Abstract:
The present invention provides ramelteon substantially in an amorphous form and a process for its preparation, by preparing solution of ramelteon by dissolving in one or more solvents capable of dissolving the ramelteon; and substantially removing the solvent from the solution to provide amorphous ramelteon.
AMORPHOUS RAMELTEON AND PROCESS FOR THE PREPARATION THEREOF

FIELD OF THE INVENTION

PRIORITY

[0001] This application claims the benefit of Indian Provisional Application No. 2081/MUM/2007, filed on October 19, 2007, and entitled "AMORPHOUS RAMELTEON AND PROCESS FOR THE PREPARATION THEREOF", the contents of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention relates to ramelteon substantially in an amorphous form and a process its preparation. The invention also relates to a composition that includes ramelteon in a solid form, wherein at least 80% by weight of the solid ramelteon is an amorphous form of ramelteon.

2. Description of the Related Art

[0003] Ramelteon is a melatonin MT1 and MT2 agonist. It is marketed under the name ROZEREM™ for the primary insomnia characterized by difficulty with sleep onset. Ramelteon, chemically known as (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide, has the following structure:

\[
\text{H}_3\text{C}_2\text{CONHCH}_2\text{CH}_2
\]

[0004] US 6034239 describes a group of indenofuran derivatives including ramelteon, which have activity as melatonin MT1 and MT2 agonists and are therefore useful in the treatment of primary insomnia.

[0005] Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct
physical properties. Therefore, a single compound may give rise to a variety of
polymorphic forms where each form has different and distinct physical properties, such
as different solubility profiles, different melting point temperatures and/or different x-ray
diffraction peaks. Polymorphic forms of a compound can be distinguished in a laboratory
by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry.

Additionally, polymorphic forms of the same drug substance or active
pharmaceutical ingredient, can be administered by itself or formulated as a drug product
(also known as the final or finished dosage form), and are well known in the
pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability
and compressibility of drug substances and the safety and efficacy of drug products.

Amorphous materials do not exhibit the three-dimensional long-range
order found in crystalline materials, but is structurally more similar to liquids where the
arrangement of molecules is random. Amorphous solids do not give a definitive x-ray
diffraction pattern (XRD). In addition, amorphous solids do not give rise to a melting
point and tend to liquefy at some point beyond the glass transition point. Because
amorphous solids do not have lattice energy, they usually dissolve in a solvent more
rapidly and consequently may provide rapid bioavailability. Furthermore, amorphous
forms of a drug may offer significant advantages over crystalline forms of the same drug
in solid dosage form manufacture process such as compressibility, economically or
environmentally suitable solvents or process, or higher purity or yield of the desired
product.

SUMMARY OF THE INVENTION

In accordance with one embodiment, a process for preparing ramelteon
substantially in an amorphous form, the process comprising steps of:

(a) preparing solution of ramelteon by dissolving in one or more solvents capable
of dissolving the ramelteon;

(b) substantially removing the solvent from the solution to provide amorphous
ramelteon.
In accordance with the second embodiment of the present invention, a process for preparing ramelteon substantially in an amorphous form, the process comprising steps of:

(a) preparing solution of ramelteon by dissolving in one or more solvents capable of dissolving the ramelteon;
(b) filtering the solvent solution to remove any extraneous matter; and
(c) substantially removing the solvent from the solution to provide amorphous ramelteon.

In a third embodiment, the present invention provides ramelteon substantially in an amorphous form.

In accordance with a fourth embodiment, the present invention provides at least about 80% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with the fifth embodiment, the present invention provides at least about 90% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with the sixth embodiment, the present invention provides at least about 95% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with the seventh embodiment, the present invention provides at least about 99% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with an eighth embodiment, the present invention provides ramelteon substantially in an amorphous form having relatively low content of one or more organic volatile impurities.

In accordance with the ninth embodiment, the present invention provides a pharmaceutical composition comprising solid ramelteon in an amorphous form.

In accordance with the tenth embodiment, the present invention provides a pharmaceutical composition comprising solid ramelteon, wherein at least about 80% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with the eleventh embodiment, the present invention provides a pharmaceutical composition comprising solid ramelteon, wherein at least about 90% by weight of the solid ramelteon is an amorphous form of ramelteon.
In accordance with a twelfth embodiment, the present invention provides a pharmaceutical composition comprising solid ramelteon, wherein at least about 95% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with a thirteenth embodiment, the present invention provides a pharmaceutical composition comprising solid ramelteon, wherein at least about 99% by weight of the solid ramelteon is an amorphous form of ramelteon.

In accordance with a fourteenth embodiment, the present invention provides a pharmaceutical composition comprising amorphous ramelteon and pharmaceutical excipients.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Fig.1 illustrates a powder X-ray diffraction pattern of amorphous ramelteon.

**DETAILED DISCRIPTION OF THE PREFERRED EMBODIMENT**

The degree of crystalinity of the portion of the crystalline material is established using powder X-ray diffraction. The integrated peak intensity of the crystalline peaks divided by the overall integrated area of the pattern is used to deduce the percent of the crystalline portion. Crystalline peaks produced by an X-ray diffraction measurement, are characterized by having a half- value width below 2 degrees.

The present invention provides a process for preparing ramelteon substantially in an amorphous form, the process includes: preparing solution of ramelteon by dissolving in one or more solvents capable of dissolving the ramelteon; and substantially removing the solvent from the solution to provide amorphous ramelteon.

A further process for the preparation of ramelteon substantially in an amorphous form is also provided and includes: providing a solution of ramelteon in one or more solvents capable of dissolving the ramelteon; filtering the solvent solution to remove any extraneous matter; and substantially removing the solvent from the solution to provide ramelteon substantially in an amorphous form.
The ramelteon in the solution may be any crystalline or other form of ramelteon, including various solvates and hydrates, as long as amorphous ramelteon is produced during the process of the invention or ramelteon obtaining an existing solution from a previous processing step.

The step of providing a solution of ramelteon may include dissolving any form of ramelteon, in a suitable solvent. Suitable solvents include, but not limited to water, C1-4 alcohols, C3-7 ketones, C3-7 ester, C5-7 linear, branched or cyclic, saturated or unsaturated hydrocarbons, C2-8 ethers, nitriles, halogenated hydrocarbons, or mixtures thereof.

Preferably, the solvent is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropanol, n-butanol, iso-butanol, 2-butanol, acetone, methyl ethylketone, methylisobutyl ketone, ethylacetate, isobutyl acetate, n-butyl acetate, n-propyl acetate, isopropyl acetate, heptane, hexane, cyclohexane, toluene, xylene, tetrahydrofuran, 1,4-dioxane, diethylether, diisopropyl ether, methyl isobutylether, methyl tert-butylether, acetonitrile, methylene chloride, or mixtures thereof, and, more preferably, is methanol, ethanol, acetone, ethyl acetate, toluene, cyclohexane, methylene chloride, acetonitrile, or water and mixtures thereof. Most preferably the solvent is methanol, ethanol, acetone, ethyl acetate, acetonitrile or water and mixtures thereof.

Preferably, the solvent contains less than about 20% water by volume, more preferably, less than about 10% water by volume, and, most preferably, less than about 2% water by volume. Ramelteon can be present in any amount that will produce the amorphous form upon the process of the present invention. Preferably, the ramelteon is present in an amount of about 1% to about 50% by weight of the solvent, more preferably about 1% to about 30% by weight, more preferably about 1% to about 20% by weight, and most preferably about 2% to about 10% by weight. One skilled in the art would understand that depending on the choice of solvent, the amount of ramelteon used may be varied.

The solution may be heated to dissolve the ramelteon. The temperature suitable for dissolving ramelteon depends on the solvent used and the amount of ramelteon in the solution. Typically, the solution is heated at a temperature of at least about 30°C to about reflux. Preferably, the solution is heated at about 40°C to about
85°C, and more preferably at about 40°C to about 60°C. The solution may be prepared at other suitable temperatures as long as the ramelteon is sufficiently dissolved. Increasing the amount of ramelteon would generally require the use of higher temperatures. Routine experimentation will provide the approximate range of suitable temperatures for a given solvent and amount of ramelteon.

[0030] The process includes optional step of filtration in order to remove. The clear solution optionally filtered to remove any extraneous matter present in the solution using any standard filtration techniques known in the art.

[0031] Removal of solvent is accomplished by, for example, substantially complete evaporation of the solvent, concentrating the solution, cooling to obtain amorphous form and filtering the solid under inert atmosphere. Alternatively, the solvent may also be removed by evaporation. Evaporation can be achieved at sub-zero temperatures by the lyophilisation or freeze-drying technique. The solution may also be completely evaporated in, for example, a pilot plant Rota vapor, a Vacuum Paddle Dryer or in a conventional reactor under vacuum above about 720 mm Hg by flash evaporation techniques by using an agitated thin film dryer ("ATFD"), or evaporated by spray drying to obtain a dry amorphous powder.

[0032] One of the preferred methodologies to remove the solvent involves spray-drying, in which a solution of ramelteon is sprayed into the spray drier at the flow rate ranging from 10 to 300 ml/hr, preferably flow rate is 40 to 200ml/hr. The air inlet temperature to the spray drier used may range from 25 to 200°C and preferably from 25°C to 150°C. An "inlet temperature" is the temperature at which the solution enters the spray dryer. The outlet air temperature used may range from 5°C to 100°C, preferably outlet temperature is from about 50°C to about 60°C, and most preferably outlet temperature is from about 5°C to about 45°C. An "outlet temperature" is the temperature at which the gas exits the spray dryer.

[0033] Another preferred method is vertical agitated thin-film drying (or evaporation). Agitated thin film evaporation technology involves separating the volatile component using indirect heat transfer coupled with mechanical agitation of the flowing film under controlled condition. In vertical agitated thin-film drying (or evaporation) (ATFD-V), the starting solution is fed from the top into a cylindrical space between a
centered rotary agitator and an outside heating jacket. The rotor rotation agitates the downside-flowing solution while the heating jacket heats it.

[0034] The method using cooling the solution to preparing the amorphous ramelteon comprises cooling the resultant solution after dissolution of starting ramelteon in one or more solvents capable of dissolving the ramelteon to temperature ranges from about -20 to about 20°C, preferably from about -10 to about 10°C, more preferably about 0 to about 5°C. The resulting solid can then be filtered, to provide ramelteon substantially in an amorphous form.

[0035] The ramelteon substantially in an amorphous form obtained by the above processes may be further dried in, for example, Vacuum Tray Dryer, Rotocon Vacuum Dryer, Vacuum Paddle Dryer or pilot plant Rota vapor, to further lower residual solvents.

[0036] The present invention provides a chemical composition comprising ramelteon, wherein at least about 80% by weight of the solid ramelteon is an amorphous form of ramelteon, preferably at least about 90%, more preferably about 95%, most preferably at least about 99%.

[0037] In another aspect of the present invention provides ramelteon, having a chemical purity of 96% or more as measure by HPLC, preferably 99% or more, more preferably 99.5% or more. Moreover, the highly purified ramelteon may be obtained substantially free of any unknown impurity, e.g., a content of less than about 0.1% of impurities.

[0038] According to another aspect of the present invention, there is provided ramelteon substantially in an amorphous form having relatively low content of one or more organic volatile impurities.

[0039] The ramelteon substantially in an amorphous form obtained by the process disclosed herein, having less than about 200 parts per million (ppm) C1-4 alcohols, less than about 200 ppm ethyl acetate, less than about 200 ppm cyclohexane, less than about 100 ppm tetrahydrofuran, and less than about 100 ppm n-hexane.

[0040] Preferably the ramelteon substantially in an amorphous form obtained by the process disclosed herein, having less than about 50 parts per million (ppm) C1-4 alcohols, less than about 50 ppm ethyl acetate, less than about 50 ppm cyclohexane, less than about 20 ppm tetrahydrofuran, and less than about 20 ppm n-hexane.
Preferably the ramelteon substantially in an amorphous form obtained by the process disclosed herein having the overall level of organic volatile impurities less than about 200 ppm, more preferably less than about 50 ppm, and more preferably less than about 20 ppm.

In yet another aspect of the present invention, when a pharmaceutical composition comprising ramelteon substantially in an amorphous form thereof prepared according to the present invention is formulated for oral administration. Accordingly, D<sub>50</sub> and D<sub>90</sub> particle size of the unformulated substantially in an amorphous form used as starting material in preparing a pharmaceutical composition generally is less than 300 microns preferably less than about 200 microns, more preferably less than 150 microns, still more preferably less than about 50 microns and still more preferably less than about 10 microns.

The present invention further provides a pharmaceutical comprising solid ramelteon, wherein at least about 80% by weight of the solid ramelteon is an amorphous form of ramelteon, preferably at least about 90%, more preferably at least about 95% most preferably at least about 99%.

Any milling, grinding micronizing or other particle size reduction method known in the art can be used to bring the solid state ramelteon substantially in an amorphous form thereof into any desired particle size range as set forth above.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations.

For purposes of the present invention, the following terms are defined below.
The term "composition" includes, but is not limited to, a powder, a suspension, an emulsion and/or mixtures thereof. The term composition is intended to encompass a product containing the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. A "composition" may contain a single compound or a mixture of compounds.

The term 'pharmaceutical composition" is intended to encompass a product comprising the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing the active ingredient, additional active ingredient(s), and pharmaceutically acceptable excipients.

The term "excipient" means a component of a pharmaceutical product that is not the active ingredient, such as filler, diluent, carrier, and so on. The excipients that are useful in preparing a pharmaceutical composition are preferably generally safe, non-toxic and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as; well as human pharmaceutical use. "A pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

The term "isolating" is used to indicate separation of the compound being isolated regardless of the purity of the isolated compound from any unwanted substance which presents with the compound as a mixture. Thus, degree of the purity of the isolated or separated compound does not affect the status of isolating.

It is known that different solid forms of the same drug may have substantial differences in certain pharmaceutically important properties such as dissolution characteristics and bioavailability, as well as stability of the drug. Furthermore, different physical forms may have different particle size, hardness and glass transition temperatures.
The invention also relates to a composition of solid ramelteon wherein at least 80% of the total weight of ramelteon is in the amorphous form. A preferred form of this composition, the solid ramelteon is suitable for use as a bulk active ingredient in formulating pharmaceutical products. The remainder of the solid ramelteon in the composition, i.e., 20% or less of the total weight of ramelteon, may be other forms of ramelteon, e.g., crystalline forms. In an embodiment of the invention, the composition may include at least 95% of the amorphous form of ramelteon with respect to total weight of the solid ramelteon in the composition. In another embodiment of the invention, the composition may include at least 99% of the amorphous form of ramelteon with respect to total weight of the solid ramelteon in the composition.

In addition to X-ray powder diffraction, amorphous ramelteon, or the presence of some amorphous ramelteon, can be distinguished from crystalline ramelteon, using Raman spectroscopy, solution calorimetry, differential scanning calorimetry, solid state nuclear magnetic resonance spectra (ssNMR) or infra-red spectroscopy. Each of these techniques is well established in the art. Amorphous ramelteon can also be identified based on the morphology of the particles seen under an electron microscope.

Furthermore, ramelteon substantially in an amorphous form is likely to be much more soluble than crystalline ramelteon because the former is lack of lattice energy, providing another means of discriminating between the crystalline and amorphous ramelteon forms, or detecting an amount of amorphous form within a ramelteon preparation.

In another embodiment, the invention provides pharmaceutical compositions containing the ramelteon substantially in an amorphous form, which can be formulated with a one or more pharmaceutically acceptable carriers, also known as excipients, which ordinarily lack pharmaceutical activity, but have various useful properties which may, for example, enhance the stability, sterility, bioavailability, and ease of formulation of a pharmaceutical composition. These carriers are pharmaceutically acceptable, meaning that they are not harmful to humans or animals when taken appropriately and are compatible with the other ingredients in a given formulation. The carriers may be solid, semi-solid, or liquid, and may be formulated with the compound in bulk.
[0057] The resulting mixture may be manufactured in the form of a unit-dose formulation (i.e., a physically discrete unit containing a specific amount of active ingredient) such as a tablet or capsule. Generally, the pharmaceutical compositions of the invention may be prepared by uniformly admixing the active ingredient with liquid or solid carriers and then shaping the product into the desired form. The pharmaceutical compositions may be in the form of suspensions, solutions, elixirs, aerosols, or solid dosage forms.

[0058] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. A tablet may be prepared by direct compression, wet granulation, or molding, of the active ingredient(s) with a carrier and other excipients in a manner known to those skilled in the art. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made on a suitable machine. A mixture of the powdered compound moistened with an inert liquid diluent is suitable in the case of oral solid dosage forms (e.g., powders, capsules, and tablets). If desired, tablets may be coated by standard techniques.

[0059] The compounds of this invention may be formulated into typical disintegrating tablets, or into controlled or extended release dosage forms. The amount of active ingredient included in a unit dosage form depends on the type of formulation that is formulated. A pharmaceutical composition of the invention will generally include about 0.1% by weight to about 99% by weight of active ingredient, preferably about 1% by weight to 50% by weight.

[0060] Suitable carriers include but are not limited to fillers, binders, lubricants, inert diluents, surface active/dispersing agents, flavorants, antioxidants, bulking and granulating agents, adsorbants, preservatives, emulsifiers, suspending and wetting agents, glidants, disintegrants, buffers and preadjusting agents, and colorants. Examples of carriers include celluloses, modified celluloses, cyclodextrins, starches, oils, polyols, sugar alcohols and sugars, and others. For liquid formulations sugar, sugar alcohols, ethanol, water, glycerol, and polyalkylene glycols are particularly suitable, and may also
be used in solid formulations. Cyclodextrins may be particularly useful for increasing bioavailability. Formulations for oral administration may optionally include enteric coatings known in the art to prevent degradation of the formulation in the stomach and provide release of the drug in the small intestine. One example of pharmaceutical tablet of the amorphous ramelteon may include, as inactive ingredients, hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin and 1 or more of synthetic red and yellow iron oxides and talc.

[0061] The active ingredient of the invention may also be administered via fast dispersing or fast dissolving dosage forms or in the form of high energy dispersion or as coated particles. Suitable pharmaceutical composition of the invention may be in coated or uncoated form as desired.

[0062] Tabletting compositions may have few or many components depending upon the tabletting method used, the release rate desired and other factors. For example, the compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted cellulosics; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

[0063] Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.
Capsule dosages will contain the solid composition within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric coating.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

EXAMPLES

Instrument:

The amorphous form of ramelteon, produced by the methods of the present invention can be analyzed by Powder x-ray diffraction (PXRD) was performed on an X-ray powder diffractometer, equipped with a Cu-anode ($\lambda=1.54$ Angstrom), X-ray source operated at 45kV, 40 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=2-50° 2Θ, step width=0.017°; and measuring time per step=5 sec.

Example 1:
Dissolving 5 grams of ramelteon in 25 ml methanol and heating the solution to 50-55°C. Concentrating the solution under reduced pressure at temperature below 50°C. Cooling the concentrated foamy material and collecting amorphous ramelteon powder.

Example 2:
Dissolving 5 grams of ramelteon in 35 ml ethyl acetate and heating the solution to 65°C. Concentrating the solution under reduced pressure at temperature below 50°C. Cooling the concentrated foamy material and collecting amorphous ramelteon powder.

**Example 3:**
Dissolving 5 grams of ramelteon in 60 ml acetonitrile and heating the solution to 55°C. Adding 30 ml of water to the resultant solution and cooling the solution to 0°C and filtering the solid.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.
Claims:

1. Amorphous form of ramelteon.

2. The amorphous form of ramelteon of claim 1, substantially as depicted in figure 1.

3. The amorphous form of ramelteon of claim 1, containing at least about 80% by weight of the solid ramelteon is an amorphous form of ramelteon.

4. The amorphous form of ramelteon of claim 3, containing at least about 90% by weight of the solid ramelteon is an amorphous form of ramelteon.

5. The amorphous form of ramelteon of claim 4, containing at least about 95% by weight of the solid ramelteon is an amorphous form of ramelteon.

6. The amorphous form of ramelteon of claim 5, containing at least about 99% by weight of the solid ramelteon is a amorphous form of ramelteon.

7. A process for preparing ramelteon in an amorphous form, comprising preparing solution of ramelteon by a) dissolving in one or more solvents capable of dissolving the ramelteon; b) substantially removing the solvent from the solution to provide amorphous ramelteon.

8. The process of claim 7, further comprising the step of filtering the solvent solution from step (a) to remove extraneous matter.

9. The process of claim 7, wherein the solvent is selected from the group consisting of water, C1-4 alcohols, C3-7 ketones, C3-7 ester, C5-7 linear, branched or cyclic, saturated or unsaturated hydrocarbons, C2-8 ethers, nitriles, halogenated hydrocarbons, and mixtures thereof.

10. The process of claim 9, wherein the solvent is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropanol, butanol, acetone, methyl ethylketone, methylisobutyl ketone, ethylacetate, isobutyl acetate, heptane, hexane, cyclohexane, toluene, xylene, tetrahydrofuran, 1,4-dioxane, diethylether, diisopropyl ether, methyl isobutylether, -methyl tert-butylether, acetonitrile, methylene chloride, or mixtures thereof.

11. The process of claim 10, wherein the solvent is methanol, ethanol, acetone, ethyl acetate, acetonitrile or water and mixtures thereof.
12. The process of claim 7, wherein the solvent is removed by solvent evaporation, or cooling the solution.
13. The process of claim 12, wherein the solvent evaporation is performed in a rotavapor, a Vacuum Paddle Dryer, an agitated thin film dryer, a freeze-dryer, or a spray dryer.
14. The process of claim 12, wherein the solvent evaporation is performed under atmospheric pressure or reduced pressure.
15. The process of claim 14, wherein the solvent evaporation is performed under reduced pressure.
16. The amorphous form of ramelteon of claim 1, further having less than about 200 ppm C1-4 alcohols, less than about 200 ppm ethyl acetate, less than about 200 ppm cyclohexane, less than about 100 ppm tetrahydrofuran, and less than about 100 ppm n-hexane.
17. The compound of claim 16, wherein the amorphous form of ramelteon has less than about 50 ppm C1-4 alcohols, less than about 50 ppm ethyl acetate, less than about 50 ppm cyclohexane, less than about 20 ppm tetrahydrofuran, and less than about 20 ppm n-hexane.
18. The compound of claim 16, wherein the amorphous form of ramelteon has the overall level of organic volatile impurities less than 200 ppm.
19. The compound of claim 18, wherein the amorphous form of ramelteon has the overall level of organic volatile impurities less than 20 ppm.
20. A pharmaceutical composition comprising solid ramelteon in an amorphous form.
21. The pharmaceutical composition of claim 20, containing at least about 80 % by weight of the solid ramelteon is an amorphous form of ramelteon.
22. The pharmaceutical composition of claim 20, containing at least about 90 % by weight of the solid ramelteon is an amorphous form of ramelteon.
23. The pharmaceutical composition of claim 20, containing at least about 95 % by weight of the solid ramelteon is an amorphous form of ramelteon.
24. The pharmaceutical composition of claim 20, containing at least about 99 % by weight of the solid ramelteon is an amorphous form of ramelteon.
Figure 1