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(54) Title: CRYSTALLINE FORMS OF TAPENTADOL SALTS AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: The present invention relates to crystalline forms of Tapentadol salts and process for preparation thereof. The structural formula of Tapentadol salts is represented as follows: [Formula should be inserted here].

Formula- 1

OH

Acid

N

CH₃

CH₃

Formula-1
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CRYSTALLINE FORMS OF TAPENTADOL SALTS AND PROCESS FOR PREPARATION THEREOF

Related application:

This application claims the benefit of priority of our Indian patent application number 6191/CHE/2015 filed on 17th November 2015 which is incorporated herein by reference.

Field of the invention:

The present invention relates to crystalline forms of Tapentadol salts and process for preparation thereof. The structural formula of Tapentadol salts is represented as follows:

\[
\text{OH} \\
\text{Acid} \\
\text{CH}_3 \\
\text{CH}_3
\]

Formula- 1

Background of the invention:

Tapentadol HCl is chemically known as 3-[(IR,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride and is represented as the following structural formula.

\[
\text{OH} \\
\text{CH}_3 \\
\text{HCl}
\]

Formula- 1a

Tapentadol HCl is a centrally acting analgesic which is used in the management of pain. It has a dual mode of action, as an agonist at the µ-opioid receptor and as a norepinephrine reuptake inhibitor. Due to the dual mechanism of action as an opioid agonist and norepinephrine reuptake inhibitor, there is potential for off label use in chronic pain.
the US, 3-[(lR,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride is approved by FDA for the treatment of moderate to severe acute pain.

Tapentadol hydrochloride is commercially available as, immediate release dosage forms and as extended release dosage forms in the form of film coated tablets. These are currently marketed by Grunenthal under the brand name of Palexia® film coated tablets and Palexia® SR prolonged release tablets in Europe. In USA, Ortho McNeil Janssen markets it under the brand name of Nucynta® tablets and Nucynta® ER tablets.


The basic patent for tapentadol, EP0693475B1, discloses processes for the preparation of tapentadol or a pharmaceutically acceptable salt thereof. While it mentions that some of the disclosed compounds can Form salts with physiologically acceptable acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid and/or aspartic acid, only the hydrochloride salt. However, out of the entire range of proposed salts it was only the crystalline hydrochloride that was prepared, isolated and sufficiently described. The polymorph of tapentadol hydrochloride isolated this way was identified as Form B.

European patents EP1612203 and EP 1799633 disclose polymorphic Forms A and B of tapentadol hydrochloride, and characterize them by powder X-ray diffraction (P-XRD), Infra-Red spectroscopy (IR), Raman spectroscopy and crystal structure analysis. EP16 12203 further teaches that the procedure described in example 25 of U.S. Pat. No. 6,248,737 and
U.S. Pat. No. 6,344,558 as well as EP 0693475 B1 produces crystalline Form B of tapentadol hydrochloride.

US201 1071 120 claims novel solid state forms of tapentadol salts, process for their preparation, pharmaceutical compositions, and method of treating thereof. The tapentadol salts include an L-(-)-camphorsulphonate salt, a dibenzoyl-(L)-tartrate salt, a dibenzoyl-(D)-tartrate salt, a maleate salt, a maleate salt, or a salicylate salt. However, salts with high molecular weight acids (e.g. camphor sulfonic, dibenzoyl tartaric acids and the like) are not suitable for pharmaceutical use as they may unacceptably increase the size of the dosage form (Handbook of Pharmaceutical Salts, Wiley, 2011, Chapter 7). This problem must be taken into account especially in the case of tapentadol as commercially available dosage forms contain 50 to 250 mg of tapentadol (as the hydrochloride).

A specific form of tapentadol hydrobromide was also described in WO201 205 1246. A wide range of salts and co-crystals is described in the application WO2012 0103 16; however, most of the forms were not physically characterized in any way and no particular process of their preparation was mentioned. Only the preparation and isolation of tapentadol salts/co-crystals with (2S,3S)-dibenzoyl tartaric acid, sebacic acid, 1-hydroxy-2-naphthoic acid, embonic acid, nitric acid, nicotinic acid, hydrobromic acid, sulfuric acid, fumaric and malonic acid is disclosed in the examples. The said patent also discloses the PXRD of Tapentadol hemi-fumarate.

Polymorphs are distinct solids having the same molecular formula yet having distinct advantageous physical properties compared to other polymorphic forms of the same compound. The difference in the physical properties of different polymorphic forms results from the orientation and intermolecular interactions of adjacent molecules in the bulk solid.

Polymorphism, occurrence of different crystalline forms, is the property of some molecules and molecular complexes. It is generally known that various salts or polymorphs of pharmaceutically active substances may have different physico-chemical, and consequently pharmacological properties. Then, such salts and their polymorphs can be used
to obtain an ideal composition of pharmaceutical formulations containing the given active substance or its salt. This means that it is very important to keep looking for suitable salts or polymorphic forms of pharmaceutically active substances. Discovering new salts and polymorphic forms of tapentadol may provide new methods of improving the characteristics of tapentadol as the active pharmaceutical component of formulations.

There remains a need for novel salts and novel solid state forms of tapentadol salts. The discovery of new polymorphic form of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product.

**Brief description of the invention:**

The first aspect of the present invention is to provide crystalline form of Tapentadol tartrate compound of formula-Ib, herein after designated as crystalline form-M.

The second aspect of the present invention is to provide a process for the preparation of Tapentadol tartrate.

The third aspect of the present invention is to provide crystalline form of Tapentadol fumarate compound of formula-Ic, herein after designated as crystalline form-S.

The fourth aspect the present invention is to provide crystalline form of Tapentadol fumarate compound of formula-Ic, herein after designated as crystalline form-N.

The fifth aspect of the present invention is to provide a process for the preparation of Tapentadol fumarate compound of formula-Ic.

The sixth aspect of the present invention is to provide crystalline form of Tapentadol bisulfate compound of formula-Id, herein after designated as crystalline form-L.

The seventh aspect of the present invention is to provide the process for the preparation of crystalline form-L of Tapentadol bisulfate compound of formula-Id.

**Brief description of the drawings:**

**Figure 1:** Illustrates the PXRD pattern of crystalline form-M of Tapentadol tartrate

**Figure 2:** Illustrates the PXRD pattern of crystalline form-S of Tapentadol fumarate.

**Figure 3:** Illustrates the PXRD pattern of crystalline form-N of Tapentadol fumarate
Figure 4: Illustrates the DSC thermogram of crystalline form-M of Tapentadol tartrate.

Figure 5: Illustrates the DSC thermogram of crystalline form-S of Tapentadol fumarate.

Figure 6: Illustrates the DSC thermogram of crystalline form-N of Tapentadol fumarate.

Figure 7: Illustrates the IR spectrum of crystalline form-M of Tapentadol tartrate.

Figure 8: Illustrates the IR spectrum of crystalline form-S of Tapentadol fumarate.

Figure 9: Illustrates the TGA of crystalline form-M of Tapentadol tartrate.

Figure 10: Illustrates the TGA of crystalline form-S of Tapentadol fumarate.

Figure 11: Illustrates the PXRD pattern of crystalline form-L of Tapentadol bisulfate.

**Detailed description of the invention:**

As used herein the term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; "ether solvents" such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, 1, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; "polar solvents" such as water or mixtures thereof.
The term "acid" used in the present invention refers to inorganic acids selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; organic acids such as acetic acid, maleic acid, malic acid, tartaric acid, oxalic acid, trifluoroacetic acid, methane sulfonic acid, p-toluene sulfonic acid; chiral acids such as S-(+) mandelic acid, R-(-) mandelic acid, L-(+)-tartaric acid, D-(−)-tartaric acid, L-malic acid, D-malic acid, D-maleic acid, (−)-naproxen, (+)-naproxen, (IR)-(−)-camphor sulfonic acid, (IS)-(+) camphor sulfonic acid (IR)-(+) bromocamphor-10-sulfonic acid, (IS)-(−) bromocamphor-10-sulfonic acid, (−)-Dibenzoyl-L-tartaric acid, (−)-Dibenzoyl-L-tartaric acid monohydrate, (+)Dibenzoyl-D-tartaric acid, (−)-Dibenzoyl-D-tartaric acid monohydrate, (+)-dipara-tolyl-D-tartaric acid, (−)-dipara-tolyl-L-tartaric acid, L(-)-pyroglutamic acid, L(+)-pyroglutamic acid, (−)-lactic acid, L-lysine, D-lysine etc., and like.

The term "salts" used in the present invention refers to acid addition salts selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; organic acids such as acetic acid, maleic acid, malic acid, oxalic acid, trifluoroacetic acid, methane sulfonic acid, p-toluene sulfonic acid; chiral acids such as S-(+) mandelic acid, R-(−) mandelic acid, L-(+)tartaric acid, D-(−)tartaric acid, L-malic acid, D-malic acid, D-maleic acid, (−)-naproxen, (+)-naproxen, (IR)-(−)-camphor sulfonic acid, (IS)-(+) camphor sulfonic acid (IR)-(−)bromocamphor-10-sulfonic acid, (IS)-(−) bromocamphor-10-sulfonic acid, (−)-DibenzozyL-L-tartaric acid, (−)-DibenzozyL-L-tartaric acid monohydrate, (+)-DibenzozyL-D-tartaric acid, (−)-DibenzozyL D-tartaric acid monohydrate, (+)-dipara-tolyl-D-tartaric acid, (−)-dipara-tolyl-L-tartaric acid, L(-)-pyroglutamic acid, L(+)-pyroglutamic acid, (−)-lactic acid, L-lysine, D-lysine etc., and like.

The first aspect of the present invention provides crystalline form-M of Tapentadol tartrate compound of formula-lb. The crystalline form-M of the present invention is characterized by its powder X-Ray diffraction pattern having peaks at about 12.7, 14.1, 18.6, 20.0, 21.1, 21.6, 22.1, 23.7, 25.6 & 28.5± 0.2 degrees of 2-theta. The crystalline form-M is further characterized by the PXRD pattern as illustrated in figure-1, its differential scanning calorimetric (DSC) thermogram having an endotherm at 132.76°C±3°C as illustrated in
figure-4 and is further characterized by absorption peaks at 3319, 3237, 2960, 1731, 1597, 1305, 1263, 1213, 791, 679 and 485 cm⁻¹ in its infrared spectrum as illustrated in figure-7.

The second aspect of the present invention provides a process for the preparation of Tapentadol tartrate comprising of:

a) Treating the (2R, 3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentan-1'-amine hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base,
b) optionally isolating tapentadol free base,
c) treating tapentadol free base obtained in step-a) or step-b) with tartaric acid in a suitable solvent to provide Tapentadol tartrate,
d) optionally purifying the obtained compound.

Wherein, in step-c) the suitable solvent is selected from alcohol solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water; preferably ketone solvents and most preferably acetone.

Preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of Tapentadol tartrate compound of formula-1b comprising of:

![Formula-1b](image)

a) Treating the (2R, 3R)-3-(3-methoxyphenyl)-N,N,2-tri methylpentan-1'-amine hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base,
b) treating tapentadol free base in-situ with L-(+)-tartaric acid in acetone to produce crystalline form-M of Tapentadol tartrate.

Further embodiment of the present invention provides a process for the preparation of Tapentadol tartrate comprising of; treating tapentadol free base with tartaric acid in a suitable
solvent to provide Tapentadol tartrate; wherein the suitable solvent is selected from alcohol solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water; preferably ketone solvents and most preferably acetone.

Preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of Tapentadol tartrate comprising of; treating tapentadol free base with L-(+) tartaric acid in acetone to provide crystalline Tapentadol tartrate.

The third aspect of the present invention provides crystalline form-S of Tapentadol fumarate. The crystalline form-S of the present invention is characterized by its powder X-Ray diffraction pattern having peaks at about 9.3, 11.7, 12.5, 13.5, 15.0, 18.1, 20.4, 20.5, 22.2, 22.7, & 29.0± 0.2 degrees of 2-theta. The crystalline form-S is further characterized by its PXRD pattern as illustrated in figure-2, its differential scanning calorimetric (DSC) thermogram having two endotherms at 130.05°C±3°C & 140.9°C±3°C as illustrated in figure-5 and is further characterized by its IR absorption spectrum having absorption peaks at 3050, 2965, 1698, 1644, 1573, 1506, 1453, 1379, 1239, 1206, 998, 977, 789, 652 and 573 cm” as illustrated in figure-8.

The fourth aspect of the present invention provides crystalline form-N of Tapentadol fumarate. The crystalline form-N of the present invention is characterized by its powder X-Ray diffraction pattern having peaks at about 9.3, 12.5, 13.5, 15.0, 18.1, 20.4, 20.5, 22.7, & 29.0± 0.2 degrees of 2-theta. The crystalline form-N is further characterized by its PXRD pattern as illustrated in figure-3 and its differential scanning calorimetric (DSC) thermogram having an endotherm at 142.50°C±3°C as illustrated in figure-6.

The fifth aspect of the present invention provides a process for the preparation of Tapentadol fumarate compound of formula-1c comprising of:
Treating the \((2R, 3i?)-3-(3\text{-methoxyphenyl})-N,N,2\text{-trimethylpentan-1-amine}\) hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base, optionally isolating tapentadol free base, treating tapentadol free base obtained in step-a) or step-b) with fumaric acid in a suitable solvent to provide Tapentadol fumarate, optionally purifying the obtained compound.

Wherein, in step-c) suitable solvent is selected from alcohol solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water; preferably ketone solvents and most preferably acetone.

Preferred embodiment of the present invention provides a process for the preparation of crystalline Tapentadol fumarate comprising of:

a) Treating the \((2R, 3i?)-3-(3\text{-methoxyphenyl})-N,N,2\text{-trimethylpentan-1-amine}\) hydrochloride with aqueous hydrogen bromide to provide tapentadol free base, b) treating tapentadol free base in-situ with fumaric acid in acetone to provide crystalline Tapentadol fumarate.

Further embodiment of the present invention provides a process for the preparation of Tapentadol fumarate comprising of; treating Tapentadol free base with fumaric acid in a suitable solvent to provide Tapentadol fumarate; wherein the suitable solvent is selected from alcohol solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water; preferably ketone solvents and most preferably acetone.

Preferred embodiment of the present invention provides a process for the preparation
of crystalline Tapentadol fumarate comprising of; treating Tapentadol free base with fumaric acid in acetone to provide crystalline Tapentadol fumarate.

The sixth aspect of the present invention provides crystalline form-L of Tapentadol bisulfate. The crystalline form-L of the present invention is characterized by its powder X-Ray diffraction pattern having peaks at about 6.3, 11.6, 15.3, 16.7, 18.8, 20.9, 23.6, 24.2, 25.3 and 26.7± 0.2 degrees of 2-theta and is further characterized by its PXRD pattern as illustrated in figure-11.

The seventh aspect of the present invention provides a process for the preparation of crystalline Tapentadol bisulfate comprising of; treating Tapentadol free base with sulfuric acid in a suitable solvent to provide crystalline Tapentadol bisulfate; wherein the suitable solvent is selected from alcohol solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water.

Preferred embodiment of the present invention provides a process for the preparation of crystalline form-L of Tapentadol bisulfate compound of formula- Id comprising of:

![Formula- Id](image)

treating Tapentadol free base with sulfuric acid in ethanol to provide crystalline form-L of Tapentadol bisulfate.

The (2R, 3/?)-3-(3-methoxyphenyl)-N,N ,2-tri methypentan-1 -amine hydrochloride and Tapentadol free base are prepared by the known prior art processes.

Crystalline forms of Tapentadol fumarate, tapentadol bisulfate or Tapentadol tartrate of the present invention can be utilized in the preparation of pharmaceutical composition
useful for the treatment of pain.

PXRD analysis of crystalline forms of Tapentadol tartrate, tapentadol bisulfate & tapentadol fumarate were carried out using Bruker-AXS/ D8 advance X-Ray diffractometer using Cu Ka1, radiation of wavelength 1.5406 Å and continuous scan speed of 0.03°/min.

IR spectra were recorded on a Perkin-Elmer FTIR spectrometer.

Crystalline forms of Tapentadol salts such as tartrate, bisulfate & fumarate produced by the present invention can be further micronized or milled using conventional techniques to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball, roller and hammer mills, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

The best mode of carrying out the present invention was illustrated by the below mentioned examples. These examples are provides as illustration only and hence should not be construed as limitation of the scope of the invention.

Examples:

Example-I: Preparation of crystalline form-M of Tapentadol tartrate

**Step-a:** Aqueous hydrogen bromide (400 ml) was added to (2R,3i?)-3-(3-methoxyphenyl)-N,N,2-tri methylpentan-1-amine hydrochloride (100 gm) at 25-30°C. Heated the reaction mixture to reflux temperature and stirred for 1½ hour at the same temperature. Cooled the reaction mixture to 40-45°C and water was added to it. Further cooled the reaction mixture to 0-5°C. Basified the reaction mixture using aqueous ammonia at the same temperature. Ethyl acetate was added to the reaction mixture at the same temperature and raised the temperature of the reaction mixture to 25-30°C. Stirred the reaction mixture for 10 minutes and separated the both organic and aqueous layers. Distilled off the solvent from the organic layer under
reduced pressure. Acetone (234 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Filtered the reaction mixture and washed with acetone.

**Step-b:** L(+)-tartaric acid (52.87 gm) was dissolved in 780 ml of acetone at 50-55°C, filtered the obtained solution and washed with acetone. To the obtained reaction mixture added filtrate obtained in step-a) at 25-30°C. Stirred the reaction mixture for 1 ½ hour at 25-30°C. Filtered the precipitated solid, washed with acetone and dried to get the title compound.

Yield: 100 gm; Purity by RS/ HPLC: 99.94% and chiral purity by HPLC: 99.01%.

The PXRD of the obtained compound was shown in figure-1 and its DSC in figure-4.

**Example-2: Preparation of crystalline form-S of Tapentadol fumarate**

**Step-a:** Aqueous hydrogen bromide (400 ml) was added to (2R, 3Z?)-3-(3-methoxyphenyl)-N,N,2-tri methypentan-1-amine hydrochloride (100 gm) at 25-30°C. Heated the reaction mixture to reflux temperature and stirred for 1 ½ hour at the same temperature. Cooled the reaction mixture to 40-45°C and water was added to it. Further cooled the reaction mixture to 0-5°C. Basified the reaction mixture using aqueous ammonia at the same temperature. Ethyl acetate was added to the reaction mixture at the same temperature and raised the temperature of the reaction mixture to 25-30°C. Stirred the reaction mixture for 10 minutes and separated the both organic and aqueous layers. Distilled off the solvent from the organic layer under reduced pressure. Acetone (234 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Filtered the reaction mixture and washed with acetone.

**Step-b:** Fumaric acid (40.90 gm) was dissolved in 2886 ml of acetone at 50-55°C, filtered the obtained solution and washed with acetone. Distilled off the solvent completely under reduced pressure and acetone (546 ml) was added to it at 25-30°C. To the obtained reaction mixture added the filtrate obtained in step-a) at 25-30°C. Stirred the reaction mixture for 45 minutes at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid, washed with acetone and dried to get the title compound. Yield: 110 gm; Purity by HPLC: 99.97% and chiral purity by HPLC: 99.02%.

The PXRD of the obtained compound is shown in figure-2 and it's DSC in figure-5.

**Example-3: Preparation of crystalline form-M of Tapentadol tartrate**
Tartaric acid (67.82 gm) was dissolved in 1000 ml of acetone at 50-55°C, filtered the obtained solution and washed with acetone. To the obtained reaction mixture added a solution of Tapentadol free base (100 gm) in acetone (300 ml) at 25-30°C. 0.1 gm of crystalline tapentadol tartrate was added to the reaction mixture at 25-30°C and stirred the reaction mixture for 1½ hour at the same temperature. Filtered the precipitated solid, washed with acetone and dried to get the title compound. Yield: 150 gm.

The PXRD pattern of the obtained compound is similar to figure-1.

**Example-4: Preparation of crystalline form-N of Tapentadol fumarate**

Fumaric acid (52.44 gm) was dissolved in 3500 ml of acetone at 50-55°C, filtered the obtained solution and washed with acetone. Distilled off the solvent completely under reduced pressure and acetone (700 ml) was added to it at 25-30°C. To the obtained reaction mixture added a solution of tapentadol free base (100 gm) in acetone (300 ml) at 25-30°C and stirred for 10 minutes. 0.1 gm of crystalline tapentadol fumarate was added to the reaction mixture at 25-30°C and stirred for 45 minutes at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid, washed with acetone and dried to get the title compound. Yield: 142 gm.

The PXRD of the obtained compound is shown in figure-3 and it's DSC in figure-6.

**Example-5: Preparation of crystalline form-M of Tapentadol tartrate**

**Step-a:** Aqueous hydrogen bromide (400 ml) was added to (2R, 3Z?)-3-(3-methoxyphenyl)-N,N,2-tri methylpentan-1-amine hydrochloride (200 gm) at 25-30°C. Heated the reaction mixture to 115-120°C and stirred for 1½ hour at the same temperature. Cooled the reaction mixture to 40-45°C and water was added to it. Further cooled the reaction mixture to 0-5°C. Basified the reaction mixture using aqueous ammonia at the same temperature. Ethyl acetate was added to the reaction mixture at the same temperature and raised the temperature of the reaction mixture to 25-30°C. Stirred the reaction mixture for 10 minutes and separated both the organic and aqueous layers. The aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution followed by water. The organic was dried over sodium sulfate and carbon was added to the organic layer.
at 25-30°C. Stirred the reaction mixture for 45 minutes and filtered the reaction mixture. Distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with acetone. Acetone (480 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Filtered the reaction mixture and washed with acetone.

Step-b: L(+)-tartaric acid (108.5 gm) was dissolved in 2400 ml of acetone at 50-55°C, filtered the obtained solution and washed with acetone. To the obtained reaction mixture added filtrate obtained in step-a) at 25-30°C and stirred the reaction mixture for 15 minutes at the same temperature. The reaction mixture was seeded with crystalline form-M of Tapentadol tartrate at 25-30°C and stirred the reaction mixture for 6 hours at the same temperature. Cooled the reaction mixture to 0-5°C and stirred it for 2 hours at the same temperature. Filtered the precipitated solid, washed with acetone and dried to get the title compound. Yield: 210 gm; Purity by RS/HPLC: 99.96%; PXRD of the obtained compound is shown to the figure-1. Tartaric acid content by Potentiometry is 40.14% w/w.

Particle size:- D(0.1): 3.822 µm, D(0.5): 25.472 µm, D(0.9): 95.404 µm.

Example-6: Preparation of crystalline form-S of Tapentadol fumarate

Step-a: Aqueous hydrogen bromide (400 ml) was added to (2R, 3i?)-(3-(3-methoxyphenyl))-N,N,2-tri methylpentan-1-amine hydrochloride (200 gm) at 25-30°C. Heated the reaction mixture to 115-120°C and stirred for 1½ hour at the same temperature. Cooled the reaction mixture to 40-45°C and water was added to it. Further cooled the reaction mixture to 0-5°C. Basified the reaction mixture using aqueous ammonia at the same temperature. Ethyl acetate was added to the reaction mixture at the same temperature and raised the temperature of the reaction mixture to 25-30°C. Stirred the reaction mixture for 10 minutes and separated both the organic and aqueous layers. The aqueous layer was extracted with ethyl acetate.

Combined the organic layers and washed with aqueous sodium chloride solution followed by water. The organic was dried over sodium sulfate and carbon was added to the organic layer at 25-30°C. Stirred the reaction mixture for 45 minutes and filtered the reaction mixture. Distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with acetone. Acetone (480 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Filtered the reaction mixture and washed with acetone.
Step-b: Fumaric acid (83.88 gm) was dissolved in 5920 ml of acetone at 50-55°C, filtered the obtained solution and washed with acetone. Distilled off the solvent completely from the filtrate under reduced pressure. 1120 ml of acetone was added to the obtained compound at 25-30°C and stirred for 5 minutes at the same temperature. To the obtained reaction mixture added filtrate obtained in step-a) at 25-30°C and stirred the reaction mixture for 15 minutes at the same temperature. The reaction mixture was seeded with crystalline form-S of Tapentadol fumarate at 25-30°C and stirred the reaction mixture for 35 minutes at the same temperature. Cooled the reaction mixture to 0-5°C and stirred it for 1 hour at the same temperature. Filtered the precipitated solid, washed with acetone and dried to get the title compound.

Yield: 220 gm; Purity by RS/HPLC: 99.92%. Fumaric acid content by Potentiometry is 37.66% w/w. PXRD of the obtained compound is shown in figure-2.

Example-7: Preparation of crystalline form-L of Tapentadol bisulfate
Dissolved 5 gms of tapentadol free base in 15 ml of ethanol at 25-30°C. Sulfuric acid (2.2 gm) was slowly added to the reaction mixture at 25-30°C and stirred the reaction mixture for 45 minutes at the same temperature. Distilled off the solvent from the reaction mixture completely under reduced pressure and co-distilled with n-heptane. The obtained compound was kept a side for 3 days at 25-30°C, collected the solidified compound and dried to get the title compound.

Yield: 4 gm; PXRD of the obtained compound is shown in figure- 11.

Example-8: Preparation of Tapentadol tartrate
Step-a: Aqueous hydrogen bromide (200 ml) was added to (2R, 3i?-3-(3-methoxyphenyl)-N,N ,2-tri methylpentan-1 -amine hydrochloride (100 gm) at 25-30°C. Heated the reaction mixture to 115-120°C and stirred for 1 ½ hour at the same temperature. Cooled the reaction mixture to 40-45°C and water was added to it. Further cooled the reaction mixture to 0-5°C. Basified the reaction mixture using aqueous ammonia at the same temperature. Ethyl acetate was added to the reaction mixture at the same temperature and raised the temperature of the reaction mixture to 25-30°C. Stirred the reaction mixture for 10 minutes and separated both the organic and aqueous layers. The aqueous layer was extracted with ethyl acetate.
Combined the organic layers and washed with water. The organic was dried over sodium sulfate. Distilled off the solvent completely from the filtrate under reduced pressure. Methyl tertiarybutyl ether (390 ml) was added to the obtained compound at 25-30°C and stirred for 10 minutes. Filtered the reaction mixture and washed with methyl tertiarybutyl ether.

**Step-b:** L(+) - tartaric acid (52.87 gm) was dissolved in 390 ml of isopropyl alcohol at 43-48°C, filtered the obtained solution and washed with isopropyl alcohol. Heated the obtained filtrate to 43-48°C and slowly added filtrate obtained in step-a) at the same temperature stirred the reaction mixture for 15 minutes at the same temperature. The reaction mixture was seeded with crystalline Tapentadol tartrate at 40-43°C. Cooled the reaction mixture to 25-30°C and stirred for 45 minutes at the same temperature. Further cooled the reaction mixture to -10 to -5°C and stirred it for 2 hours at the same temperature. Filtered the precipitated solid, washed with the mixture of isopropanol & methyl tertiarybutyl ether and dried to get the title compound. Yield: 105 gm.
We claim:
1. Crystalline Tapentadol tartrate compound of formula-1b

```
     OH
   /   O
H3C-CH2-CH2-N-CH3
     \      \ H3C CH3
         OH
```

Formula-1b.

2. The crystalline Tapentadol tartrate according to claim 1, wherein said crystalline form is characterized by its powder X-Ray diffraction pattern having peaks at 14.1, 20.0, 21.1 and 23.7± 0.2 degrees of 2-theta.

3. The crystalline Tapentadol tartrate according to claim 2, further characterized by its powder X-Ray diffraction pattern having peaks at 12.7, 14.1, 18.6, 20.0, 21.1, 21.6, 22.1, 23.7, 25.6 & 28.5± 0.2 degrees of 2-theta.

4. The crystalline Tapentadol tartrate according to claim 1, is having the endotherm at 132°C±3°C in its differential scanning calorimetric (DSC) thermogram.

5. The crystalline Tapentadol tartrate according to claim 1, characterized by absorption peaks at 3319, 3237, 2960, 1731, 1597, 1305, 1263, 1213, 791, 679 and 485 cm⁻¹ in its infrared spectrum.

6. A process for the preparation of Tapentadol tartrate comprising of:
   a) Treating the (2R, 3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentan-1-amine hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base,
   b) optionally isolating tapentadol free base,
   c) treating tapentadol free base obtained in step-a) or step-b) with tartaric acid in a suitable solvent to provide Tapentadol tartrate,
   d) optionally purifying the compound obtained in step-c) from a suitable solvent.
7. A process for the preparation of Tapentadol tartrate comprising of: treating tapentadol free base with tartaric acid in a suitable solvent to provide Tapentadol tartrate.

8. The process according to claims 6) and 7), wherein, the suitable solvent is selected from alcohol solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water; preferably ketone solvents and most preferably acetone.

9. A process for the preparation of crystalline form-M of Tapentadol tartrate comprising of:
   a) Treating the (2R, 3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentan-1-amine hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base,
   b) treating tapentadol free base in-situ with L-(+)tartaric acid in acetone to provide crystalline form-M of Tapentadol tartrate compound of formula lb.

10. A process for the preparation of crystalline form-M of Tapentadol tartrate comprising of; treating tapentadol free base with L-(+)tartaric acid in acetone to provide crystalline form-M of Tapentadol tartrate.

11. Crystalline form-S of tapentadol fumarate which is characterized by its powder X-Ray diffraction pattern substantially in accordance with that shown in figure-2.

12. The crystalline form-S of Tapentadol fumarate according to claim 11, further characterized by its powder X-Ray diffraction pattern having peaks at about 9.3, 13.5, 15.0, 20.4, 22.2, 22.7, & 29.0± 0.2 degrees of 2-theta.

13. The crystalline form-S of Tapentadol fumarate according to claim 12, further characterized by its powder X-Ray diffraction pattern having peaks at about 9.3, 11.7, 12.5, 13.5, 15.0, 18.1, 20.4, 20.5, 22.2, 22.7, & 29.0± 0.2 degrees of 2-theta.
14. The crystalline form-S of Tapentadol fumarate according to claim 11, having one endotherm at 130°C±3°C, and second endotherm at 140°C±3°C in its differential scanning calorimetric (-DS6)-thermogram.

15. The crystalline form-S of Tapentadol fumarate according to claim 11, characterized by absorption peaks at 3050, 2965, 1698, 1573, 1506, 1453, 1379, 1239, 1206, 998, 977, 789, 652 and 573 cm\(^{-1}\) in its infrared spectrum.

16. Crystalline form-N of tapentadol fumarate which is characterized by its powder X-Ray diffraction pattern substantially in accordance with that shown in figure-3.

17. The crystalline form-N of Tapentadol fumarate according to claim 15, is further characterized by its powder X-Ray diffraction pattern having peaks at about 9.3, 12.5, 13.5, 15.0, 18.1, 20.4, 20.5, 22.7, & 29.0± 0.2 degrees of 2-theta.

18. The crystalline form-N of Tapentadol fumarate according to claim 15, having endotherm at 142.50°C±3°C in its differential scanning calorimetric (DSC) thermogram.

19. A process for the preparation of Tapentadol fumarate comprising of:

\[
\text{Formula-1c}
\]

\begin{center}
\includegraphics[width=0.5\textwidth]{formula.png}
\end{center}

a) Treating the (2R, 3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentan-1-amine hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base,

b) optionally isolating tapentadol free base,

c) treating tapentadol free base obtained in step-a) or step-b) with fumaric acid in a suitable solvent to provide Tapentadol fumarate,

d) optionally purifying the obtained compound in step-c).
20. A process for the preparation of Tapentadol fumarate comprising of: treating tapentadol free-base with fumaric acid in a suitable solvent to provide Tapentadol fumarate:

21. The process according to claims 19) and 20), wherein, the suitable solvent is selected from alcoholic solvents, ketone solvents, ester solvents, hydrocarbon solvents, ether solvents, chloro solvents and mixture thereof or optionally in combination with water; preferably ketone solvents and most preferably acetone.

22. A process for the preparation of crystalline form-S of Tapentadol fumarate comprising of:
   a) Treating the (2R, 3R)-3-(3-methoxyphenyl)-N,N,2-trimethylpentan-1-amine hydrochloride with aqueous hydrogen bromide solution to provide tapentadol free base,
   b) treating tapentadol free base in-situ with fumaric acid in acetone to provide crystalline form-S of Tapentadol tartrate compound of formula-lc.

23. A process for the preparation of crystalline Tapentadol fumarate comprising of: treating tapentadol free base with fumaric acid in acetone to provide crystalline Tapentadol fumarate.

24. Crystalline form-L of Tapentadol bisulfate compound of formula-Id which is characterized by its powder X-Ray diffraction pattern substantially in accordance with that shown in figure-11

\[
\begin{align*}
\text{OH} \\
\text{H}_3\text{C} & \text{N} \text{CH}_3 \\
\text{CH}_3 & \text{CH}_3
\end{align*}
\]

\[\text{H}_2\text{SO}_4\]

Formula-Id.
25. The crystalline form-L of Tapentadol bisulfate according to claim 24, further characterized by its powder X-Ray diffraction pattern having peaks at 6.3, 11.6, 15.3, 16.7, 18.8, 20.9, 23.6, 24.2, 25.3 and 26.7± 0.2 degrees of 2-theta.

26. A process for the preparation of crystalline form-L of Tapentadol bisulfate comprising of; treating tapentadol free base with sulfuric acid in ethanol to provide crystalline form-L of Tapentadol bisulfate.

27. The crystalline Tapentadol tartrate, tapentadol fumarate and tapentadol bisulfate obtained according to any of preceding claims having purity >95%, preferably >99% by HPLC.

28. Use of crystalline forms of tapentadol tartrate, tapentadol fumarate and tapentadol bisulfate obtained according to any of preceding claims in the preparation of pharmaceutical composition.

29. The pharmaceutical composition comprising crystalline forms of tapentadol tartrate, tapentadol fumarate and tapentadol bisulfate obtained according to any of preceding claims and a pharmaceutically acceptable carrier.
Figure-9

Figure-10
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00, A61P25/04, C07C215/00 Version=2017.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K, A61P, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patseek, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>WO 2012051246 A1 (RATIOPHARM GMBH) 19-04-2012 see Claims 1-3; page 6; example 1-3</td>
<td>1-10 (fully), 27-29 (partly)</td>
</tr>
<tr>
<td>Y</td>
<td>WO 2014108514 A1 (FARMA GRS D.O.O.) 17-07-2014 see Claims 1-20; page 6-7; example 1, 5, 6c, 10, 30 a-j</td>
<td>1-10 (fully), 27-29 (partly)</td>
</tr>
<tr>
<td>Y</td>
<td>CN 103553940 A (NANJING NMG ADDS CO LTD ) 05-02-2014 see Claims 1-7; para 18-22, 31-36 examples</td>
<td>1-10 (fully), 27-29 (partly)</td>
</tr>
<tr>
<td>Y</td>
<td>US 8981154 B2 (ACTAVIS GROUP PTC EHF ) 17-03-2015 see Claims 1-3, 6, 9; para 13, example 3-6</td>
<td>1-10 (fully), 27-29 (partly)</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search 30-03-2017
Date of mailing of the international search report 30-03-2017

Name and mailing address of the ISA/Indian Patent Office
Plot No. 32, Sector 14, Dwarka, New Delhi-110075
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Authorized officer
Kausik Bag
Telephone No. +91-1125300200
**INTERNATIONAL SEARCH REPORT**

**Box No. II**  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III**  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>Claims Nos.</th>
<th>Substantive matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1–10 (fully) and 27–29 (partially)</td>
<td>The subject matter of the claims relate to crystalline Tapendado l Tart rate compound of formula a-1b along with its characterizing X-ray</td>
</tr>
</tbody>
</table>

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   
   Claims 1–10 (fully) and 27–29 (partially)

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (January 2015)
Continuation of Observations where unity of invention is lacking (Box III)

Diffraction pattern, the process of preparation thereof, and their purity, use and pharmaceutical composition.

Group II:
Claims 11-23 (fully) and 27-29 (partially)

The subject matter of these claims relates to different crystalline form of Tapendadol fumarate of formula-1c along with its characterizing X-ray diffraction pattern, the process of preparation thereof, and their purity, use and pharmaceutical composition.

Group III:
Claims 24-26 (fully) and 27-29 (partially)

The subject matter of these claims relates to crystalline form of Tapendadol bisulfate of formula-1d along with its characterizing X-ray diffraction pattern, the process of preparation thereof, and their purity, use and pharmaceutical composition.

Reason:

The formula 1b, 1c and 1d are the different crystalline forms of tapendadol where tapendadol is the primary structure of all the crystals. The process of preparation from tapendadol free base along with their purity level, use and pharmaceutical composition are similar in nature for all the three forms of crystals of tapendadol. The only difference lies in the formula is in the complexing counterpart of the respective crystals i.e. tartaric, fumarate and bisulfate. The hydrochloride form of tapendadol, isolation of free basic tapendadol along with crystalline hydrochloride, maleate tapendadol are already well known from the documents CN 103553940 A and WO 2014108514 A1. Therefore the common technical feature tapendadol as well as its crystalline form are known from the above documents. Hence it could not be served as a special technical feature among these three groups. Further, there is no other special technical feature which co-relates these three groups of inventions. Hence the international application does not comply with the requirement of unity of invention (Rules 13.1, 13.2 and 13.3).
<table>
<thead>
<tr>
<th>Citation</th>
<th>Pub.Date</th>
<th>Family</th>
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