range of 0.001-50%, preferably in the range of 0.01-10%.

The term ‘‘inert carrier’’ refers to lactose, more preferably lactose monohydrate for dry powder inhalation compositions of the present invention. The pharmaceutical compositions of the present invention can comprise at least one inert carrier having large particle size and at least one inert carrier having small particle size and optionally at least one excipient together. The inert carrier having large particle size of the present invention is characterized by having an average particle size (d_{50}) in the range of 10-250 μ m, preferably in the range of 10-150 μ m, more preferably of 150 μ m; the inert carrier having small particle size of the present invention, on the other hand, is characterized by having an average particle size (d_{50}) in the range of 1-10 μ m, preferably of 10 μ m. The inert carriers having large particle size and small particle size can be the same or different substances.

At least one pharmaceutically acceptable excipient can be selected from carbohydrates such as lactose, glucose, fructose, galactose, sucrose, maltose, trehalose, maltodextrins, dextrans, cyclodextrins, starch and cellulose; polyalcohols such as sorbitol, mannitol and xylitol; amino acids such as glycine, arginine, lysine, aspartic acid and glutamic acid; peptides such as human serum albumin; gelatine; various salts and taste masking agents. Said at least one excipient is not limited to these substances.

In preparation process of pressurized metered-dose inhalation compositions, two formulation strategies are implemented depending on physicochemical characteristics of the active substance and propellant gas system. One of them is solution, the other one is suspension formulation. The pharmaceutical composition preferred comprises propellant gases, surface active agents and at least one basic excipient selected from the group of co-solvents and optionally at least one other pharmaceutically acceptable excipient along with the active substance.

The term “active substance” refers to crystalline compound I or crystalline compound II. The active substance comprised in the pharmaceutical composition is characterized by having an average particle size in the range of 1-10 μ m, preferably in the range of 1-5 μ m. The pharmaceutical compositions of the present invention are characterized by comprising crystalline substance I or crystalline substance II in the range of 0.001-50%, preferably in the range of 0.01-10%.

Depending on formulation strategy, at least one pharmaceutically acceptable excipient can be selected from propellant gases (propellants) such as chlorofluorocarbons, hydrofluoroalkanes and hydrocarbons; surface active agents (surfactants) such as oleic acid, polysorbates, propylene glycol, polyethylene glycol, cetyl alcohol, stearyl alcohol, sorbitan fatty acid esters, sugar esters of fatty acids, glycerides of fatty acids, isopropyl myristate and lecithin; cosolvents such as ethanol, water and diethyl ether; antioxidants such as butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulphide, gallates (such as propyl gallate), tocopherol, citric acid, malic acid, ascorbic acid, acetylcysteine, fumaric acid, lecithin, ascorbyl palmitate, ethylenediamine tetraacetate; and sweeteners.

The pharmaceutical compositions comprising crystalline substance I or crystalline substance II of the present invention can additionally comprise at least one active substance selected from the medicaments such as other anticholinergic agents, adrenergic agonists, antiallergic agents, anti-inflammatory agents, antihistaminics, steroids, leukotriene receptor antagonists, antimuscarinic agents, PDE inhibitors and EGFR inhibitors. The crystalline substance I and crystalline substance II of the present invention can be used separately, sequentially or simultaneously with at least one active substance selected from the specified group.

Another characteristic feature of the present invention is that the pharmaceutical compositions comprising the crystalline substance I and crystalline substance II of the present invention are used in treatment of respiratory tract diseases, particularly COPD (chronic obstructive pulmonary disease) and asthma.

Preparation methods of the pharmaceutical compositions comprising crystalline substance I and crystalline substance II of the present invention

Preparation process of dry powder inhalation compositions of the present invention is characterized by comprising the following steps:

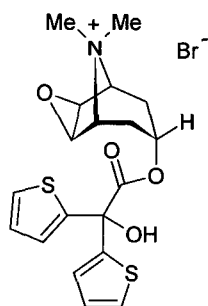
- sieving inert carriers having large particle size and small particle size separately,
- obtaining the first mixture as a result of adding the inert carrier sieved having small particle size into crystalline substance I and crystalline substance II,
- sieving the first mixture obtained,
- obtaining the second mixture as a result of adding the inert carrier sieved having large particle size into the first mixture,
- sieving and mixing the second mixture obtained,
- making ready the final mixture to be filled into capsule/blister.

Preparation process of the pressurized metered-dose inhalation compositions of the present invention is characterized by comprising the following steps:

- cooling the production vessel to -25°C,
- pumping propellant gas into the vessel,
- adding crystalline substance I or crystalline substance II into the vessel and mixing the mixture obtained,
- filling the final mixture into the appropriate cups.

Claims

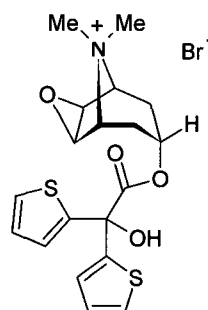
1. A crystalline compound I comprising Tiotropium bromide (formula I)



formula I

and water, characterized in that it has an FT-Raman spectrum comprising peaks at wavenumbers (expressed in $\pm 2 \text{ cm}^{-1}$) of 3070, 3053, 2982, 2967, 1743, 1479, 1429, 1238, 1078, 699, 295 and 121 cm^{-1} .

2. The crystalline compound according to claim 1, characterized in that it has an XRPD pattern with at least one characteristic peak (expressed in $2\theta \pm 0,1^\circ 2\theta$ (CuK α radiation)) at 14.9° , 17.0° , 21.7° , 23.8° and 29.9° .
3. A crystalline compound II comprising Tiotropium bromide (formula I)



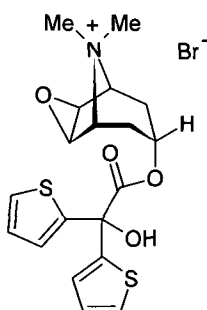
formula I

and CH_2Cl_2 or a hydrate thereof, characterized in that it has an FT-Raman spectrum comprising peaks at wavenumbers (expressed in $\pm 2 \text{ cm}^{-1}$) of 3109, 3074, 3057, 3023, 2979, 2970, 2955, 2935, 1747, 1479, 1433, 1348, 1324, 1244, 1161, 1071, 1039, 1000, 962, 886, 859, 797, 753, 665, 651, 626, 538, 432, 289, 253, 209 and 173 cm^{-1} or a hydrate thereof.

4. A pharmaceutical composition comprising the crystalline compound and optionally one or more pharmaceutically acceptable excipients according to at least one of the claims 1, 2 and/or 3.

5. The pharmaceutical composition according to claim 4, wherein said crystalline compound is comprised in the composition in the range of 0.001-50% in proportion to total weight of unit dose.
6. The pharmaceutical composition according to claim 4, wherein said composition is in dry powder form or pressurized metered dose form.
7. The pharmaceutical composition according to claim 6, wherein said composition comprises a pharmaceutically acceptable inert carrier and at least one pharmaceutically acceptable excipient different from the carrier used optionally in addition to the active substance in the case that said composition is in dry powder form.
8. The pharmaceutical composition according to claim 7, wherein said composition comprises at least one inert carrier having large particle size and at least one inert carrier having small particle size.
9. The pharmaceutical composition according to claim 8, wherein the inert carrier having large particle size of the present invention is characterized by having an average particle size (d_{50}) in the range of 10-350 μ m; the inert carrier having small particle size is characterized by having an average particle size (d_{50}) in the range of 1-10 μ m.
10. The pharmaceutical composition according to claim 4, wherein said composition can comprise at least one active substance selected from the medicaments such as other anticholinergic agents, adrenergic agonists, antiallergic agents, anti-inflammatory agents, antihistaminics, steroids, leukotriene receptor antagonists, antimuscarinic agents, PDE inhibitors and EGFR inhibitors.
11. A process for obtaining the crystalline compound II according to claim 3 comprising the steps of:

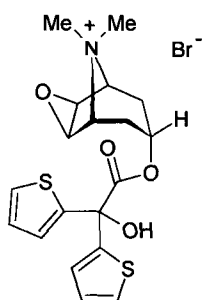
a) providing Tiotropium bromide (formula I)



formula I

- b) adding CH_2Cl_2 to the composition of step a)
 - c) optionally concentrating the composition of step b)
 - d) crystallizing
 - e) optionally equilibrating the obtained suspension of step d)
 - f) isolating the obtained precipitate.
12. The process according to claim 11, characterized in that in step d) and/or in step e) seed crystals are added.
13. A process for obtaining the crystalline compound I according to claim 1 or 2 comprising the steps of:

- a) providing Tiotropium bromide (formula I) in a suitable solvent or mixture of solvents



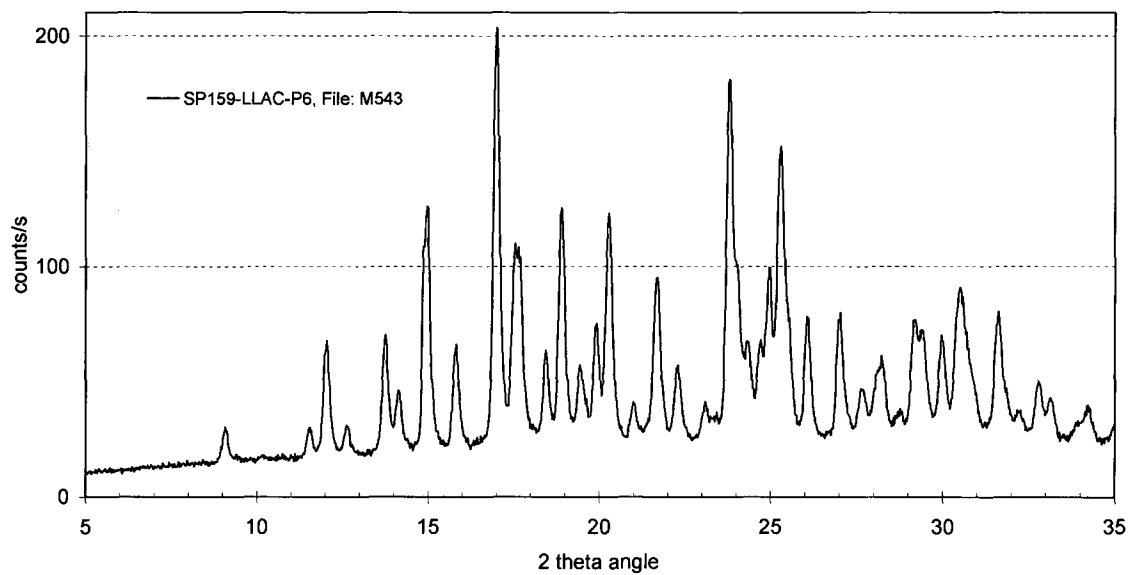
formula I

or providing the compound of claim 3 in a suitable solvent or mixture of solvents, wherein the water activity of the composition is adjusted to have a value of from 0,1 to 0,6.

- b) optionally concentrating the composition of step a)
 - c) crystallizing
 - d) optionally equilibrating the obtained suspension of step c)
 - e) isolating the obtained precipitate.
 - f) drying the obtained precipitate under a water activity of 0.1 to 0.6, preferably at a water activity of 0.1 to 0.5.
14. The process according to claim 13, characterized in that in step c) and/or in step d) seed crystals are added.
15. The process according to claim 13 or 14, characterized in that in step a) Tiotropium bromide is provided in form of crystalline compound II according claim 3.

Figure 1

Powder X-ray diffraction pattern of crystalline compound I

**Figure 2**

Powder X-ray diffraction pattern of crystalline compound II

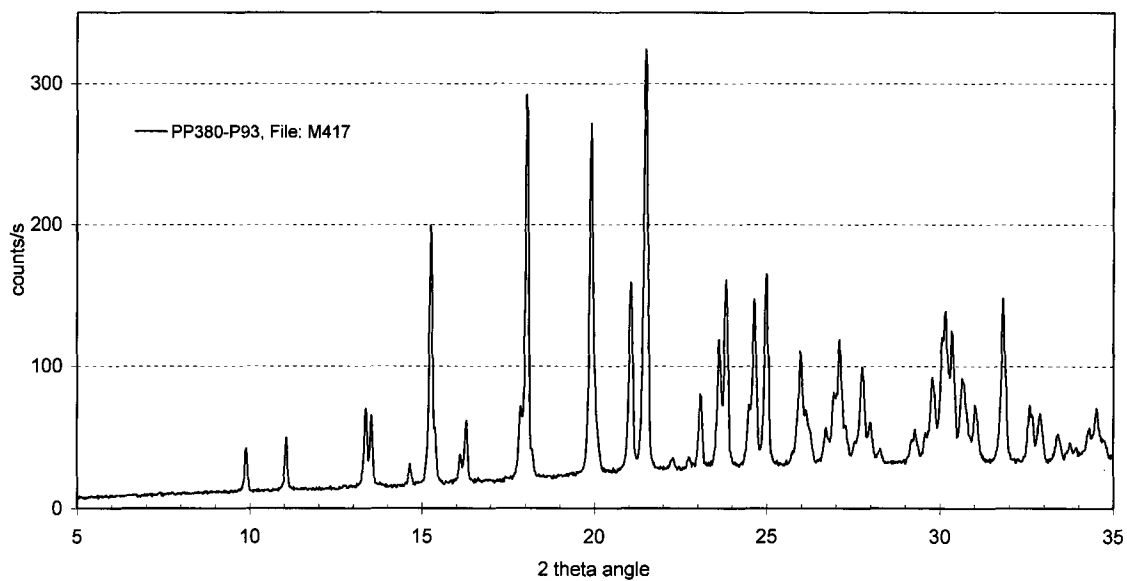
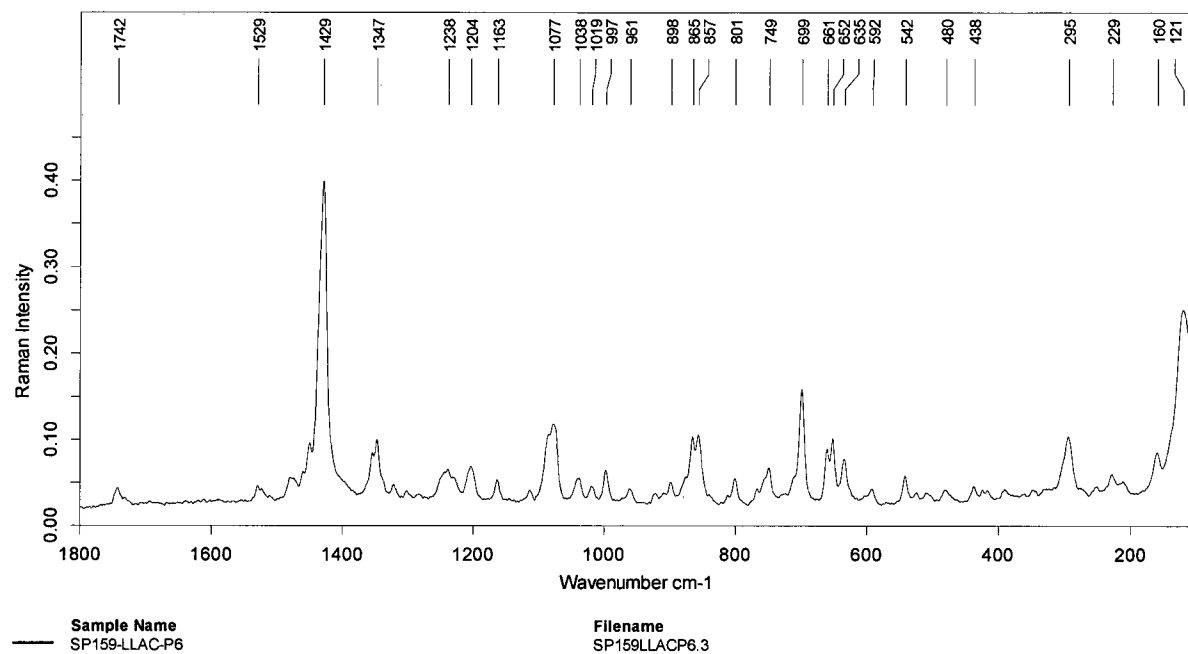
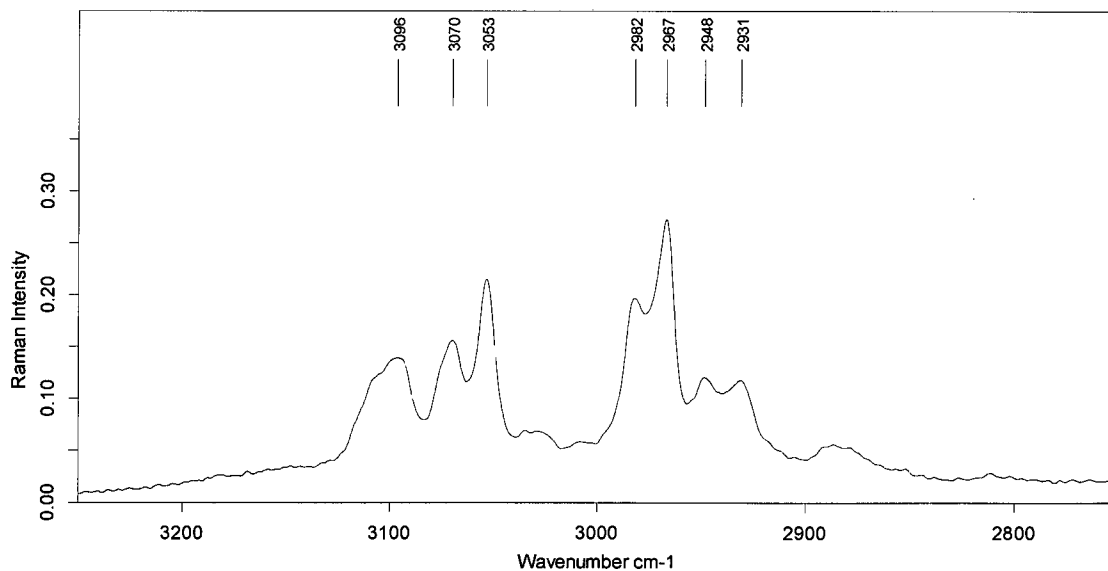


Figure 3

FT Raman spectrum of the crystalline compound I in the range from 1800 to 100 cm^{-1}

**Figure 4**

FT Raman spectrum of the crystalline compound I in the range from 3250 to 2750 cm^{-1}

**Figure 5**

FT Raman spectrum of the crystalline compound II in the range from 1800 to 100 cm^{-1}

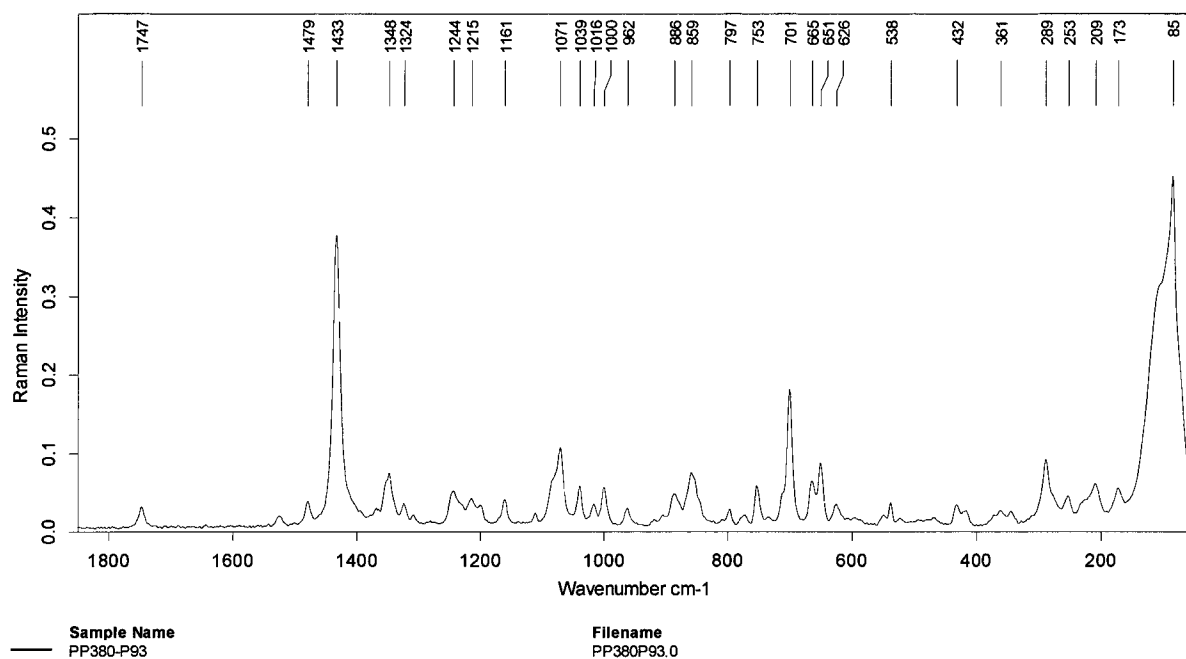


Figure 6

FT Raman spectrum of the crystalline compound II in the range from 3250 to 2750 cm^{-1}

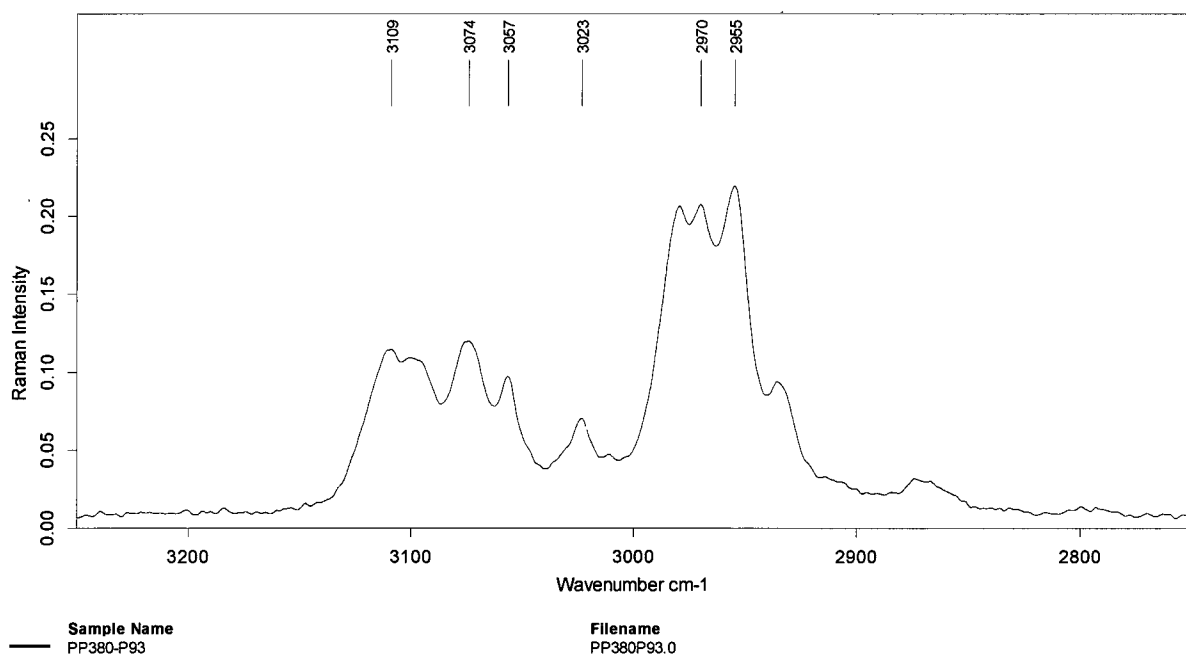


Figure 7

FT Raman spectrum of the tiotropium bromide monohydrate (reference example) in the range from 1800 to 100 cm^{-1}

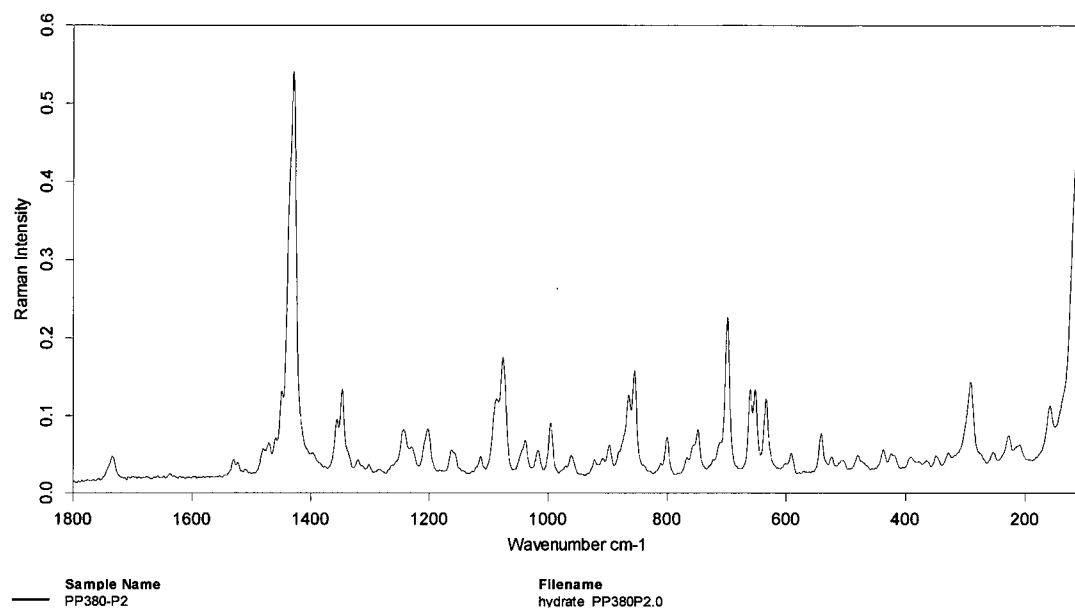
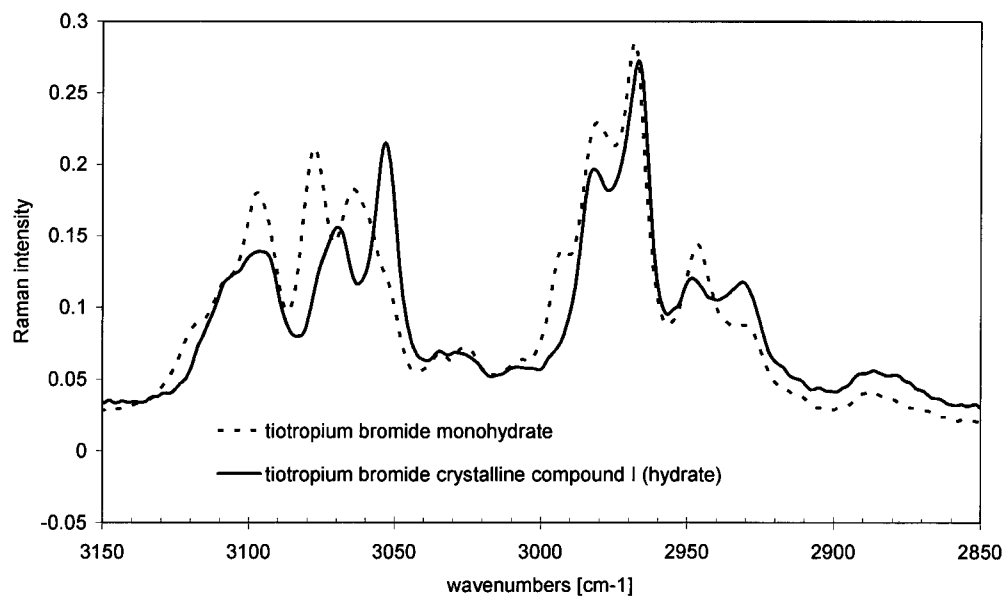


Figure 8

Overlay plot of the FT Raman spectra of the known tiotropium bromide monohydrate and the crystalline compound I in the range from 3250 to 2750 cm^{-1}



INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000049

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D451/10 A61K31/56 A61P11/06 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P		
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 practicable, search terms used) EPO-Internal, CHEM ABS Data, INSPEC		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2008/008376 A2 (SICOR INC [US]; SCARPITTA FRANCESCA [IT]; BUSOLLI JONATHAN [IT]; DIULG) 17 January 2008 (2008-01-17) example 18 ----- -/-	1,2, 4-10, 13-15
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 July 2012	Date of mailing of the international search report 30/07/2012	
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 Gregoire, Ariane	

INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2012/000049

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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