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(54) **Title:** ANHYDROUS CRYSTALLINE FORM OF TIOTROPIUM BROMIDE

(57) **Abstract:** The present invention relates to the crystalline substance comprising Tiotropium bromide and process that shall be used in production of the said substance.

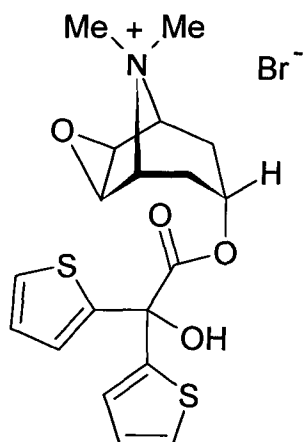


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ANHYDROUS CRYSTALLINE FORM OF TIOTROPIUM BROMIDE

The present invention relates to crystalline compound comprising Tiotropium bromide and the process that shall be used in production of said compound.

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



Tiotropium bromide is a long-acting, highly effective anticholinergic agent. It can be used in treatment of respiratory tract diseases, particularly in COPD (chronic obstructive pulmonary disease) and asthma.

Tiotropium bromide is preferably administered by the inhalation route in treatment of abovementioned diseases. In addition to the administration of broncholytically active agents in the form of metered aerosols and inhalable solutions, inhalable dry powders comprising the active agent also have particular importance.

Tiotropium bromide is preferably administered by the inhalation route. It can be used in powder form as filled into appropriate capsules or blisters suitable for inhalation. Alternatively, it can also be used in inhalable aerosol form. These forms also comprise powdered inhalable aerosols comprising HFA134a, HFA227 or a combination thereof as propellant gases.

Since tiotropium bromide is highly effective, only a small amount of the pharmaceutical active agent for each dose is sufficient in order to obtain desired therapeutic effect. Therefore, it is required that the pharmaceutical active agent should be diluted with a suitable excipient in order to prepare an inhalable powder. The amount of inhalable composition in each dose should be measured precisely. Due to high excipient content, inhalable powder properties are

significantly affected from excipient selection. Furthermore, particle size of the pharmaceutical active agent and excipient is important in terms of emptying capacity of capsule or blister used in inhaler.

5 The active agent 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.

Furthermore, the other physical characteristics such as water absorption and ease of grinding of the pharmaceutical active agent have also significant importance.

10 Proper production of the compositions of the abovementioned pharmaceutical active agent which are suitable for administration by inhalation depends on many parameters related to the nature of the active agent. In pharmaceutical compositions which are used in inhalable powder or aerosol forms such as tiotropium bromide, the crystalline active agent is used in ground (micronized) form in order to prepare the formulation. Since pharmaceutical quality of the
15 pharmaceutical formulation requires active agent to always have the same crystalline modification, the stability and characteristics of the crystalline active agent are the necessities that should be complied with from this point of view.

Furthermore, micronized powders to be taken by the inhalation route which have moisture ratio as low as possible prevent the product from agglomerating and provide it to be
20 transmitted into the target area more effectively. Therefore, one purpose of the present invention is to develop crystalline forms which have lower moisture content and are more stable as compared to the known crystalline forms.

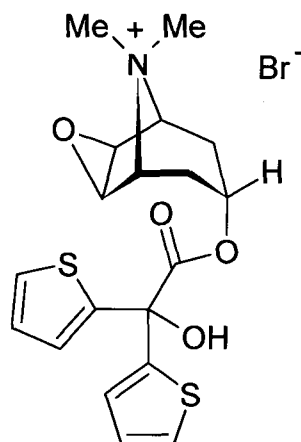
One purpose of the present invention is to provide salt form of tiotropium bromide having good chemical and/or physical stability and/or processability both as active agent and in
25 preparation of pharmaceutical compositions comprising tiotropium bromide.

Another purpose of the present invention is to provide a controlled and inexpensive production process and permanently qualified and reproducible Tiotropium bromide crystalline salts.

Tiotropium bromide has therapeutic efficiency even in very low doses as the pharmaceutical
30 active agent and this reveals the requirement that other active agents suitable for being

administered in the form of inhalable composition should be found. Therefore, another technical problem that the present invention relates to is to prepare useful tiotropium bromide dosage forms in inhalable composition form.

The technical problem underlying the present invention has been solved by the compound (Tiotropium bromide) figured in Formula I and having monoclinic elementary cell parameters of $a = 17.82 \text{ \AA}$, $b = 11.38 \text{ \AA}$, $c = 11.71 \text{ \AA}$, $\beta = 120.96^\circ$.



(Formula I)

The crystalline compound of the present invention can be mixed with suitable excipients so as to obtain an inhalable composition. The crystalline compound can be ground in order to adjust particle size exactly.

Grinding process can be applied to the crystalline compound of the present invention singly as well as applied to the crystalline compound of the present invention which is in combination with an excipient. At this point, grinding process can be performed by using the methods of hammer mill, jet mill, blade mill etc. Grinding process can be performed before preparation of the pharmaceutical composition comprising the crystalline compound of the present invention as well as during preparation of the pharmaceutical composition or before post-production storage of the pharmaceutical composition prepared.

In the case that blade mill is used, pulverization process is performed by the impact of the rotating blades in the device.

In the case that hammer mill is used, pulverization is performed by the impact of the rotating hammers in the device.

In the case that jet mill is used, pulverization is performed by providing collision of the particles with each other with the help of high-pressured and high-speed airstream.

Furthermore, the inhalable composition comprising the crystalline compound of the present invention can be stored without losing its effectiveness.

In addition to this, the crystalline compounds of the present invention are also stable in accelerated conditions. The crystalline compound can be stored at 40 °C without presenting any degradation or transformation. Consequently, the crystalline compound of the present invention can be used as a drug also in the countries which generally have high temperatures. The drug does not lose its effectiveness under high temperature.

One characteristic feature of the present invention is the pharmaceutical compositions comprising a pharmaceutically acceptable, nontoxic and therapeutically effective amount of the crystalline form of tiotropium bromide of the present invention and preparation methods thereof. The pharmaceutical compositions comprising the crystalline form of tiotropium bromide of the present invention are in the form of dry powder or pressurized metered dose-inhalation composition, preferably dry powder inhalation composition.

During preparation process of dry powder inhalation compositions, two methods are commonly implemented in order to transmit effective amount of the drug to the targeted area. One of them is based on controlled agglomeration of undiluted drug; the other one is based on adhesion of micronized drug 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 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 agent.

The term "micronized drug particles" refers to the crystalline of tiotropium bromide in accordance with the present invention.

Tiotropium bromide in crystalline form in accordance with 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 crystalline form 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" signifies that the carrier can be selected from a group comprising monosaccharides such as glucose or arabinose; disaccharides such as lactose, saccharose,

maltose; polysaccharides such as oligosaccharides, dextrans; polyalcohols such as sorbitol, mannitol, xylitol; salts such as sodium chloride, calcium carbonate. Preferably lactose, more preferably lactose monohydrate is used.

5 The pharmaceutical compositions of the present invention can comprise at least one inert carrier having large particle size or small particle size and optionally at least one excipient together. The inert carrier having large particle size is characterized by having an average particle size (d_{50}) in the range of 10-250 μm , preferably in the range of 10-150 μm , more preferably of 150 μm ; the inert carrier having small particle size, on the other hand, is characterized by having an average particle size (d_{50}) in the range of 1-10 μm , preferably of 10 μm . The inert carriers having large particle size and small particle size can be the same or different compounds.

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, gallats (such as propyl gallate), tocopherol, citric acid, malic acid, ascorbic acid, acetylcysteine, fumaric acid, lecithin, ascorbyl palmitate, ethylenediamine tetraacetate; carbohydrates such as sweeteners, lactose, glucose, fructose, galactose, sucrose, maltose, trehalose, maltodextrins, dextrans, cyclodextrins, starch and cellulose; polyalcohols such as sorbitol, mannitol and xylitol; aminoacids such as glycine, arginine, lysine, aspartic acid and glutamic acid; peptides such as human serum albumin; gelatine; various salts and taste masking agents. The 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 agent 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 agent.

The term “active agent” refers to the crystalline form of tiotropium bromide of the present invention. The crystal 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 the crystalline form of tiotropium bromide according to the present invention in the range of 0.001-50%, preferably in the range of 0.01-10%.

The term “average particle size” refers to 50% of volume distribution measured with a laser diffractometer.

The pharmaceutical compositions comprising the crystalline form of tiotropium bromide of the present invention can additionally comprise at least one active agent selected from drugs 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 form of tiotropium bromide of the present invention can be used separately, sequentially or simultaneously with at least one active agent selected from the specified group.

Another characteristic feature of the present invention is that the pharmaceutical compositions comprising the crystalline form of tiotropium bromide 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 the crystalline form of the present invention

Preparation process of dry powder inhalation compositions of the present invention comprises 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 sieved inert carrier having small particle size into tiotropium bromide in crystalline form in accordance with the present invention,
- 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 the final mixture ready to be filled into capsule/blister.

Preparation process of the pressurized metered-dose inhalation compositions comprises the following steps:

- 5 - cooling the production vessel to -25°C,
- pumping propellant gas into the vessel,
- adding tiotropium bromide in crystalline form in accordance with the present invention into the vessel and mixing the mixture obtained,
- filling the final mixture into the appropriate cups,

10 The terms “crystalline form of tiotropium bromide of the present invention” or “tiotropium bromide in crystalline form in accordance with the present invention” refer to tiotropium bromide having monoclinic elementary cell parameters of $a = 17.82 \text{ \AA}$, $b = 11.38 \text{ \AA}$, $c = 11.71 \text{ \AA}$, $\beta = 120.96$.

Examples for the pharmaceutical compositions comprising the crystalline form of the present invention

- 15 The examples of pharmaceutical formulation of the present invention are below. These examples are given in order to elucidate the subject of the present invention, though the subject of the present invention is not limited to these examples.

Example 1: Dry powder inhalation formulation

Content	Amount (mg)
Tiotropium bromide	0.0220
Lactose monohydrate ($d_{50}=150\mu\text{m}$)	19.9500
Lactose monohydrate ($d_{50}=10\mu\text{m}$)	5.0280
Total weight	25

20 Example 2: Dry powder inhalation formulation

Content	Amount (mg)
Tiotropium bromide	0.0215
Lactose monohydrate ($d_{50}=150\mu\text{m}$)	19.9500
Lactose monohydrate ($d_{50}=10\mu\text{m}$)	5.0285
Total weight	25

Example 3: Pressurized metered-dose inhalation formulation

Content	Amount (mg)
Tiotropium bromide	0.0225
HFA 134	74.98
Total weight	75.0025

Example 4: Pressurized metered-dose inhalation formulation

Content	Amount (mg)
Tiotropium bromide	0.0217
HFA 227	74.98
Total weight	75.0017

- 5 In another aspect, the present invention relates to the methods which are used in production of the crystalline form of tiotropium bromide of the present invention.

The crystalline form of tiotropium bromide of the present invention can be obtained by the method of crystallizing any crystalline form of Tiotropium bromide existing in the prior art with organic solvents.

- 10 The organic solvent or solvents that can be used are selected from a group comprising ethanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), benzene, toluene, diethyl ether, tetrahydrofuran, methanol, acetonitrile, acetone, ethyl acetate, methyl ethyl ketone, dichloromethane, dioxane, dimethylacetamide, N-methyl pyrrolidone, hexane, heptane or a combination thereof.
- 15 The following method is preferably implemented in preparation of the crystalline form of tiotropium bromide of the present invention;
- I. Tiotropium bromide is dissolved in dichloromethane
 - II. The mixture obtained is mixed
 - III. The solvent in the mixture is removed under low pressure
 - 20 IV. The solid substance obtained is dried under low pressure
 - V. The solid substance dried is mixed with a solvent combination comprised of acetone and methanol mixture

- VI. The suspension obtained is brought to boiling point and heating process continues until a clear solution is obtained
- VII. The clear solution obtained is put into an ice bath quickly
- VIII. The crystals precipitated are separated by filtration method
- 5 IX. The crystals obtained are dried under low pressure at a temperature of 100-115 °C.

Mixing process is implemented at a temperature of 20-50 °C, preferably at a temperature of 25-40 °C, more preferably at room temperature (approximately in the range of 20-30 °C) in step II.

- 10 The ratio of acetone and methanol, which are used, to each other by volume is in the range of 1:1 to 1:10, preferably in the range of 1:1 to 1:8, more preferably in the range of 1:2 to 1:6 in step V.

A method preferred that can be used in preparation of the crystalline form of tiotropium bromide of the present invention is composed of the following steps:

- 15 I. Dissolving tiotropium bromide in dichloromethane
- II. Stirring the mixture obtained at 25 °C
- III. Removing the solvent in the mixture under low pressure
- IV. Drying the solid substance obtained under low pressure
- V. Mixing the dried solid substance with a solvent combination comprising acetone
- 20 and methanol mixture in the ratio of 1:2 to 1:6
- VI. Bringing the suspension obtained to boiling point and heating until clear solution is obtained
- VII. Putting the clear solution occurred into an ice bath
- VIII. Separating the crystals precipitated by filtration method
- 25 IX. Drying the crystals obtained under low pressure at a temperature of 100-115 °C.

In both of the production methods clarified, the solid compound obtained as a result of implementing step IV comprises Tiotropium bromide (Formula I) and CH₂Cl₂ combination or a hydrate thereof, and the solid compound is characterized by having peaks at wavenumbers

30 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 (stated as ± 2 cm⁻¹) in FT-Raman spectrum.

The term “compound comprising tiotropium bromide (Formula I) and CH₂Cl₂ combination or a hydrate thereof” signifies that these two substances are in the same crystalline matrix or different crystalline/amorphous matrices.

5 The said compound comprising tiotropium bromide and CH₂Cl₂ combination is hereinafter referred to as “tiotropium bromide DCM solvate”.

Another method that can be used in preparation of the crystalline form of tiotropium bromide of the present invention is composed of the following steps;

- I. Dissolving tiotropium bromide DCM solvate in water
- II. Drying the solution obtained under low pressure at a temperature of 0 to -100 °C
- 10 III. Mixing the solid substance obtained with a solvent combination comprising acetone and methanol mixture
- IV. Mixing the mixture at a temperature of 0 to 20 °C
- V. Separating the crystals precipitated by filtration method
- VI. Drying the crystals obtained under low pressure at a temperature of 100-115 °C.

15

Optionally, between the steps III and IV, the following steps can be implemented:

- IIIa. Stirring the solution until precipitation is observed
- IIIb. Adding a solvent combination comprising acetone methanol mixture equivalent to the amount added in the step III after precipitation is observed.

20 In step III, the ratio of acetone and methanol, which are used, to each other by volume is in the range of 1:1 to 1:10, preferably in the range of 1:1 to 1:8, more preferably in the range of 1:2 to 1:6.

In step IV, the mixture is mixed preferably at a temperature of 1 to 15 °C, more preferably at a temperature of 3 to 10 °C.

25 Examples related to preparation method of crystalline form of tiotropium bromide of the present invention:

The examples related to preparation method of the crystalline form of tiotropium bromide of the present invention are given below. These examples are given in order to elucidate the

subject of the present invention, though the subject of the present invention is not limited to these examples.

X-Ray Powder Diffraction

The measurements have been carried out with Bruker D8 Advance powder X-ray
5 diffractometer which uses Cu K α source of radiation in Bragg-Brentano reflection geometry. Generally, the 2 θ values are accurate within an error of ± 0.1 - 0.2° . Relative peak intensity can change significantly for different samples which have the same crystalline form due to different positioning of crystals. The samples have not been subjected to any special operation except a slight pressure applied in order to obtain a smooth surface. Single-crystal silicon
10 sample holders having 1.0, 0.5 mm or 0.1 mm depth and 12 mm cavity diameter have been used. Tube voltage and current values are respectively 40 kV and 40 mA. The X-ray powder diffractometer is equipped with a LynxEye detector. A variable divergence slight is used with a 3° window. Step size is $0.02^\circ 2\theta$, and step time is 37 seconds. The samples have been rotated at the rotation speed of 0.5 per second during measurement.

15 Structural resolution and refinement of crystalline structure is implemented with the help of direct methods (programmes such as SHELXS86, SHELXS97) and FMLQ refinement (programmes such as TeXsan, SMART etc.).

The pattern analysis implemented has shown that the crystalline anhydrous tiotropium bromide has a monoclinic cell having the following sizes:

20 $a = 17.82 \text{ \AA}$, $b = 11.38 \text{ \AA}$, $c = 11.71 \text{ \AA}$, $\beta = 120.96$.

FT-Raman spectroscopy

Raman spectrums have been recorded by Bruker RFS100 Raman spectrometer equipped with a germanium detector and Nd:YAG laser with an excitation wavelength of 1064 nm. A few milligrams of the substance have been pressed into aluminium sample holders. Spectra have
25 been measured in the range of 50-3500 cm^{-1} and with resolution of 2 cm^{-1} by using laser power of 300 mW. 64 scans have been collected.

Example 1:

Tiotropium bromide (10 g) is dissolved in 50 ml of dichloromethane. The mixture is mixed at room temperature for 24 hours. Then, dichloromethane comprised in the mixture is removed under low pressure. The solid substance obtained is dried under low pressure. The substance
5 dried is mixed with 100 ml acetone methanol mixture in the ratio of (1:4). The mixture obtained is heated at boiling point until a clear solution is obtained. After a clear solution is obtained, heating process is stopped and the cup comprising the solution is transferred into an ice bath. Said mixture is kept in ice bath for 5 hours. After this time, the crystals occurred are separated from the mixture by filtration method. The crystals obtained are dried under low
10 pressure at a temperature of 110 to 115 °C. Tiotropium bromide having monoclinic elementary cell parameters of $a = 17.82 \text{ \AA}$, $b = 11.38 \text{ \AA}$, $c = 11.71 \text{ \AA}$, $\beta = 120.96^\circ$ determined by X-ray analysis is obtained (52 % efficiency).

Example 2:

Tiotropium bromide (10g) is dissolved in 50 ml of dichloromethane. The mixture is stirred at
15 room temperature for 24 hours. Then, dichloromethane comprised in the mixture is removed under low pressure at room temperature. The solid substance obtained is dried under low pressure. The substance dried is dissolved in 100 ml of water. The mixture occurred is dried (lyophilized) under low pressure at a temperature of -80 °C. 100 ml of acetone methanol mixture in the ratio of (1:5) is added into the solid substance obtained and the solution is
20 mixed at a temperature of 8 °C for 10 hours. After this time, the crystals occurred are separated from the mixture by filtration method. The crystals obtained are dried under low pressure at the temperature of 110 to 115 °C. Tiotropium bromide having monoclinic elementary cell parameters of $a = 17.82 \text{ \AA}$, $b = 11.38 \text{ \AA}$, $c = 11.71 \text{ \AA}$, $\beta = 120.96^\circ$ determined by X-ray analysis is obtained. (82% efficiency)

CLAIMS

1. An anhydrous crystalline tiotropium bromide having monoclinic elementary cell parameters of $a=17,82 \text{ \AA}$, $b=11,38 \text{ \AA}$, $c=11,71 \text{ \AA}$, $\beta=120,96^\circ$ determined by X-ray analysis.
- 5 2. The anhydrous crystalline tiotropium bromide according to claim 1, characterized in that said anhydrous crystalline tiotropium bromide is comprised in a pharmaceutical composition.
3. The pharmaceutical composition according to claim 2, characterized in that said composition is in the form of dry powder or pressurized metered-dose inhalation
10 composition.
4. The pharmaceutical composition according to claim 2, characterized in that said composition comprises at least one pharmaceutically acceptable inert carrier in addition to tiotropium bromide.
5. The pharmaceutical composition according to claims 3-4, wherein the inert carrier is
15 lactose.
6. The pharmaceutical composition according to claims 3-5, wherein the inert carrier is lactose monohydrate.
7. The pharmaceutical composition according to claims 3-6, wherein the inert carrier is composed of two different fractions as large particle-size and small particle-size.
- 20 8. The pharmaceutical composition according to claim 7, wherein the small particle-size inert carrier has an average particle size in the range of 10-250 μm .
9. The pharmaceutical composition according to claim 7, wherein the small particle-size inert carrier has an average particle size in the range of 1-10 μm .
10. The pharmaceutical composition according to claims 7-9, wherein the large particle-size
25 and small particle-size inert carriers can be the same or different compounds.
11. The pharmaceutical composition according to claims 2-10, wherein said composition comprises at least one excipient along with the inert carrier.

12. The pharmaceutical composition according to claim 11, wherein the excipient is 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; aminoacids such as glycine, arginine, lysine, aspartic acid and glutamic acid; peptides such as human serum albumin; gelatine; various salts and taste masking agents; 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 ethers; antioxidants such as butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulphide, gallats (such as propyl gallate), tocopherol, citric acid, malic acid, ascorbic acid, acetylcysteine, fumaric acid, lecithin, ascorbyl palmitate, ethylenediamine tetraacetate; and sweeteners.
13. The pharmaceutical composition according to claims 2-12, wherein tiotropium bromide comprised in the composition has an average particle size in the range of 1-10 μm .
14. The pharmaceutical composition according to claims 2-13, wherein tiotropium bromide comprised in the composition has an average particle size in the range of 1-5 μm .
15. The pharmaceutical composition according to claims 2-14, wherein said composition comprises tiotropium bromide in the range of 0.001 – 10%.
16. The pharmaceutical composition according to claims 2-14, wherein said composition comprises at least one active agent selected from drugs such as other anticholinergic agents, adrenergic agonists, antiallergic agents, anti-inflammatory agents, antihistaminics, steroids, leukotriene receptor antagonists, antimuscarinic agents, PDE inhibitors and EGFR inhibitors.
17. The pharmaceutical composition according to claim 16, wherein tiotropium bromide and the agent used in addition to tiotropium bromide can be used separately, sequentially or simultaneously.
18. A method that shall be used in preparation of anhydrous tiotropium bromide having monoclinic elementary cell parameters of $a = 17,82 \text{ \AA}$, $b = 11,38 \text{ \AA}$, $c = 11,71 \text{ \AA}$, $\beta =$

120,96° determined by X-ray analysis, characterized in that said method is composed of the following steps:

- I. Dissolving tiotropium bromide in dichloromethane
- II. Stirring the mixture obtained
- 5 III. Removing the solvent in the mixture under low pressure
- IV. Drying the solid substance obtained under low pressure
- V. Mixing the solid substance dried with a solvent combination comprising the acetone and methanol mixture
- VI. Bringing the suspension occurred to boiling point and heating until a clear solution
10 is obtained
- VII. Putting the clear solution occurred into an ice bath
- VIII. Separating the crystals precipitated by filtration method
- IX. Drying the crystals obtained under low pressure at a temperature of 100-115 °C.

19. The method according to claim 18, characterized in that mixing process clarified in step II
15 is applied at a temperature between 20-50 °C.

20. The method according to claims 18-19, wherein the ratio of acetone and methanol, which are used, to each other in the step V is in the range of 1:1 to 1:10 by volume.

21. The method according to claims 18-20, characterized in that said method composed of the following steps:

- 20 I. Dissolving tiotropium bromide in dichloromethane
- II. Stirring the mixture obtained at a temperature of 25 °C
- III. Removing the solvent in the mixture under low pressure
- IV. Drying the solid substance obtained under low pressure
- V. Mixing the solid substance dried with a solvent combination comprising acetone
25 and methanol mixture in the ratio of 1:2 to 1:6
- VI. Bringing the suspension occurred to boiling point and heating until a clear solution is obtained
- VII. Putting the clear solution occurred into an ice bath
- VIII. Separating the crystals precipitated by filtration method
- 30 IX. Drying the crystals obtained under low pressure at a temperature of 100-115 °C.

22. The method according to claims 18-21, characterized in that tiotropium bromide dichloromethane (DCM) solvate is obtained as a result of step IV.

23. A method that shall be used in preparation of anhydrous tiotropium bromide having monoclinic elementary cell parameters of $a = 17,82 \text{ \AA}$, $b = 11,38 \text{ \AA}$, $c = 11,71 \text{ \AA}$, $\beta = 120,96^\circ$ determined by X-ray analysis, characterized in that said method is composed of the following steps:

- 5 I. Dissolving tiotropium bromide DCM solvate in water
- II. Drying the solution obtained under low pressure at a temperature between 0 and -100 °C
- III. Mixing the solid substance with a solvent combination comprising acetone and methanol mixture
- 10 IV. Stirring the mixture at a temperature between 0 and 20 °C
- V. Separating the crystals precipitated by filtration method
- VI. Drying the crystals obtained under low pressure at a temperature between 100-115 °C.

24. The method according to claim 23, characterized in that said method is composed of the
15 steps:

IIIa. Mixing the solution obtained until precipitation is observed

IIIb. Adding a solvent combination comprising acetone methanol mixture equivalent to the amount added in step III after precipitation is observed.

25. The method according to claims 23 and 24, characterized in that the ratio of acetone and
20 methanol, which are used, to each other is in the range of 1:1 to 1:10 by volume in step III.

26. The method according to claims 23-25, characterized in that the mixture is mixed at a temperature between 1 and 15 °C in step IV.

27. The anhydrous tiotropium bromide having monoclinic elementary cell parameters of $a = 17.82 \text{ \AA}$, $b = 11.38 \text{ \AA}$, $c = 11.71 \text{ \AA}$, $\beta = 120.96^\circ$ determined by X-ray analysis,
25 characterized in that said anhydrous tiotropium bromide is used in production of a drug that shall be used in treatment of asthma and COPD.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000050

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

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

International application No
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