Abstract: Disclosed herein are the novel amorphous hydrated and crystalline forms of Rimonabant, process(s) for their preparation and pharmaceutical compositions containing it.
NOVEL FORMS OF RIMONABANT

FIELD OF THE INVENTION

The present invention describes novel amorphous and two crystalline forms of Rimonabant, process(s) for their preparation and pharmaceutical compositions containing it. The present invention also describes method of treatment of obesity, smoking cessation, overweight and related diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of the said amorphous and crystalline Rimonabant and pharmaceutical composition containing it. The present invention relates to the use of amorphous and crystalline Rimonabant disclosed herein and pharmaceutical compositions containing it for the treatment of obesity, smoking cessation, overweight and related diseases.

BACKGROUND OF THE INVENTION

Obese patients are at higher risk for coronary artery disease, hypertension, hyperlipidemia, and diabetes mellitus, among other diseases and thus their risk of morbidity and mortality increases. Due to many complex pathophysiological components which lead to obesity, the disease remains a challenging and significant clinical problem. Cannabinoids acting via cannabinoid receptors stimulate food intake and a particularly attractive antiobesity target is the cannabinoid CB₁ receptor, which has also been shown to play a role in reinforcing reward. (LA. Sorbera et al, Drugs of Future 2005; 30(2): 128-137). Rimonabant in the form of its hydrochloride salt is a promising CB₁ receptor antagonist that has shown to inhibit motivational and consummatory aspects of feeding, as well as alcohol and nicotine intake in animal models. Rimonabant has recently received its first approval in UK for the treatment of obesity. The agent also exhibited efficacy in phase III clinical trials and hold promise in the treatment of smoking cessation.

Rimonabant is 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)pyrazole-3-carboxamide, having structural formula I.
It is developed by Sanofi as its hydrochloride salt, as a $\text{CB}_1$ antagonist, as a potential treatment for obesity, smoking cessation, Alzheimer's disease, Parkinson's disease etc. This compound is disclosed in EP 0576357, EP 0656354, EP 0658546, US 5624941 and US 5462960, all of them are hereby incorporated by reference in their entirety.

The therapeutic applications of Rimonabant has been described in US 6344474, US 6642258, WO 0158450, WO 0185092, WO 0318060, WO 0382256 etc. which are also incorporated in their entirety as reference.

WO 03040105 (Sanofi) discloses one new crystalline form of Rimonabant designating it as Form II, which also states the earlier form disclosed in EP 0656354 is the Form I. It also states that the new form, Form II can be obtained by particular crystallization conditions, and the Form II is more stable than the Form I. This application also differentiates the Form II from the earlier disclosed Form I in the fact that the Form II is less soluble at all temperatures between 10 °C to 70 °C and therefore thermodynamically more stable. The application also described that the Form II can be obtained from the Form I by dissolving Form I in suitable solvent like methylcyclohexane containing 1-10 % water or acetonitrile or acetone etc. in the hot state and subsequently cooling the mixture to obtain the crystals of Form II. According to the application, the process of manufacture as described therein has better industrial applicability. However, no data are provided exemplifying the advantage claimed. This application is also hereby incorporated as reference in its entirety.

Recently, Ranbaxy has disclosed crystalline forms III, IV, V and an amorphous form of Rimonabant in their publication EP 1816125.

Thus, it is clear that there is possibility of existence of various polymorphic forms of Rimonabant, having different beneficial effects. Some of these forms may have superior properties which will be better suited either in formulating or in better delivery of the drug or better bioavailability or pharmacokinetics or in terms of ease of manufacturing etc.

We have disclosed novel polymorphs of Rimonabant hydrochloride in our published patent application, WO 2006087732.

The present inventors have surprisingly found when Rimonabant Form II is dissolved in suitable solvents, a new amorphous form of Rimonabant is obtained, which has not been reported earlier in any literature. This amorphous form, is stabilized by the presence of -1-4 % water, making it different from the form disclosed in EP 1816125.
The present inventors have also found a new crystalline form of Rimonabant which surprisingly shows better pharmacokinetic profile than the Form II of Rimonabant which is available commercially, when tested in Beagle dogs. Thus, the new crystalline form has the potential to have superior bioavailability and pharmacokinetic profile thereby solving potential problems of the commercial form of Rimonabant which is well known to have serious pharmacokinetic and bioavailability problems.

The present inventors have also surprisingly found that the novel crystalline form of Rimonabant, (hereinafter represented as Forms VI & VII) can be used to prepare different forms of Rimonabant, including Form I and Form II (both these forms are described in EP 0656354 and WO 03040105). It has also been noted that when amorphous form of the present invention is exposed to atmospheric temperature, the amorphous form gradually gets converted into Form II Rimonabant.

The present invention thus discloses novel amorphous (hydrated) and two crystalline forms of Rimonabant and processes for preparation of the amorphous (hydrated) and the crystalline forms.

**EMBODIMENTS OF THE INVENTION**

Accordingly, the present invention provides new amorphous (hydrated) and crystalline forms of Rimonabant.

In another embodiment is provided processes for the preparation of the amorphous (hydrated) and crystalline forms of Rimonabant.

Yet in another embodiment is provided pharmaceutical compositions comprising the said amorphous (hydrated) and crystalline form of Rimonabant.

In a still further embodiment is provided uses of the amorphous (hydrated) and crystalline form of Rimonabant for the treatment of obesity, Parkinson's disease, Alzheimer's disease, smoking cessation and other related diseases.

**Figures:**

Fig.1: X-ray powder diffraction (XRD) pattern of crystalline form VI of Rimonabant.
Fig.2: X-ray powder diffraction (XRD) pattern of crystalline form VII of Rimonabant.
Fig.3: X-ray powder diffraction (XRD) pattern of amorphous (hydrated) form of Rimonabant.

Fig.4: Pharmacokinetic profile of Rimonabant vs. amorphous form (PMI) and crystalline form VI (PM 2) of the present invention in Wister male rats.
Fig.5: Pharmacokinetic profile of Rimonabant vs. amorphous form (PMI) and crystalline form VI (PM 2) of the present invention in Wister female rats.
DESCRIPTION OF THE INVENTION

Rimonabant is 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)pyrazole-3-carboxamide, having structural formula (I).

The present invention provides crystalline form VI of Rimonabant, having melting point in the range of 85-105 °C, having characteristic XRD pattern, as shown in Fig. 1.

The crystalline form of Rimonabant is characterized by unique XRD pattern which is different from the various forms reported in the above mentioned applications.

The present invention also provides another crystalline form VII of Rimonabant, having melting point in the range of 100-108 °C, having characteristic XRD pattern, as shown in Fig. 2.

This crystalline form of Rimonabant is characterized by unique XRD pattern which is different from the various forms reported in the above mentioned applications.

The present invention further provides amorphous form of Rimonabant, having from 1-4 % water, which stabilizes the amorphous form, having melting point in the range of 105 to 110 °C, having characteristic XRD pattern, as shown in Fig. 3.

The amorphous form presented in this invention is non-sticky, free flowing, pharmaceutically processable and stable with distinct physico-chemical properties. The term "amorphous", as used herein, relates to solid material which lacks a regular crystalline structure. In a powder X-ray diffractogram such material gives no good intensity peaks. Without being bound by theory, it is believed and also observed that the amorphous solids offer the advantages of faster dissolution due to reduced dissolution energy requirement. Rapid dissolution is important for poorly soluble compounds administered orally, since there is a direct correlation between dissolution...
rate and bioavailability. This is evident from the pharmacokinetic profile of the amorphous form (PM1) when tested in Wistar rats and Beagle dogs (Figures 5 & 6).

The crystalline Form VI of the present invention has been found to be stable (three month stability data provided alongwith). Graphpad generated graphs for Rimonabant & its polymorphs, which clearly indicate that Form VI is having lower Cmax in both speies (rats & dogs). Graphs also shows that polymorph-2 has faster Tmax in rats. This profile is desirable for development of safer therapeutic agent based on CNS-based adverse event profile of Rimonabant.

The present invention also discloses process(s) for the preparation of the said amorphous (hydrated) and two crystalline forms of Rimonabant and pharmaceutical compositions containing them and their use in medicine.

**PREPARATION OF RIMONABANT**

**Step 1:**
Preparation of diketo ester (10):

4-chloropropiophenone 2 is reacted with diethyl oxalate in the presence of sodium ethoxide to form diketo ester compound 10 which is used in the next step. The reaction may be carried out in suitable solvents such as ethanol, methyl tertiary butyl ether and the like or mixtures thereof. Temperature in the range of 20 to 60 °C may be used. Inert atmosphere may be maintained using N2, Ar, He gas but not critical.

**Step 2:**
Preparation of cyclic ester compound (6):

This diketo ester compound 10 is then reacted with 4-chloro phenyl hydrazine hydrochloride 4 in solvent and HCl in presence of IPA.HCl solution to give cyclic ester 6. Suitable solvent may be selected from ethanol, ethanolic HCl, methanolic HCl, diisopropyl ether and the like or mixtures thereof. Temperature in the range of 78 to 80 °C to reflux may be used.

**Step 3:**
Preparation of acid (7):

The cyclic ester compound 6 is converted into cyclic acid compound 7 by hydrolyzing with an alkali and an alcohol. Alkali such as LiOH, NaOH, KOH, t-BuOH may be used. Suitable alcohol may be methanol, ethanol, propanol, isobutanol, isopropyl alcohol and the like or mixtures thereof. KOH/Methanol is a preferred combination. Temperature in the range of 80 to 85 °C to reflux may be used.

**Step 4:**
Preparation of acid chloride (8):

The cyclic acid compound 7 is reacted with thionyl chloride to give acid chloride 8 by techniques known in the art. Catalytic DMF helps the reaction. Solvent is not critical and essential. But when solvent is used, preferred solvents are benzene, toluene and the like or mixtures thereof.

Step 5:

Preparation of Rimonabant (1):

The acid chloride 8 formed is finally reacted with 1-amino piperidine 9 in presence of a suitable amine such as triethyl amine to give Rimonabant 5 by processes known in the art.

Rimonabant base so prepared may be further used for preparing amorphous (hydrated) and crystalline forms of Rimonabant, which may be further used in preparing pharmaceutical preparations.

PREPARATION OF AMORPHOUS FORM

The novel amorphous form of Rimonabant may be prepared by the process comprising dissolving/contacting Rimonabant in suitable solvents such as methanol, ethanol, benzene, propanol, n-butanol, dichloromethane, dichloroethane, acetone, cyclohexane, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran or mixtures thereof and 2-4 % amount of water, evaporating and drying the residue to obtain amorphous hydrated form of Rimonabant (different batches).

PREPARATION OF CRISTALLINE FORM

a) The novel crystalline form VI of Rimonabant may be prepared by the process comprising dissolving Rimonabant in suitable solvents such as methanol, ethanol, propanol, n-butanol, acetone, acetonitrile, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran. The solid may be obtained either by slow cooling and filtering the above reaction mixture or by adding 2-15% amount of water to the reaction mixture followed by filtration and slow drying to obtain crystalline form of Rimonabant (different batches).

b) The novel crystalline form VI of Rimonabant may also be prepared by the process comprising dissolving Rimonabant in suitable solvents such as methanol, ethanol, propanol, n-butanol, acetone, acetonitrile, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran stirring and evaporating the solvent to dryness and subsequently adding 2-15% amount of water, stirring and evaporating the solvent to dryness to obtain crystalline form of Rimonabant (different batches).
c) The novel crystalline form VII of Rimonabant may be prepared by the process comprising dissolving Rimonabant in a suitable alcohols such as ethanol, methanol or mixtures thereof, followed by addition of suitable solvents selected from cyclohexane and the like, heating to dissolve and reprecipitating, filtering and drying to obtain crystalline form VII of Rimonabant (different batches).

The amorphous (hydrated) and two crystalline forms of Rimonabant of the present invention may be used for the treatment of obesity, Parkinson's disease, Alzheimer's disease, smoking cessation and other related diseases in a mammal including human.

The following non-limiting examples illustrate the inventor's improved process for the preparation of amorphous (hydrated) and two crystalline forms of Rimonabant, Forms VI & VII and their pharmaceutically acceptable salts of formula (I) discussed in the invention and should not be construed to limit the scope of the invention in any way.

EXAMPLE 1

Preparation of amorphous form of Rimonabant

Rimonabant (2 gm) was dissolved in dichloromethane 20 ml with stirring at 25-30 °C. Water (0.26 ml) was added to the solution at 25-30 °C. The reaction mixture was stirred for 10 min. and solvent evaporated under reduced pressure at 50-55 °C, to give off white powder (1.5 gm) which characterization data showed to be the hydrated amorphous form.

EXAMPLE 2

Preparation of amorphous form of Rimonabant

Rimonabant (6 g) was dissolved in dichloromethane (60 ml) with stirring at 25-30 °C. Water (0.78 ml) was added to the solution at 25-30 °C. The reaction mixture was stirred for 20 min. Then the solvent was evaporated under reduced pressure at 50-55 °C, to give white powder (6.2 g), which characterization data showed to be the hydrated amorphous form.

EXAMPLE 3

Preparation of crystalline form VI of Rimonabant

Rimonabant (2 g) was dissolved in methanol (20 ml) with stirring at 25-30 °C. Water (0.26 ml) was added to the solution at 25-30 °C. The reaction mixture was stirred
for 5 min., filtered and dried at 45-50 °C in vacuum oven for about 8 hours, to obtain off white powder (1.8 gm), which on characterization showed to be the crystalline form, Form VI.

EXAMPLE 4
Preparation of crystalline form VI of Rimonabant
Rimonabant (6 g) was dissolved in methanol (60 ml) with stirring at 25-30 °C. To this, water (0.8 ml) was added. The reaction mixture was stirred for 5 min., filtered, washed with cold methanol (6 ml) and dried at 45-50 °C in vacuum oven for about 8 hours, to obtain off white powder (4.5 gm) which on characterization showed to be the crystalline form.

EXAMPLE 5
Preparation of crystalline form VII of Rimonabant
Rimonabant (1 g) is dissolved in methanol (5 ml) with stirring at 25-30 °C. To this, cyclohexane (1 ml) is added. The reaction mixture is heated to clear solution. Then, gradually cooled to 20-25 °C. The reaction mixture is stirred for about 30 min., filtered, washed with cold methanol (2 ml) and dried at 45-50 °C in vacuum oven for about 8 hours, to obtain off white powder (650 mg) which on characterization showed to be the crystalline form.

The crystalline forms of Rimonabant of the present invention have surprisingly found to be stable, have potentially improved pharmacokinetic properties and therefore in preliminary studies shows the potential to solve some of the problems, specifically the problem with low bioavailability and poor elimination associated with the commercial form of Rimonabant. Thus, for example, the stability data of the novel form VI (Table 1) shows that it is at least as stable as Rimonabant at room temperature.

The pharmacokinetic study of Rimonabant and its polymorphic forms were carried out in Wister rats and dogs. The doses used in the study were: 30 mpk p.o in Wister rats and 10 mpk p.o in dogs. The results have been depicted in enclosed figures 4, 5 and 6. Graphpad generated graphs for Rimonabant & its polymorphs, which clearly indicate that Form VI is having lower Cmax in both species (rats & dogs). Graphs also shows that polymorph-2 has faster Tmax in rats. This profile is desirable for development of safer therapeutic agent based on CNS-based adverse event profile of Rimonabant

The various pharmaceutical compositions and formulations of the amorphous (hydrated) and two crystalline forms of Rimonabant of the present invention can be
prepared by processes known in the art or suitable variations of them. The dosage of the amorphous and crystalline forms of Rimonabant of the present invention is selected according to the usage and may vary as per the requirement of the patient.

The advantages of the present invention are:

1. The crystalline forms are easy to purify, stable and easily reproducible and easy to scale up at production level, hence suitable for commercial use.

2. The amorphous form can be used to prepare crystalline forms of Rimonabant.

3. The crystalline forms show improved pharmacokinetic profile than the commercially available form of Rimonabant. They therefore have the potential to solve some of the problems associated with the existing form of Rimonabant.
We claim:

1. A novel crystalline form VI of Rimonabant characterized by X-ray diffraction pattern substantially as depicted in fig.1.


3. A process for the preparation of crystalline Form VI of Rimonabant as claimed in claims land 2 comprising
   a) dissolving Rimonabant base in suitable solvents selected from methanol, ethanol, propanol, n-butanol, acetone, acetonitrile, dimethyl formamide, dimethyl acetamide, 1,4-dioxane, tetrahydrofuran or mixtures thereof,
   b) slow cooling and filtering the reaction mixture or by adding 2-15 % amount of water to the reaction mixture followed by filtration and slow drying.

4. A process for the preparation of crystalline for VI of Rimonabant as claimed in claim 3 which further comprises, optionally,
   a) initially stirring and evaporating the solvent to dryness
   b) subsequently adding 2-15 % amount of water, stirring and further slowly evaporating the solvent to dryness.

5. A novel crystalline form VII of Rimonabant characterized by X-ray diffraction pattern substantially as depicted in fig.2.


7. Amorphous hydrated form of Rimonabant.

8. Amorphous hydrated form of Rimonabant as claimed in claim 7 and characterized by X-ray diffraction pattern substantially as depicted in fig.3.

9. The process for the preparation of amorphous hydrated form of Rimonabant as claimed in claims 7 and 8 comprising,
   a) dissolving/contacting Rimonabant base in suitable solvents selected from methanol, ethanol, benzene, propanol, n-butanol, dichloromethane, dichloroethane, acetone, cyclohexane, dimethyl formamide, dimethyl
acetamide, 1,4-dioxane, tetrahydrofuran or mixtures thereof and 2-4 % amount of water,
b) evaporating and drying the residue.
10. A pharmaceutical composition comprising the amorphous hydrated and crystalline forms of Rimonabant as claimed in any of the preceding claims, comprising either single form or their mixtures in combination with pharmaceutically acceptable excipients.
11. A pharmaceutical dosage form comprising the pharmaceutical compositions containing amorphous hydrated and crystalline forms of Rimonabant of the present invention as claimed in any of the preceding claims.
12. Use of crystalline form of Rimonabant of the present invention or their pharmaceutically acceptable compositions as claimed in any of the preceding claims for preparing medicaments suitable for the treatment of obesity, smoking cessation, overweight, Alzheimer's disease, Parkinson's disease and other related diseases in a mammal including human.
13. Method of treatment comprising administering to a person in need thereof, pharmaceutical compositions or pharmaceutically acceptable dosage forms containing the amorphous (hydrated) and/or crystalline form of Rimonabant of the present invention as claimed in any of the preceding claims for the treatment of obesity, smoking cessation, overweight, Alzheimer's disease and Parkinson's disease.
14. An improved process for the preparation of Rimonabant of formula I., suitable for preparation of polymorphic forms VI and VII as claimed in any one of the claims above,
comprising the steps of:
a) reacting 4-chloropropiophenone 2 with diethyl oxalate in presence of sodium ethoxide in suitable solvent(s) to form diketo ester 10, followed by reaction of 10 with 4-chlorophenyl hydrazine hydrochloride 4 in suitable solvent(s) and HCl in suitable solvent(s) preferably IPA.HCl solution to give cyclic ester 6.

b) converting cyclic ester compound 6 into cyclic acid compound 7 in presence of KOH/methanol.

c) reacting cyclic acid compound 7 with thionyl chloride to give acid chloride 8.
d) reacting acid chloride 8 with 1-amino piperidine 9 in presence of triethyl amine to give Rimonabant 1.
Fig. 4

PK of Rimonabant (plain) & its polymorphs in Male Wistar rats
(Dose 30 mpk, p.o.)

[Graph showing concentration vs. time for different polymorphs]
Fig. 5

PK of Rimonabant (plain) & its polymorphs in Female Wistar rats
(Dose 30 mpk, p.o.)
Fig. 6

PK of Rimonabant (plain) & its polymorphsin male Dogs
(10 mpk, p.o.)
# Stability Study – Form VI of Rimonabant

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