“NOVEL POLYMORPH OF SAMIDORPHAN L-MALATE AND PROCESS FOR PREPARATION THEREOF”

ABSTRACT

The present invention relates to novel polymorph of Samidorphan L-malate and process for preparation thereof.

Applicant: Intas Pharmaceutical Limited Total no. of Sheets 01

Application No.: Sheet 01 of 01

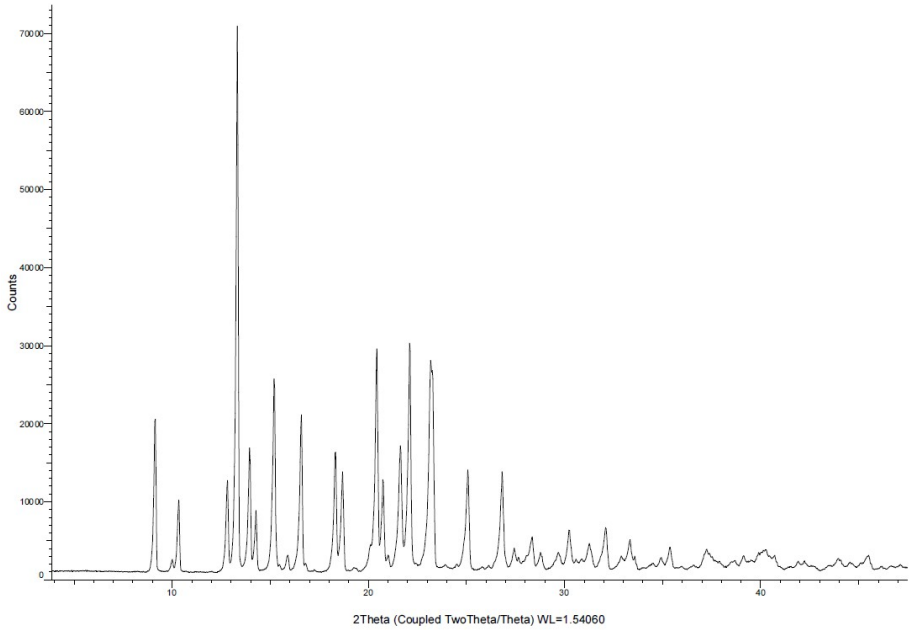

Fig.1: Illustrates the X-ray powder diffraction (XRPD) pattern of Novel polymorph of Samidorphan L-malate obtained according to example 1.

Dated this 12th day of Jun., 2023

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To,
The Controller of Patents,
The Patent Office,
At Mumbai.

FORM 2

THE PATENT ACT, 1970

(39 of 1970)

&

THE PATENTS RULES, 2003

COMPLETE SPECIFICATION

[See section 10 and rule 13]

TITLE: NOVEL POLYMORPH OF SAMIDORPHAN L-MALATE AND PROCESS FOR PREPARATION THEREOF

NAME AND ADDRESS OF APPLICANT

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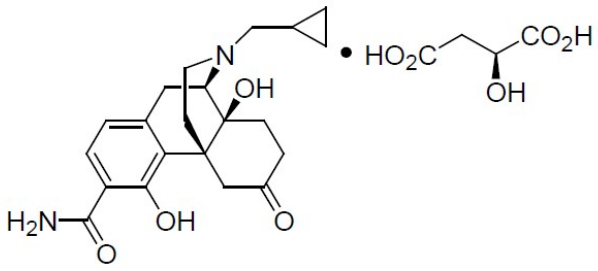
The following specification describes the invention and the manner in which it is to be performed

FIELD OF THE INVENTION

The present invention relates to novel crystalline polymorph of samidorphan L-malate and its process for preparation thereof. The present invention also relates to pharmaceutical composition comprising novel crystalline polymorph of samidorphan L-malate, an antipsychotic, preferably selected from olanzapine, clozapine, risperidone, quetiapine, aripiprazole and ziprasidone and one or more pharmaceutically acceptable excipients.

BACKGROUND OF THE INVENTION

Samidorphan L-malate is marketed under brand name “LYBALVI” (combination of olanzapine and samidorphan) for treatment of schizophrenia and bipolar disorder. Samidorphan L-malate is chemically known as 17-(Cyclopropylmethyl)-4, 14-dihydroxy-6-oxomorphinan-3-carboxamide; (2S)-2-hydroxybutanedioic acid and is represented by following general Formula (I).



(Formula-1)

US7262298B2 discloses process for preparation of samidorphan and its pharmaceutically acceptable salts thereof.

US9119848B2 discloses samidorphan L-malate salt and its process for preparation.

Polymorphism occurred because the difference in the physical properties of different solid forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid.

The present invention provides a novel crystalline polymorph of samidorphan-L malate and process for preparation thereof.

OBJECTS OF THE INVENTION

The main object of the present invention provides a novel crystalline polymorph of samidorphan L-malate.

Another object of the present invention relates to the process for preparation of novel crystalline polymorph of samidorphan L-malate.

Yet, another object of the present invention relates to pharmaceutical composition comprising novel crystalline polymorph of samidorphan L-malate, an antipsychotic, preferably selected from olanzapine, clozapine, risperidone, quetiapine, aripiprazole and ziprasidone and one or more pharmaceutically acceptable excipients.

SUMMARY OF THE INVENTION

The present invention provides a novel crystalline polymorph of samidorphan L-malate and processes for preparation thereof.

An aspect of the present invention provides novel crystalline polymorph of samidorphan L-malate, which is characterized by an X-ray diffraction (XRD) pattern having peaks at about 9.1, 10.3, 12.7, 13.2, 15.1, 16.5, 20.3, 22.0, and 23.2° ± 0.2° 2θ.

Another aspect of the present invention provides a process for preparation of novel crystalline polymorph of samidorphan L-malate, comprising the steps:

a) dissolving samidorphan in mixture of alcohol solvents;

b) adding alcoholic solution of L-malic acid; and

c) stirring, isolating the solid compound.

Yet, another aspect of the present invention relates to pharmaceutical composition comprising novel crystalline polymorph of samidorphan L-malate, an antipsychotic, preferably selected from olanzapine, clozapine, risperidone, quetiapine, aripiprazole and ziprasidone and one or more pharmaceutically acceptable excipients.

Detail description of the drawings:

Figure 1: X-ray powder diffraction pattern (XRPD) of Novel crystalline polymorph of samidorphan L-malate according to example 1

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel crystalline polymorph of samidorphan L-malate and process for preparation thereof.

One aspect of present invention provides novel crystalline polymorph of samidorphan L-malate characterized by an X-ray powder diffraction pattern (XRPD) having peaks at about 9.1, 10.3, 12.7, 13.2, 15.1, 16.5, 20.3, 22.0, and 23.2° ± 0.2° 2θ.

The novel crystalline polymorph of samidorphan L-malate can also be characterized by an X-ray powder diffraction (XRPD) pattern as in Figure 1.

Another aspect of present invention provides a process for preparation of novel crystalline polymorph of samidorphan L-malate comprising the steps of dissolving samidorphan in mixture of alcoholic solvents by heating at 40 °C to reflux temperature, preferably 50 to 70 °C, more preferably 60 to 70 °C. Filtering the reaction mixture to remove any undissolved particles, if any. The reaction mixture is heated to 50 to 70° C, more preferably 60 to 70 ° C and slowly adding alcoholic solution of L-malic acid. Further, stirring the reaction mixture, cooling and isolating the compound.

The alcoholic solvents/solution can be selected from group comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, 2-butanol, isobutanol, n-pentanol or the like and mixture thereof.

Another aspect of the present invention provides a process for preparation of novel crystalline polymorph of samidorphan L-malate, comprising the steps:

a) heating samidorphan in mixture of methanol and ethanol at 60-70 °C;

b) filtering, adding ethanolic solution of L-malic acid at 60-70 °C;

c) stirring, cooling the reaction mixture; and

d) isolating the solid compound.

The compound can be isolated by known method such as filtration, evaporation of solvents and like thereof.

The compound samidorphan used in the preparation of novel crystalline polymorph of samidorphan L-malate can be prepared by any method known in the art.

In another aspect, the present invention relates to a pharmaceutical composition comprising novel crystalline polymorph of samidorphan L-malate and an antipsychotic, preferably selected from olanzapine, clozapine, risperidone, quetiapine, aripiprazole and ziprasidone.

In another aspect, the present invention provides novel crystalline polymorph of samidorphan L-malate, which is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used.

In another further aspect, the present invention also encompasses pharmaceutical compositions comprising novel crystalline polymorph of samidorphan L-malate, of present invention. As used herein, the term "pharmaceutical compositions" or

"pharmaceutical formulations" include injection, tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or preparations.

In another further aspect, the present invention provides pharmaceutical composition comprising novel crystalline polymorph of samidorphan L-malate characterized by an X-ray powder diffraction pattern (XRPD) having peaks at about 9.1, 10.3, 12.7, 13.2, 15.1, 16.5, 20.3, 22.0, and 23.2° ± 0.2° 2θ, an antipsychotic, preferably selected from olanzapine, clozapine, risperidone, quetiapine, aripiprazole, ziprasidone and one or more pharmaceutically acceptable excipients wherein, the pharmaceutically acceptable excipients include binders, diluents, disintegrants, surfactants and lubricants. Suitable binders that can be include polyvinyl pyrolidone, copovidone, starches such as pregelatinized starch, cellulose derivatives such as hydroxypropyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose and carboxymethylcellulose, gelatine, acacia, agar, alginic acid, carbomer, chitosan, dextrates, cyclodextrin, dextrin, glycerol dibehenate, guargum, hypromellose, maltodextrin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, sodium alginate, sucrose, mixtures thereof; suitable diluents that can be include anhydrous lactose, lactose monohydrate, modified lactose, dibasic calcium phosphate, tribasic calcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, maize starch, pregelatinized starch, calcium carbonate, sucrose, glucose, dextrates, dextrins, dextrose, fructose, lactitol, mannitol, sorbitol starch, calcium lactate or mixtures thereof; suitable disintegrants that can be include magnesium aluminometa silicate (or magnesium aluminum silicate), starch, pregelatinized starch, sodium starch glycolate, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, alginic acid, carboxy methyl cellulose sodium, sodium alginate, calcium alginate and chitosan; suitable lubricantsthat can be include (but are not limited to) magnesium stearate, stearic acid, palmitic acid, talc, and aerosil. Suitable surfactants that can be include (but are not limited to) polysorbate polyoxyethylene sorbitan, polyoxyethylene-polyoxy-propylene copolymer and

sodium lauryl sulphate; beta-cyclodextrin include (but are not limited to) sulfobutylalkyl ether-betacyclodextrin, betadex-sulfobutylether sodium, or hydroxypropyl-beta-cyclodextrin.

Although following examples illustrated in the present invention in more detail, but the examples are not intended in any way to limit the scope of the present invention. It will thus be readily apparent to the one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modifications and variation of the concepts herein disclosed may be resorted to by those skilled in the art and that such modifications and variations are considered to be falling within the scope of the invention.

EXAMPLES

Example 1

Preparation of novel crystalline polymorph of samidorphan L-malate

The mixture of samidorphan (75 gm) in methanol (225 ml) and ethanol (225 ml) is heated to 60 to 70 °C. The reaction mixture is filtered through hyflo, filtrate is heated to 60 to 70 °C and slowly added a solution of L-malic acid in ethanol (32 gm in 225 ml). The reaction mixture was stirred for 1 hour at 60 to 70 °C, further cooled to at 25 to 30 °C and stirred for 1 hour. Filtered, washed with ethanol and dried under vacuum to obtained titled compound.

We Claim:

1. A novel crystalline polymorph of samidorphan L-malate characterized by an X-ray powder diffraction pattern (XRPD) having peaks at about 9.1, 10.3, 12.7, 13.2, 15.1, 16.5, 20.3, 22.0, and 23.2° ± 0.2° 2θ.

2. The polymorph as claimed in claim 1, prepared by the process comprising the steps of:

a) dissolving samidorphan in mixture of alcohol solvents;

b) adding alcoholic solution of L-malic; and

c) stirring, isolating the solid compound.

3. The process as claimed in claim 2, wherein the solvent is selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, 2-butanol, isobutanol, n-pentanol or mixtures thereof.

4. The polymorph as claimed in claim 1, prepared by the process comprising the steps of:

a) heating samidorphan in mixture of methanol and ethanol;

b) filtering, adding ethanolic solution of L-malic acid;

c) stirring, cooling the reaction mixture; and

d) isolating the solid compound.

5. The pharmaceutical composition comprising crystalline polymorph as claimed in claim 1, an antipsychotic selected from olanzapine, clozapine, risperidone, quetiapine, aripiprazole, ziprasidone and one or more pharmaceutically acceptable excipients.

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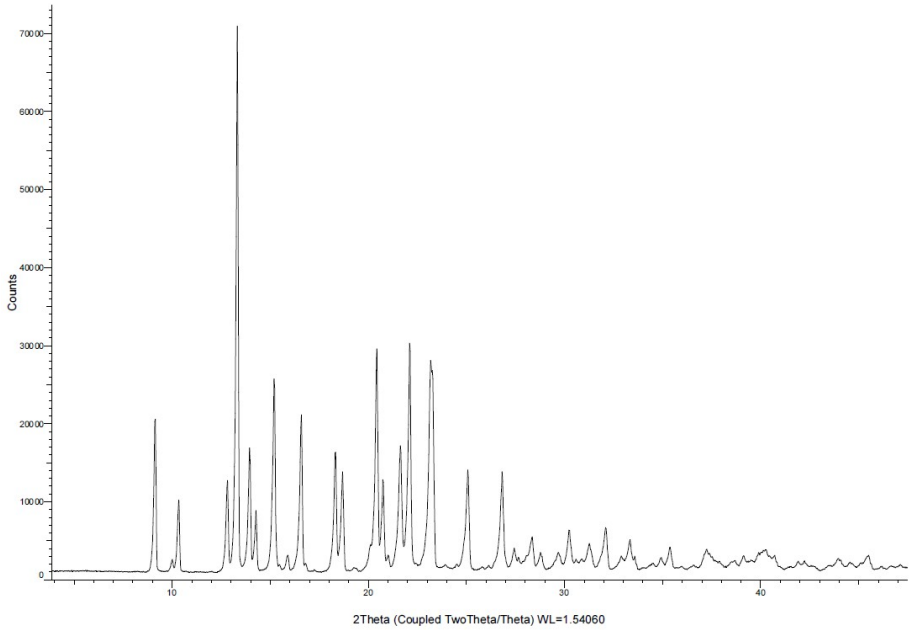

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