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US-A- 3 717 634
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CHEMICAL ABSTRACTS, vol.96, no. 19, May 10, 1982, Columbus, Ohio, USA; BRISTOL-MYERS CO.: "Quaternary ammonium compounds and n-[[N-(2-pyrimidinyl)piperazinyl]alkyl] azaspiroalkanediones", page 761, column 1 , abstract-no. 162739g

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CHEMICAL ABSTRACTS, vol. 107, no. 1, July 6, 1987, Columbus, Ohio, USA; VILA CASAS A. et al.: "Process for the preparation of 8-[[4-(2-pyrimidinyl)-1-piperazinyl]alkyl]-8-azaspiro[4.5]decane-7,9-diones", page 668, column 1, abstract-no. 7215k

CHEMICAL ABSTRACT, vol. 108, no. 1, January 4, 1988, Columbus, Ohio,USA; AGUIRRE ORMAZA V.: "Process for the preparation of heterocyclyl-substituted piperazinyl- and perhydrodiazepinylalkylazaspirodecanediones", page 576,column 2, abstract-no. 6045p

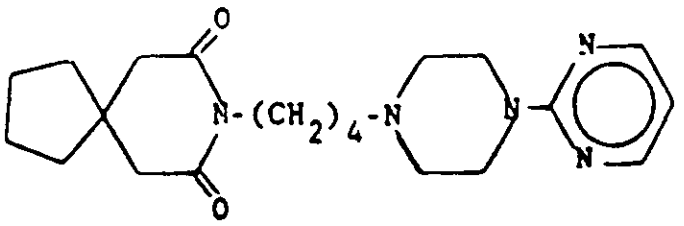
CHEMICAL ABSTRACTS, vol. 106, no. 3, January 19, 1987, Columbus, Ohio, USA; COLL PALLARES R.: "(Pyrimidinylpiperazinylalkyl)azaspirodecanediones", page 615, column 1, abstract-no. 18622w

CHEMICAL ABSTRACTS, vol. 106, no. 9, March 2, 1987, Columbus, Ohio, USA; VILA CASAS A. et al.: "Process for the preparation of 8-[[4-(2-pyrimidinyl)-1-piperazinyl]alkyl]-8-azaspiro[4,5]decane-7,9-diones", page 617, column 1, abstract-no. 67350q

Description

This invention relates to the lower melting polymorphic crystalline form of buspirone hydrochloride having a melting point of about 188-192 °C,
a process for preparing and a pharmaceutical composition containing this compound.

The psychotropic compound with which the present invention is concerned has the following structural formula:



and is known as buspirone. The hydrochloride salt has been referred to in the prior art as MJ 9022-1 and as buspirone hydrochloride. Other acid addition salts thereof are named by combining "buspirone" with the appropriate word to define the acid from which it is prepared as in "buspirone hydrochloride". The latter is the United States Adopted Name (USAN): refer to J. American Med. Assoc. 225, 520 (1973). Buspirone is currently approved for marketing as an effective clinical anti-anxiety agent.

The synthesis of the compound and the disclosure of its psychotropic properties are described in the following representative patents and publications.

1. Y. H. Wu. et al., J. Med. Chem., 15.477 (1972).
2. Y. H. Wu. et al., U. S. Pat. No. 3.717.634 which issued Feb. 20, 1973.
3. L. E. Allen et al., Arzneium Forsch., 24 No. 6 917-922 (1974).
4. G. L. Sathananthan, et al., Current Therapeutic Research. 18/5, 701-705 (1975).
5. Y. H. Wu. et al., U. S. Pat. No. 3,976,776, issued Aug. 24, 1976.
6. J. C. Simms. U. S. Pat. No. 4,351,939, issued Sept. 28, 1982.

The melting point disclosed for buspirone hydrochloride in the above-listed references is 201.5 to 202.5 °C. No other melting point values outside a range of 201 to 205° for pure buspirone hydrochloride has been previously disclosed. As one aspect of the instant invention it has been discovered that solid buspirone hydrochloride can exist in two different crystalline phases. The capacity to occur in different crystal structures is known as polymorphism and is known to occur in many organic compounds including drugs. These different crystalline forms are known as "polymorphic modifications" or "polymorphs" and are realized only in the crystalline state. While polymorphic modifications have the same chemical composition, they differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. As such, these modifications may have different solid-state physical properties such as shape, color, density, hardness, deformability, stability, dissolution properties, and the like. Polymorphism of an organic drug molecule and its consequences would be appreciated by one skilled in the pharmaceutical arts.

In the manufacture of pharmaceutical supplies of buspirone hydrochloride, certain specified criteria, such as the melting point for example, defining physical characterization and purity of the pure drug substance must be met before it can be incorporated into pharmaceutical compositions for medicinal purposes. Satisfying these criteria is one requirement of the approvability process allowing continued distribution of drug product under good manufacturing procedure guidelines and regulations set forth by governmental agencies such as the Food and Drug Agency (FDA) in the U. S. Compliance with governmental regulations for drug manufacture requires meeting with requisite drug substance specifications as well as keeping related records and other quality assurance procedures for each batch of drug substance to be put into the pharmaceutical product manufacturing process. These requirements are required of every drug manufacturer for every drug falling under purview of the FDA or other appropriate governmental drug agency.

In the course of preparing larger batch lots of buspirone hydrochloride, a problem was experienced in meeting the specified melting point criterion. Closer examination led to the unexpected discovery of a second polymorphic modification of buspirone hydrochloride. This second polymorphic modification displays a melting point of about 188° as compared with the melting point of about 202 to 204° for the originally discovered polymorphic form. Since the extensive, expensive and time-consuming clinical studies required for drug approval were done with the original polymorph (designated P203), the specifications for

drug substance are for this polymorph in the approved New Drug Application (NDA) of buspirone. However, increasing difficulty was experienced in continued preparation of P203 and, to add further complication, some batches of P203 underwent partial conversion to P188 during storage.

It is therefore an object of this invention to be able to reliably provide a crystalline form of buspirone hydrochloride which can be produced, stored, and compounded while continuing to meet its required specifications for a pure drug substance. It is a further object of this invention to provide a reliable process whereby whichever polymorphic form desired, P188 or P203, can be conveniently and reproducibly prepared.

Other objects, aspects and advantages of this invention will become apparent from reading the remaining specification and the claims which follow.

SUMMARY OF THE INVENTION

It has been found that buspirone hydrochloride can exist in two distinct polymorphic forms and when crystallized under equilibrium conditions at temperatures above about 95 °C, the higher melting polymorphic modification is obtained and when crystallization proceeds under equilibrium conditions at temperatures below about 95 °C, the lower melting polymorphic modification is obtained. It has also been found that the lower melting polymorph is the thermodynamically-favored form at pharmaceutically relevant temperatures. As a result of these discoveries, processes have been developed for the reliable production of either polymorphic modification of buspirone hydrochloride. In addition it has been found that the newly discovered lower melting polymorph provides a manufacturing advantage over the higher melting polymorph due to its retention of specified physical characteristics under pharmaceutically relevant storage and manufacturing conditions.

DETAILED DESCRIPTION OF THE INVENTION

Research carried out to investigate solid state behavior of the useful anxiolytic drug, buspirone hydrochloride, has resulted in the discovery that it can exist in the solid state in the form of two polymorphic modifications. Further it was discovered that the two polymorphic modifications of solid buspirone hydrochloride could exist in equilibrium with each other at a transition temperature of about 95 °C and that the lower-melting polymorph, P188, was thermodynamically favored at temperatures below and the higher-melting polymorph, P203, was favored at temperatures above this transition temperature. These discoveries have led to the development of useful, reliable processes which enable one to produce whichever polymorph one desires.

Previous methods of crystallization of buspirone hydrochloride generally employed alcoholic solvents, usually ethanol or isopropanol, and temperatures below 95 °C. Under conditions of these methods, solid crystalline buspirone hydrochloride was forced from solution by chilling and the liberal use of P203 seed crystals. These conditions are understood to favor kinetic, or rate, control of product crystals and the high melting polymorph was usually produced with such methodology. It turned out that use of such kinetic-controlled methods, where rate of crystallization favored the P203 polymorph, became less and less reliable and the resultant crystalline product was usually contaminated with the P188 polymorph. The problem that this other polymorph contamination causes is that an entire batch or lot of drug substance now does not meet the required physical specifications for incorporation into pharmaceutical products and must be reworked. It is to be appreciated that considerable time and expense is involved in reworking large lots of buspirone hydrochloride in order to meet FDA specifications.

One aspect of this invention is a process which reliably converts the higher melting polymorph or a mixture of the two buspirone hydrochloride polymorphs into the lower melting polymorph. In its most general form this process comprises the steps of:

a) disrupting the crystalline structure of solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the two starting polymorphic forms of buspirone hydrochloride; and

b) allowing recrystallization to occur under equilibrium conditions at temperatures lower than about 95 °C.

Disruption of the crystalline structure encompasses processes ranging from crystal structure relaxation due to application of heat, to dissolution of the solid crystal by a suitable solvent, a combination of heat and dissolution, and even sublimation processes. Dissolution need only be partial, and in fact polymorph conversion can proceed under certain conditions of high humidity. In these humidity promoted polymorphic conversions, moisture-mediated dissolution: crystallization equilibrium is established and sorption processes, in particular capillary condensation, come into play. The strong influence of humidity on some

polymorphic transformations is discussed by Ramberger, et al., Ber. Bunsenges. Phys. Chem. 84, 1261-1264 (1980).

Similarly, polymorphic conversions can be accomplished in solvents in which buspirone hydrochloride has only low solubility even at elevated temperatures. In these instances, usually selected for obtaining P203, the solid is heated above the transition temperature until conversion is complete and then the mixture is allowed to cool and the desired polymorph is isolated with negligible contamination.

Preferred processes of this invention are carried out in a liquid medium with agitation. The process temperature is suitably slected and the liquid medium selected is generally one in which buspirone hydrochloride has some solubility.

The preferred process involves the following steps:

a) disrupting the crystal structure of solid buspirone hydrochloride by dissolution by the liquid medium,

b) allowing recrystallization to occur in a selected temperature range below 95 °C,

c) agitating the solid buspirone hydrochloride: liquid medium mixture for a time sufficient to obtain solid:solution equilibrium in the mixture; and

d) separating the desired crystalline polymorph from the liquid component of the mixture.

Disruption of the crystalline structure of solid buspirone hydrochloride by dissolution of the liquid medium encompasses a range of dissolution processes from complete dissolution to only slight dissolution. Degree of dissolution can be modified by selection of the appropriate liquid media and/or by selection of process temperature within the specified allowable temperature range. Recrystallization temperatures are selected ranging below a temperature of about 95 °C The agitation of the process mixture is carried out in the same temperature range as for the recrystallization and continues until solid/solution equilibrium has been established. The establishment of equilibrium conditions is required for these thermal processes so that thermodynamic selection of the favored polymorph dominates. The crystalline polymorph is then isolated, preferably by simple filtration.

The preferred process comprises the steps of:

a) disrupting the crystal structure of solid buspirone hydrochloride by dissolution in a suitable liquid medium;

b) allowing recrystallization to occur while the temperature is kept below about 95 °C;

c) while maintaining the temperature below about 95 °C, the solid buspirone hydrochloride: liquid medium mixture is agitated for a period of time sufficient to obtain solid/solution equilibrium; and

d) separating the desired low-melting polymorph from the liquid component of the mixture.

The process for production of the high melting polymorph is described in EP-A-88 113 969.

Certain preferred processes are those in which steps a), b), and c) are combined so that the solid buspirone hydrochloride is continuously undergoing liquid medium mediated dissolution-crystallization processes at the selected temperatures until the solid buspirone hydrochloride is constituted entirely of the desired polymorph. This crystalline product is then isolated according to step d). For these preferred processes most of the buspirone hydrochloride is suspended in the liquid medium as a solid with only minor amounts in solution. The production of P188 is preferably carried out in solvents such as isopropyl alcohol, acetonitrile and methyl ethyl ketone. The preferred process for production of P188 employs isopropyl alcohol in the temperature range of about 25 to 60 °C. Identification and semi-quantification of the polymorph utilize micro-methods such as thermomicroscopy, infrared spectroscopy and thermal analysis, especially differential scanning calorimetry (DSC) which was particularly useful in investigating the polymorphic forms and their transformations according to the instant invention.

In essence, the polymorph production processes developed for buspirone hydrochloride are intended to encompass any and all thermal processes which rely on thermodynamic selection of the polymorph below the transition temperature. Choice of temperatures and conversion media will affect the rates of conversion. Disclosure of these processes will be extended by reference to the specific examples which can be found hereinbelow appearing before the claims.

Another aspect of the invention is the discovery that the low-melting polymorphic modification is the energetically favored form under pharmaceutically relevant conditions and temperatures. This aspect becomes very useful for medicinal production because of the unique regulatory climate governing manufacture of pharmaceuticals. "Good manufacturing practices" as set forth and overseen by governmental drug regulatory agencies such as FDA in the U. S. require establishment of specifications for all pure drug substances and all lots of drug must be in compliance with these specifications. In the case of buspirone hydrochloride, prior art crystallization procedures which rely on kinetic control of crystallization have now been found to result in a mixture of both polymorphs, thereby causing additional expense and process time in order to produce the P203 form in order to meet NDA specifications. Additionally, lots of P203 occasionally undergo partial transformation during bulk storage thereby causing rejection of those lots for

subsequent manufacture of the final pharmaceutical composition product. Not only is rework of these converted lots costly but orderly manufacture of product can be interrupted by a shortage of pure drug substance. These delays and added expenses can be eliminated by adoption of the P188 polymorph as a pure drug substance and amendment of the buspirone NDA to incorporate the P188 specifications. Utilization of the P188 polymorph will improve manufacturability of buspirone pharmaceutical products. Procedures for buspirone pharmaceutical products are given in selected references listed in the Background of the Invention section, supra. In particular, U.S. 3,717,634 and U.S. 4,182,763 describe pharmaceutical compounding of buspirone hydrochloride and its analogs and these patents are hereby incorporated herein by reference. The P188 polymorph can be substituted readily for P203 and maintain operability of these procedures for compounding buspirone pharmaceutical products. The P188 polymorph can also be utilized for the therapeutic purposes already shown for the P203 polymorph, such as for treatment of anxiety in patients in need of such treatment.

In summary, utilization of the newly discovered P188 polymorph of buspirone hydrochloride improves manufacturability of buspirone pharmaceutical products.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS.

Polymorphic modifications and the processes for their preparation and interconversion which constitute this invention will appear more fully from a consideration of the following examples which are given for the purpose of illustration only and are not to be construed as limiting invention in sphere or scope. All temperatures are understood to be in degrees C when not specified. In addition to the elemental analysis data which is given, spectra of the product polymorphs was consistent with the assigned buspirone hydrochloride structure.

Preparation of P188 Buspirone Hydrochloride

Example 1

Buspirone HCl P203 to P188 Conversion in Isopropanol

A suspension of 5 g (0.118 mol) of buspirone HCl P203 polymorph in 17 mL of isopropanol was heated at 40-42 °C for 20 hrs. The suspension was cooled to ambient temperature and the solid collected on a filter, washed with several portions of anhydrous ether, and dried under reduced pressure at 50 °C. giving 4 g buspirone HCl, P188 polymorph, mp 190-192 °C (uncorr).

Anal. Calc'd. for $C_{21}H_{31}N_5O_2 \cdot HCl$			
C,59.77;	H,7.65;	N,16.60;	Cl,8.40
C,59.97;	H,7,49;	N,16.56;	Cl,8.17

IR (KBr) and NMR ($CDCl_3$) spectra were consistent with structure.
DSC, 3.03 mg sample 10 deg/min, onset, 189.6 °C

Example 2

Buspirone HCl P203 to P188 Conversion in Acetonitrile

A suspension of 5 g (0.0118 mol) of buspirone HCl P203 polymorph in 25 mL of acetonitrile was heated at reflux until a complete solution was obtained. The solution was allowed to cool at 60 °C at which temperature crystallization occurred. The reaction mixture was stirred at 60 °C for 22 hrs., then cooled at 25.5 °C The solid was collected on a filter and washed with THF. After drying under reduced pressure at 50 °C, 3.8 g of buspirone HCl P188 polymorph was obtained, mp 189-191 °C

Anal. Calc'd. for $C_{21}H_{31}N_5O_2 \cdot HCl$			
C,59.77;	H,7.65;	N,16.60;	Cl,8.40
C,59.50;	H,7.46;	N,16.60;	Cl,8.25

IR (KBr) and NMR ($CDCl_3$) spectra were consistent with structure.
DSC 6.55 mg sample 10 deg/min. onset 190 °C

Example 3

Buspirone HCl P203 to P188 Conversion in Methyl Ethyl Ketone

A suspension of 5 g (0.0118 mol) of buspirone HCl P203 polymorph in 25 mL of methyl ethyl ketone was heated to reflux for one hour. The solid did not dissolve. The suspension was cooled to 60 °C and stirred at this temperature for 25 hrs. After cooling to ambient temperature, the solid was collected on a filter, washed with several portions of anhydrous ether, and dried under reduced pressure at 50 °C giving 2.5 g of buspirone P188 polymorph, mp 189-190 °C.

Anal. Calc'd. for $C_{21}H_{31}N_5O_2 \cdot HCl$			
C,59.77;	H,7.65;	N,16.60;	Cl,8.40
C,59.61;	H,7.62;	N,16.24;	Cl,8.30

IR (KBr) and NMR ($CDCl_3$) spectra were consistent with structure.
DSC. 3.81 mg sample, 10 deg/min, onset 189.3 °C.

Example 4

Large-Scale Preparation of P188 Buspirone Hydrochloride

A 30 gallon glass reactor was charged with isopropyl alcohol (47.6 Kg), buspirone free base (17.0 Kg) and hydrochloric acid, 37% (4.4 Kg) with continuous stirring. The mixture was heated to reflux and Darco G-60 (0.85 Kg) was added. The resulting hot mixture was filtered through a filter aid bed and washed with hot isopropyl alcohol (8.0 Kg). The resulting solution was slowly cooled and allowed to stir for 24 hrs. at approximately 25 °C. The resulting slurry was then cooled to 5 °C and the white solid collected and dried under vacuum at 60 °C.
Yield: 16.86 Kg; 91%; P188 buspirone hydrochloride.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The lower melting polymorphic crystalline form of buspirone hydrochloride, characterized by a melting point of about 188 °C to 192 °C.

2. The use of the lower melting buspirone hydrochloride polymorph of Claim 1 for preparing a pharmaceutical composition for treating anxiety in a patient in need of such treatment.

3. A pharmaceutical composition comprising the lower melting buspirone hydrochloride polymorph of Claim 1 and a carrier.

4. A process for preparing the lower melting polymorphic crystalline form of buspirone hydrochloride as defined in Claim 1 comprising
   a) disrupting the crystalline structure of solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the higher and lower melting crystalline form of buspirone hydrochloride, and
   b) allowing recrystallization to occur under equilibrium conditions at a temperature lower than about 95 °C.

5. The process of Claim 4 wherein the crystalline structure of said solid buspirone hydrochloride is disrupted by dissolution in a liquid medium and the lower melting polymorphic crystalline form is separated from the liquid medium.

6. The process of Claim 5, wherein solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the higher and lower melting crystalline form of buspirone hydrochloride is agitated in a liquid medium at a temperature lower than about 95 °C, for a time sufficient to ensure that the solid buspirone hydrochloride is constituted entirely of the lower melting polymorph.

7. The process of Claim 5 or 6, wherein the liquid medium is selected from the group consisting of acetonitrile, isopropanol, and methyl ethyl ketone.

8. The process of Claim 6, wherein the liquid medium is isopropanol and the temperature is from 25 °C to 60 °C.

Claims for the following Contracting State : ES

1. A process for preparing the lower melting polymorphic crystalline form of buspirone hydrochloride, having a melting point of about 188 °C to 192 °C, comprising
   a) disrupting the crystalline structure of solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the higher and lower melting crystalline form of buspirone hydrochloride, and
   b) allowing recrystallisation to occur under equilibrium conditions at a temperature lower than about 95 °C.

2. The process of Claim 1 wherein the crystalline structure of said solid buspirone hydrochloride is disrupted by dissolution in a liquid medium and the lower melting polymorphic crystalline form is separated from the liquid medium.

3. The process of Claim 2, wherein solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the higher and lower melting crystalline form of buspirone hydrochloride is agitated in a liquid medium at a temperature lower than about 95 °C, for a time sufficient to ensure that the solid buspirone hydrochloride is constituted entirely of the lower melting polymorph.

4. The process of Claim 2 or 3, wherein the liquid medium is selected from the group consisting of acetonitrile, isopropanol, and methyl ethyl ketone.

5. The process of Claim 3, wherein the liquid medium is isopropanol and the temperature is from 25 °C to 60 °C.

6. A process for preparing a pharmaceutical composition which comprises incorporating the lower melting buspirone hydrochloride polymorph as defined in Claim 1 into a carrier.

Claims for the following Contracting State : GR

1. The lower melting polymorphic crystalline form of buspirone hydrochloride, characterized by a melting point of about 188 °C to 192 °C.

2. The use of the lower melting buspirone hydrochloride polymorph of Claim 1 for preparing a pharmaceutical composition for treating anxiety in a patient in need of such treatment.

3. A process for preparing a pharmaceutical composition which comprises incorporating the lower melting buspirone hydrochloride polymorph of Claim 1 into a carrier.

4. A process for preparing the lower melting polymorphic crystalline form of buspirone hydrochloride as defined in Claim 1 comprising

a) disrupting the crystalline structure of solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the higher and lower melting crystalline form of buspirone hydrochloride, and

b) allowing recrystallisation to occur under equilibrium conditions at a temperature lower than about 95 °C.

5. The process of Claim 4 wherein the crystalline structure of said solid buspirone hydrochloride is disrupted by dissolution in a liquid medium and the lower melting polymorphic crystalline form is separated from the liquid medium.

6. The process of Claim 5, wherein solid buspirone hydrochloride containing the higher melting polymorphic crystalline form or a mixture of the higher and lower melting crystalline form of buspirone hydrochloride is agitated in a liquid medium at a temperature lower than about 95 °C, for a time sufficient to ensure that the solid buspirone hydrochloride is constituted entirely of the lower melting polymorph.

7. The process of Claim 5 or 6, wherein the liquid medium is selected from the group consisting of acetonitrile, isopropanol, and methyl ethyl ketone.

8. The process of Claim 6, wherein the liquid medium is isopropanol and the temperature is from 25 °C to 60 °C.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Niedriger schmelzende, polymorphe, kristalline Form von Buspironhydrochlorid, gekennzeichnet durch einen Schmelzpunkt von etwa 188 °C bis etwa 192 °C.

2. Verwendung des niedriger schmelzenden, polymorphen Buspironhydrochlorids gemäß Anspruch 1 zur Herstellung eines pharmazeutischen Mittels zur Behandlung von Angst bei einem Patienten, der dieser Behandlung bedarf.

3. Pharmazeutisches Mittel, umfassend das niedriger schmelzende, polymorphe Buspironhydrochlorid gemäß Anspruch 1 und einen Träger.

4. Verfahren zur Herstellung der niedriger schmelzenden, polymorphen, kristallinen Form von Buspironhydrochlorid gemaß Anspruch 1, wobei man

a) die kristalline Struktur von festem Buspironhydrochlorid zerstört, das die höher schmelzende, polymorphe, kristalline Form oder ein Gemisch aus höher und niedriger schmelzender kristalliner Form von Buspironhydrochlorid enthält,

und man

b) eine Rekristallisation unter Gleichgewichtsbedingungen bei einer Temperatur von weniger als etwa 95 °C erfolgen läßt.

5. Verfahren nach Anspruch 4, worin die Zerstörung der kristallinen Struktur von festem Buspironhydrochlorid durch Auflösen in einem Flüssigmedium erfolgt und die niedriger schmelzende, polymorphe, kristalline Form aus dem Flüssigmedium abgetrennt wird.

6. Verfahren nach Anspruch 5, worin festes Buspironhydrochlorid, welches die höher schmelzende, polymorphe, kristalline Form oder ein Gemisch aus höher und niedriger schmelzender kristalliner Form von Buspironhydrochlorid enthält, in einem Flüssigmedium bei einer Temperatur von weniger als etwa 95 °C über eine Zeitspanne bewegt wird, die ausreicht, um zu gewährleisten, daß das feste Buspironhydrochlorid ausschließlich aus der niedriger schmelzenden, polymorphen Form besteht.

7. Verfahren nach Anspruch 5 oder 6, worin das Flüssigmedium ausgewählt ist unter Acetonitril, Isopropanol und Methylethylketon.

8. Verfahren nach Anspruch 6, worin das Flüssigmedium Isopropanol ist und die Temperatur 25 °C - 60 °C beträgt.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung der niedriger schmelzenden, polymorphen, kristallinen Form von Buspironhydrochlorid mit einem Schmelzpunkt von etwa 188 °C bis 192 °C, wobei man
   a) die kristalline Struktur von festem Buspironhydrochlorid zerstört, das die höher schmelzende, polymorphe, kristalline Form oder ein Gemisch aus höher und niedriger schmelzender kristalliner Form von Buspironhydrochlorid enthält,
   und man
   b) eine Rekristallisation unter Gleichgewichtsbedingungen bei einer Temperatur von weniger als etwa 95 °C erfolgen läßt.

2. Verfahren nach Anspruch 1, worin die Zerstörung der kristallinen Struktur von festem Buspironhydrochlorid durch Auflösen in einem Flüssigmedium erfolgt und die niedriger schmelzende, polymorphe, kristalline Form aus dem Flüssigmedium abgetrennt wird.

3. Verfahren nach Anspruch 2, worin festes Buspironhydrochlorid, welches die höher schmelzende, polymorphe, kristalline Form oder ein Gemisch aus höher und niedriger schmelzender kristalliner Form von Buspironhydrochlorid enthält, in einem Flüssigmedium bei einer Temperatur von weniger als etwa 95 °C über eine Zeitspanne bewegt wird, die ausreicht, um zu gewährleisten, daß das feste Buspironhydrochlorid ausschließlich aus der niedriger schmelzenden, polymorphen Form besteht.

4. Verfahren nach Anspruch 2 oder 3, worin das Flüssigmedium ausgewählt ist unter Acetonitril, Isopropanol und Methylethylketon.

5. Verfahren nach Anspruch 3, worin das Flüssigmedium Isopropanol ist und die Temperatur 25 °C - 60 °C beträgt.

6. Verfahren zur Herstellung eines pharmazeutischen Mittels, wobei man die niedriger schmelzende, polymorphe Form von Buspironhydrochlorid gemäß Anspruch 1 in einem Träger aufnimmt.

Patentansprüche für folgenden Vertragsstaat : GR

1. Niedriger schmelzende, polymorphe, kristalline Form von Buspironhydrochlorid, gekennzeichnet durch einen Schmelzpunkt von etwa 188 °C bis etwa 192 °C.

2. Verwendung des niedriger schmelzenden, polymorphen Buspironhydrochlorids gemäß Anspruch 1 zur Herstellung eines pharmazeutischen Mittels zur Behandlung von Angst bei einem Patienten, der dieser Behandlung bedarf.

3. Verfahren zur Herstellung eines pharmazeutischen Mittels, wobei man die niedriger schmelzende, polymorphe Form von Buspironhydrochlorid gemäß Anspruch 1 in einem Träger aufnimmt.

4. Verfahren zur Herstellung der niedriger schmelzenden, polymorphen, kristallinen Form von Buspironhydrochlorid gemäß Anspruch 1, wobei man
   a) die kristalline Struktur von festem Buspironhydrochlorid zerstört, das die höher schmelzende, polymorphe, kristalline Form oder ein Gemisch aus höher und niedriger schmelzender kristalliner Form von Buspironhydrochlorid enthält,
   und man
   b) eine Rekristallisation unter Gleichgewichtsbedingungen bei einer Temperatur von weniger als etwa 95 °C erfolgen läßt.

5. Verfahren nach Anspruch 4, worin die Zerstörung der kristallinen Struktur von festem Buspironhydrochlorid durch Auflösen in einem Flüssigmedium erfolgt und die niedriger schmelzende, polymorphe, kristalline Form aus dem Flüssigmedium abgetrennt wird.

6. Verfahren nach Anspruch 5, worin festes Buspironhydrochlorid, welches die höher schmelzende, polymorphe, kristalline Form oder ein Gemisch aus höher und niedriger schmelzender kristalliner Form von Buspironhydrochlorid enthält, in einem Flüssigmedium bei einer Temperatur von weniger als etwa 95 °C über eine Zeitspanne bewegt wird, die ausreicht, um zu gewährleisten, daß das feste Buspironhydrochlorid ausschließlich aus der niedriger schmelzenden, polymorphen Form besteht.

7. Verfahren nach Anspruch 5 oder 6, worin das Flüssigmedium ausgewählt ist unter Acetonitril, Isopropanol und Methylethylketon.

8. Verfahren nach Anspruch 6, worin das Flüssigmedium Isopropanol ist und die Temperatur 25 °C - 60 °C beträgt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Forme cristalline polymorphe à plus faible point de fusion du chlorhydrate de buspirone, caractérisée par un point de fusion d'environ 188 °C à 192 °C.

2. Utilisation du polymorphe de chlorhydrate de buspirone à plus faible point de fusion de la revendication 1 pour la préparation d'une composition pharmaceutique pour le traitement de l'anxiété chez un patient nécessitant un tel traitement.

3. Composition pharmaceutique comprenant le polymorphe de chlorhydrate de buspirone à plus faible point de fusion de la revendication 1 et un support.

4. Procédé de préparation de la forme cristalline polymorphe à plus faible point de fusion du chlorhydrate de buspirone selon la revendication 1, où l'on:
   a) interrompt la structure cristalline du chlorhydrate de buspirone solide contenant la forme cristalline polymorphe à plus fort point de fusion ou un mélange des formes cristallines à plus faible et plus fort point de fusion du chlorhydrate de buspirone et
   b) permet la recristallisation en conditions d'équilibre à une température inférieure à environ 95 °C.

5. Procédé selon la revendication 4, où la structure cristalline dudit chlorhydrate de buspirone solide est interrompue par dissolution dans un milieu liquide et la forme cristalline polymorphe à plus faible point de fusion est séparée du milieu liquide.

6. Procédé de la revendication 5, où le chlorhydrate de buspirone solide contenant la forme cristalline polymorphe à plus fort point de fusion ou un mélange des formes cristalline à plus faible et plus fort point de fusion du chlorhydrate de buspirone est soumis à agitation dans un milieu liquide à une température plus faible qu'environ 95 °C, pendant un temps suffisant pour garantir que le chlorhydrate de buspirone solide sera constitué totalement du polymorphe à plus faible point de fusion.

7. Procédé de la revendication 5 ou 6, où le milieu liquide est choisi dans le groupe consistant en acétonitrile, isopropanol et méthyl éthyl cétone.

8. Procédé de la revendication 6, où le milieu liquide est l'isopropanol et la température est comprise entre 25 °C et 60 °C.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation de la forme cristalline polymorphe à plus faible point de fusion du chlorhydrate de buspirone ayant un point de fusion d'environ 188 à 192 °C, où l'on:
   a) interrompt la structure cristalline du chlorhydrate de buspirone solide contenant la forme cristalline polymorphe à plus fort point de fusion ou un mélange des formes cristallines à plus faible et plus fort point de fusion du chlorhydrate de buspirone et
   b) permet la recristallisation en conditions d'équilibre à une température inférieure à environ 95 °C.

2. Procédé de la revendication 1, où la structure cristalline dudit chlorhydrate de buspirone solide est interrompue par dissolution dans un milieu liquide et la forme cristalline polymorphe à plus faible point de fusion est séparée du milieu liquide.

3. Procédé de la revendication 2, où le chlorhydrate de buspirone solide contenant la forme cristalline polymorphe à plus fort point de fusion ou un mélange des formes cristallines à plus faible et plus fort point de fusion du chlorhydrate de buspirone est soumis à agitation dans un milieu liquide à température plus faible qu'environ 95 °C, pendant un temps suffisant pour garantir que le chlorhydrate de buspirone solide sera constitué totalement du polymorphe à plus faible point de fusion.

4. Procédé de la revendication 2 ou 3, où le milieu liquide est choisi dans le groupe consistant en acétonitrile, isopropanol et méthyl éthyl cétone.

5. Procédé selon la revendication 3, où le milieu liquide est l'isopropanol et la température est comprise entre 25 °C et 60 °C.

6. Procédé de préparation d'une composition pharmaceutique qui comprend l'incorporation du polymorphe de chlorhydrate de buspirone à plus faible point de fusion, selon la revendication 1, dans un support.

Revendications pour l'Etat contractant suivant : GR

1. Forme cristalline polymorphe à plus faible point de fusion du chlorhydrate de buspirone, caractérisée par un point de fusion d'environ 188 °C à 192 °C.

2. Utilisation du polymorphe de chlorhydrate de buspirone à plus faible point de fusion de la revendication 1, pour la préparation d'une composition pharmaceutique pour le traitement de l'anxiété chez un patient nécessitant un tel traitement.

3. Procédé de préparation d'une composition pharmaceutique qui comprend l'incorporation du polymorphe de chlorhydrate de buspirone à plus faible point de fusion de la revendication 1 dans un support.

4. Procédé de préparation de la forme cristalline polymorphe à plus faible point de fusion du chlorhydrate de buspirone selon la revendication 1, où l'on:
   a) interrompt la structure cristalline du chlorhydrate de buspirone solide contenant la forme cristalline polymorphe à plus fort point de fusion ou un mélange des formes cristallines à plus faible et plus fort point de fusion du chlorhydrate de buspirone et
   b) permett la recristallisation en conditions d'équilibre à une température inférieure à environ 95 °C.

5. Procédé selon la revendication 4, où la structure cristalline dudit chlorhydrate de buspirone solide est interrompue par dissolution dans un milieu liquide et la forme cristalline polymorphe à plus faible point de fusion est séparée du milieu liquide.

6. Procédé de la revendication 5, où le chlorhydrate de buspirone solide contenant la forme cristalline polymorphe à plus fort point de fusion ou un mélange des formes cristallines à plus faible et plus fort point de fusion du chlorhydrate de buspirone est soumis à agitation dans un milieu liquide à une température plus faible qu'environ 95 °C, pendant un temps suffisant pour garantir que le chlorohydrate de buspirone solide sera constitué totalement du polymorphe à plus faible point de fusion.

7. Procédé de la revendication 5 ou 6, où le milieu liquide est choisi dans le groupe consistant en acétonitrile, isopropanol et méthyl éthyl cétone.

8. Procédé de la revendication 6, où le milieu liquide est l'isopropanol et la température est comprise entre 25 °C et 60 °C.

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