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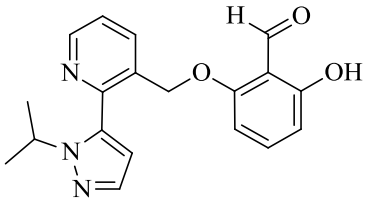
Novel polymorphs of Voxelotor and their processes for preparation thereof

MSN Laboratories Private Limited, R&D Center; Srinivasan Thirumalai Rajan; Sajja Eswaraiah; Vijayavitthal T. Mathad; Saladi Venkata Narasayya and Kammari Balraju.

Novel polymorphs of Voxelotor and their processes for preparation thereof

Field of the invention:

The present invention relates to novel polymorphs of Voxelotor of formula-1, which is represented by the following structural formula-1 and process for preparation thereof.



Formula-1.

Background of the invention:

Voxelotor of Formula-1 is chemically known as 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde is the first hemoglobin oxygen-affinity modulator.

Voxelotor is sold under the brand name of Oxbryta. It is approved by USFDA on November 2019 for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older and on December 2021 for the treatment of sickle cell disease for those aged between four to eleven years.

US 9018210 B2 patent describes the Voxelotor product and discloses the process for the preparation of Voxelotor.

US 9447071 B2 patent describes the crystalline ansolvate forms I, II and Material N of Voxelotor of formula-1 and crystalline solvate forms such as Material E, Material F, Material G, Material H, Material J, Material K, Material L, Material M, Material O, Material P of Voxelotor of formula-1 and its preparation method thereof.

In many cases, knowledge concerning the possible existence of crystalline modifications, also described as crystalline forms or polymorphs, or of solvates (pseudo polymorphs) of the active substance in question, and knowledge of the specific properties of such modifications and solvates and methods for their preparation are of decisive importance for the production of active substances on the industrial scale and also for the formulation of active substances. A range of active substances can exist in different crystalline forms but

also in amorphous modifications.

Different modifications of the same active substance can have different properties for instance solubility, vapor pressure, dissolution rate, stability during grinding, suspension stability, optical and mechanical properties, hygroscopicity, crystal form and size, filterability, density, melting point, stability to decomposition, color and sometimes even chemical reactivity or biological activity.

Hence, there is always a need to develop different solid-state forms or polymorphs of Voxelotor to meet the pharmaceuticals requirements.

In addition, the development of new polymorphic forms of an active pharmaceutical ingredient provides new opportunity to improve the characteristics of pharmaceutical finished product performance; hence, the development of new polymorphic forms of active substance is always encouraged.

Furthermore, solid-state study of an active pharmaceutical ingredient aims to widen the variety of polymorphs that a formulation scientist have for designing a pharmaceutical dosage form with desired characteristics.

The inventors of the present application have surprisingly found novel crystalline forms of Voxelotor after significant efforts, which are useful for the preparation of various pharmaceutical compositions.

Summary of the invention:

The first embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M1 and its process.

The second embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M2 and its process.

The third embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M3 and its process.

The fourth embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M4 and its process.

The fifth embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M5 and its process.

The sixth embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M6 and its process.

The seventh embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M7 and its process.

The eighth embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M8 and its process.

The ninth embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M9 and its process.

The tenth embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M10 and its process.

The eleventh embodiment of the present invention provides novel crystalline form of Voxelotor of formula-1, herein after designated as crystalline form-M11 and its process.

Brief description of the drawings:

Figure-1: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M1 of Voxelotor.

Figure-2: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M2 of Voxelotor.

Figure-3: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M3 of Voxelotor.

Figure-4: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M4 of Voxelotor.

Figure-5: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M5 of Voxelotor.

Figure-6: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M6 of Voxelotor.

Figure-7: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M7 of Voxelotor.

Figure-8: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M8 of Voxelotor.

Figure-9: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M9 of Voxelotor.

Figure-10: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M10 of Voxelotor.

Figure-11: Illustrates the powder X-Ray diffraction {PXRD} pattern of crystalline form-M11 of Voxelotor.

Detailed description of the invention:

The various embodiments in the present invention will be described in detail with reference to the accompanying drawings. References made to particular examples and implementations are for illustrative purpose and are not intended to limit the scope of the invention or the claims.

The “suitable solvent” used in the present invention can be selected from but not limited to “hydrocarbon solvents” such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof; “ether solvents” such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and mixtures thereof; “ester solvents” such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and mixtures thereof; “polar-aprotic solvents” such as dimethylacetamide, dimethylformamide, dimethyl sulfoxide, N-methyl pyrrolidone (NMP) and mixtures thereof; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene and mixtures thereof; “ketone solvents” such as acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and mixtures thereof; “alcohol solvents” such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and mixtures thereof; “polar solvents” such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The “room temperature” used in the present invention is the temperature about 25°C-35°C.

The first embodiment of the present invention provides novel crystalline form of

Voxelotor of formula-1 designated as crystalline form-M1, which is characterized by PXRD pattern as illustrated in Figure 1.

In an aspect of the first embodiment, the present invention provides the process for preparation of crystalline form-M1 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in isobutanol,

b) isolating crystalline form-M1 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M1 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -60°C to about 25°C and followed by filtering the precipitated solid.

The second embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M2, which is characterized by PXRD pattern as illustrated in Figure 2.

In an aspect of the second embodiment, the present invention provides the process for preparation of crystalline form-M2 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in 2-butanol,

b) isolating crystalline form-M2 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M2 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -25°C to about 25°C and followed by filtering the precipitated solid.

The third embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M3, which is characterized by PXRD pattern as illustrated in Figure 3.

In an aspect of the third embodiment, the present invention provides the process for preparation of crystalline form-M3 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in isopropyl acetate,

b) isolating crystalline form-M3 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M3 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -55°C to about 25°C and followed by filtering the precipitated solid.

The fourth embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M4, which is characterized by PXRD pattern as illustrated in Figure 4.

In an aspect of the fourth embodiment, the present invention provides the process for preparation of crystalline form-M4 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in toluene,

b) isolating crystalline form-M4 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M4 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -55°C to about 25°C and followed by filtering the precipitated solid.

The fifth embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M5, which is characterized by PXRD pattern as illustrated in Figure 5.

In an aspect of the fifth embodiment, the present invention provides the process for preparation of crystalline form-M5 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in dimethyl formamide,

b) isolating crystalline form-M5 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-

M5 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -55°C to about 25°C and followed by filtering the precipitated solid.

The sixth embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M6, which is characterized by PXRD pattern as illustrated in Figure 6.

In an aspect of the sixth embodiment, the present invention provides the process for preparation of crystalline form-M6 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in acetic acid,

b) isolating crystalline form-M6 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M6 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -25°C to about 25°C and followed by filtering the precipitated solid.

The seventh embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M7, which is characterized by PXRD pattern as illustrated in Figure 7.

In an aspect of the seventh embodiment, the present invention provides the process for preparation of crystalline form-M7 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in chloroform,

b) isolating crystalline form-M7 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M7 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -55°C to about 25°C and followed by filtering the precipitated solid.

The eighth embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M8, which is characterized by PXRD pattern as illustrated in Figure 8.

In an aspect of the eighth embodiment, the present invention provides the process for preparation of crystalline form-M8 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in N-methyl pyrrolidine,

b) isolating crystalline form-M8 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M8 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -15°C to about 25°C and followed by filtering the precipitated solid.

The ninth embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M9, which is characterized by PXRD pattern as illustrated in Figure 9.

In an aspect of the ninth embodiment, the present invention provides the process for preparation of crystalline form-M9 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in N, N-dimethyl acetamide,

b) isolating crystalline form-M9 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M9 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -5°C to about 25°C and followed by filtering the precipitated solid.

The tenth embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M10, which is characterized by PXRD pattern as illustrated in Figure 10.

In an aspect of the tenth embodiment, the present invention provides the process for

preparation of crystalline form-M10 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in dimethyl sulfoxide,

b) isolating crystalline form-M10 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M10 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to about 25°C and followed by filtering the precipitated solid.

The eleventh embodiment of the present invention provides novel crystalline form of Voxelotor compound of formula-1 designated as crystalline form-M11, which is characterized by PXRD pattern as illustrated in Figure 11.

In an aspect of the eleventh embodiment, the present invention provides the process for preparation of crystalline form-M11 of Voxelotor, comprising:

a) dissolving Voxelotor of Formula-1 in chlorobenzene,

b) isolating crystalline form-M11 of the Voxelotor of Formula-1.

Wherein the dissolving Voxelotor of formula-1 in step-a) can be done at temperature ranging between about 25° C to reflux temperature of the solvent used; isolation of crystalline form-M11 of Voxelotor of Formula-1 in step-b) can be done by cooling the obtained solution to the temperature range between about -25°C to about 25°C and followed by filtering the precipitated solid.

Voxelotor used in the preparation of novel polymorphic forms is prepared by any of the processes disclosed in literature such as US 9018210 B2, US 9447071 B2 or any other relevant references.

Crystalline forms M1 to M11 of Voxelotor of formula-1 produced according to the present invention is having purity of greater than about 99%, preferably greater than about 99.5%, more preferably greater than about 99.7%, most preferably greater than about 99.8% by HPLC {High Performance Liquid Chromatography}.

Crystalline forms M1 to M11 of Voxelotor of formula-1 produced by the processes of

the present invention can be further micronized or milled to get 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 single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling or micronization may be performed before drying or after drying of the product.

Crystalline forms M1–M11 of Voxelotor of formula-1 of the present invention is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of compound of formula-1 is present in the composition in particular polymorphic form mentioned.

The twelfth embodiment of the present invention provides the use of crystalline forms M1 to M11 of Voxelotor of formula-1 for the preparation of various pharmaceutical formulations.

The thirteenth embodiment of the present invention provides a pharmaceutical composition comprising any one of the crystalline forms M1 to M11 of Voxelotor of formula-1 and at least one pharmaceutically acceptable excipient.

As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Wherein, suitable pharmaceutically acceptable excipients selected from but not limited to binders, diluents, disintegrants, surfactants and lubricants. Suitable binders that can be include polyvinylpyrolidone, copovidone, starches such as pregelatinized starch, cellulose derivatives such as hydroxypropylmethyl cellulose, ethylcellulose, hydroxypropylcellulose and carboxymethylcellulose, gelatin, acacia, agar, alginic acid, carbomer, chitosan, dextrates, cyclodextrin, dextrin, glyceryl 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 lubricants that 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 80, polyoxyethylene sorbitan, polyoxyethylene-polyoxy-propylene copolymer and sodium lauryl sulphate; beta-cyclodextrin include (but are not limited to) sulfobutylalkyl ether-beta-cyclodextrin, betadex-sulfobutylether sodium, or hydroxypropyl-beta-cyclodextrin.

P-XRD Method of Analysis:

The PXRD analysis of compound of formula-1 of the present invention was carried out by using BRUKER/D8 ADVANCE or BRUKER/D2 PHASER diffractometer using CuKα radiation of wavelength 1.5406A°.

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

Examples:

Example 1: Preparation of crystalline form-M1 of Voxelotor

Dissolved Voxelotor (300 mg) in isobutanol (1 ml) at 60°C. The obtained solution was cooled to -50°C and held. Filtered the precipitated solid and dried to get the title compound.
Yield: 210 mg. PXRD of the obtained compound is illustrated in figure-1.

Example 2: Preparation of crystalline form-M2 of Voxelotor

Dissolved Voxelotor (300 mg) in 2-butanol (1.5 ml) at 60°C. The obtained solution was cooled to -20°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 225 mg. PXRD of the obtained compound is illustrated in figure-2.

Example 3: Preparation of crystalline form-M3 of Voxelotor

Dissolved Voxelotor (300 mg) in isopropyl acetate (1 ml) at 60°C. The obtained solution was cooled to -50°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 195 mg. PXRD of the obtained compound is illustrated in figure-3

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Example 4: Preparation of crystalline form-M4 of Voxelotor

Dissolved Voxelotor (300 mg) in toluene (1 ml) at 60°C. The obtained solution was cooled to -50°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 210 mg. PXRD of the obtained compound is illustrated in figure-4.

Example 5: Preparation of crystalline form-M5 of Voxelotor

Dissolved Voxelotor (300 mg) in dimethyl formamide (0.6 ml) at 60°C. The obtained solution was cooled to -50°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 180 mg. PXRD of the obtained compound is illustrated in figure-5.

Example 6: Preparation of crystalline form-M6 of Voxelotor

Dissolved Voxelotor (300 mg) in acetic acid (0.5 ml) at 60°C. The obtained solution was cooled to -20°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 150 mg. PXRD of the obtained compound is illustrated in figure-6.

Example 7: Preparation of crystalline form-M7 of Voxelotor

Dissolved Voxelotor (300 mg) in chloroform (0.5 ml) at 60°C. The obtained solution was cooled to -50°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 200 mg. PXRD of the obtained compound is illustrated in figure-7.

Example 8: Preparation of crystalline form-M8 of Voxelotor

Dissolved Voxelotor (300 mg) in N-methylpyrrolidine (0.5 ml) at 60°C. The obtained

solution was cooled to -10°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 185 mg. PXRD of the obtained compound is illustrated in figure-8.

Example 9: Preparation of crystalline form- M9 of Voxelotor

Dissolved Voxelotor (300 mg) in N, N-dimethyl acetamide (0.5 ml) 60°C. The obtained solution was cooled to 0-5 °C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 158 mg. PXRD of the obtained compound is illustrated in figure-9.

Example 10: Preparation of crystalline form- M10 of Voxelotor

Dissolved Voxelotor (300 mg) in dimethyl sulfoxide (0.5 ml) at 60°C. The obtained solution was cooled to room temperature and held. Filtered the precipitated solid and dried to get the title compound.

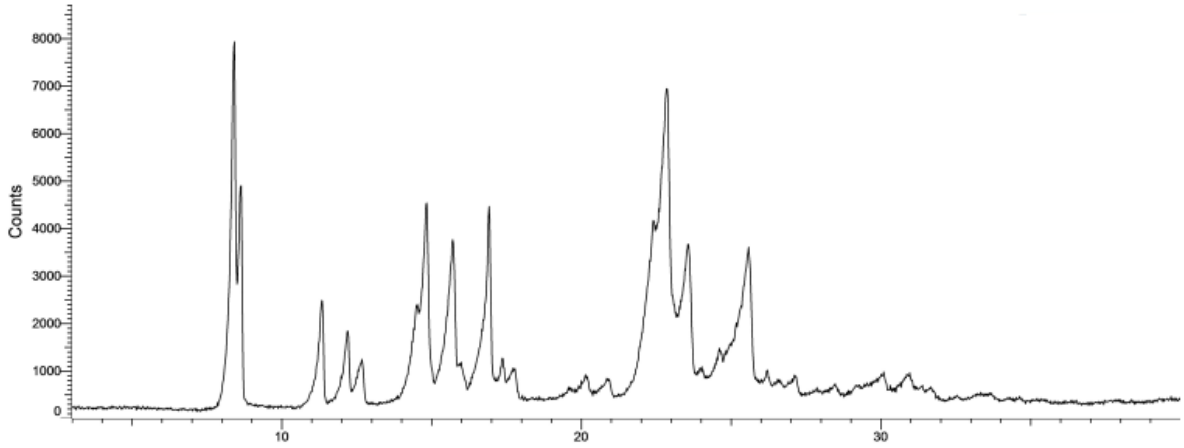
Yield: 170 mg. PXRD of the obtained compound is illustrated in figure-10.

Example 11: Preparation of crystalline form- M11 of Voxelotor

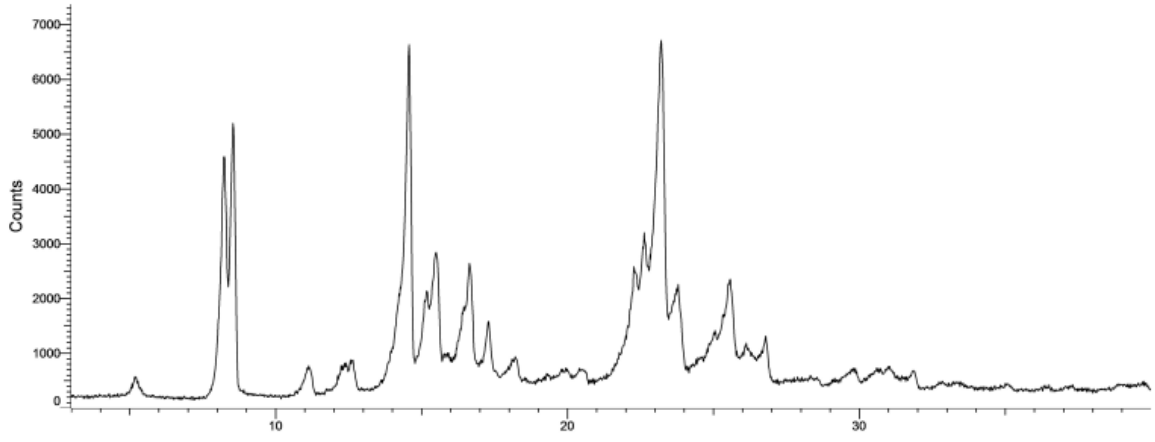
Dissolved Voxelotor (300 mg) in chlorobenzene (0.8 ml) at 60°C. The obtained solution was cooled to -20°C and held. Filtered the precipitated solid and dried to get the title compound.

Yield: 190 mg. PXRD of the obtained compound is illustrated in figure-11.

Drawings



2-Theta-Scale
Figure-1



2-Theta-Scale
Figure-2

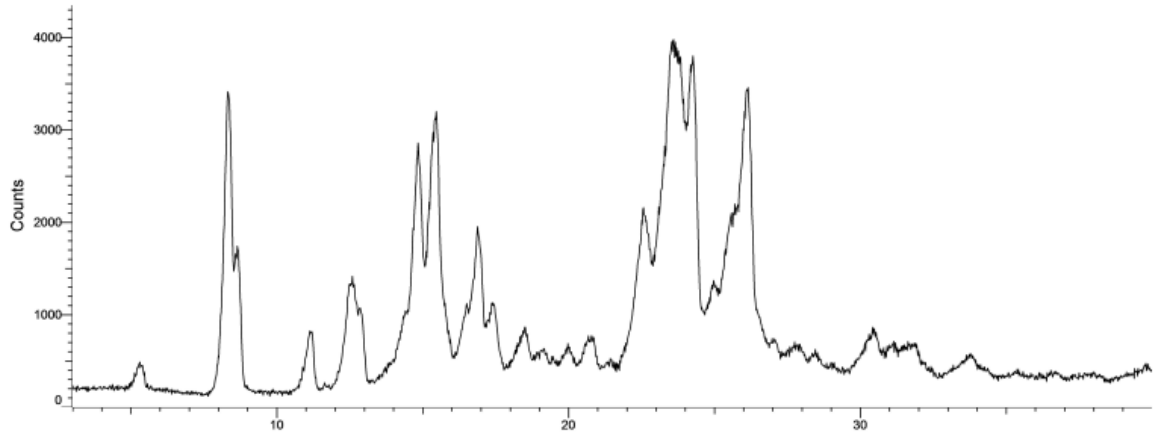


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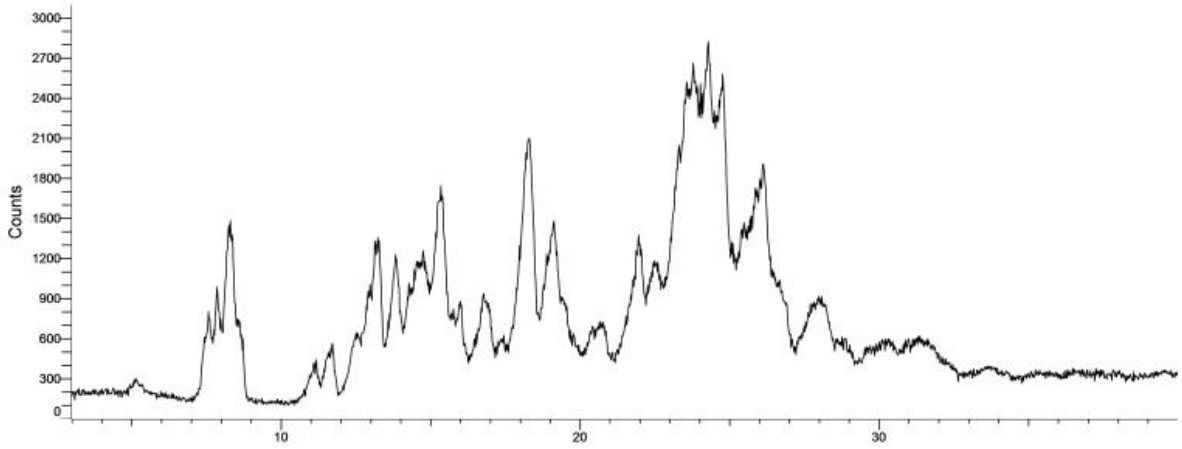
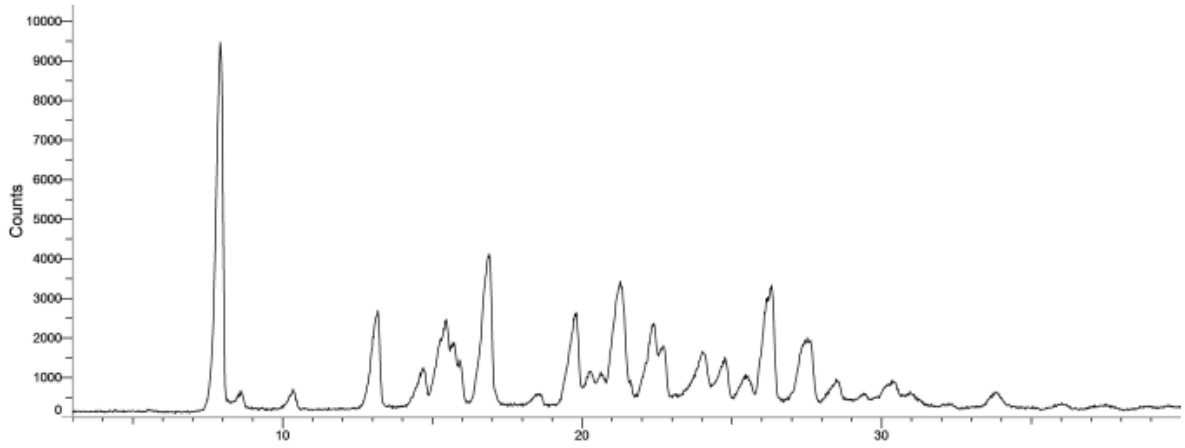
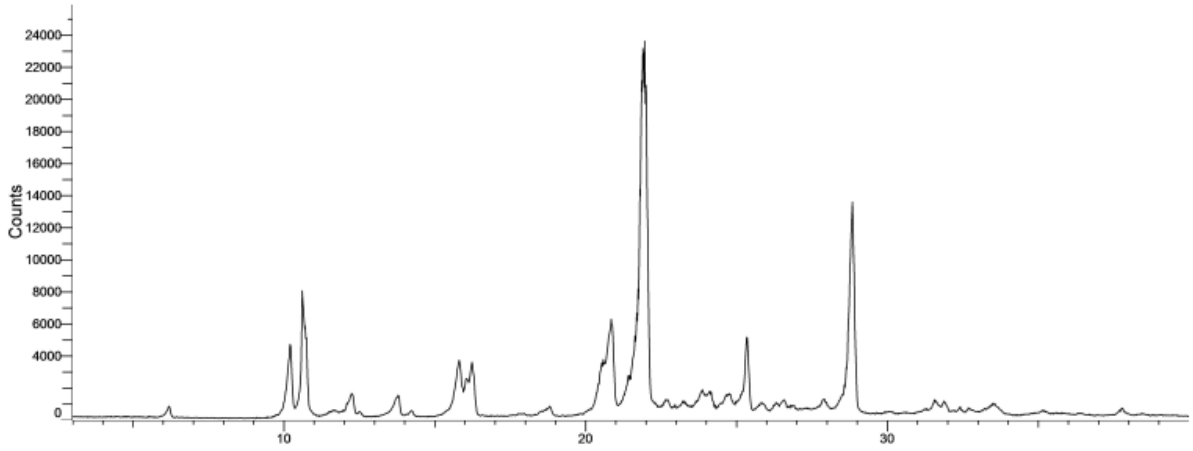
Figure-3



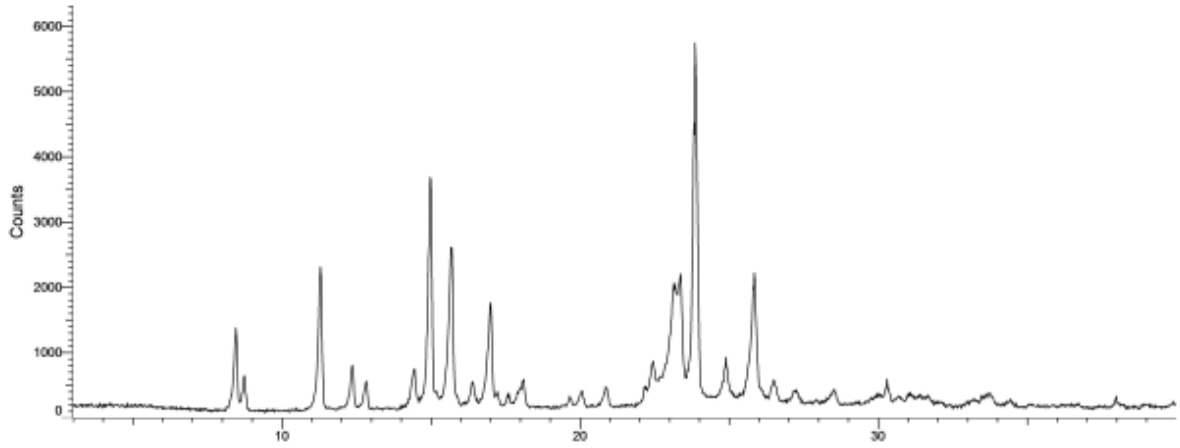
2-Theta-Scale
Figure-4



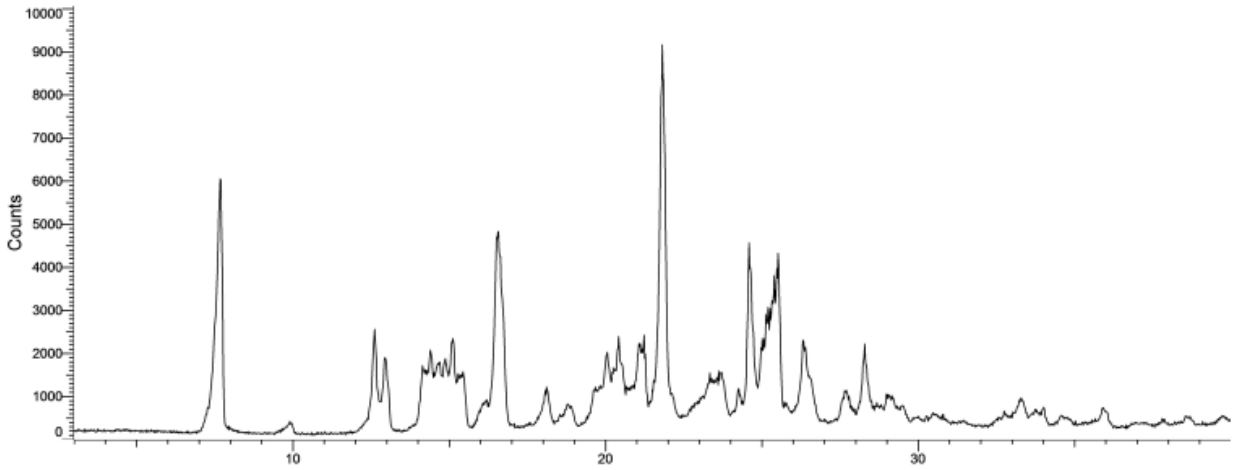
2-Theta-Scale
Figure-5



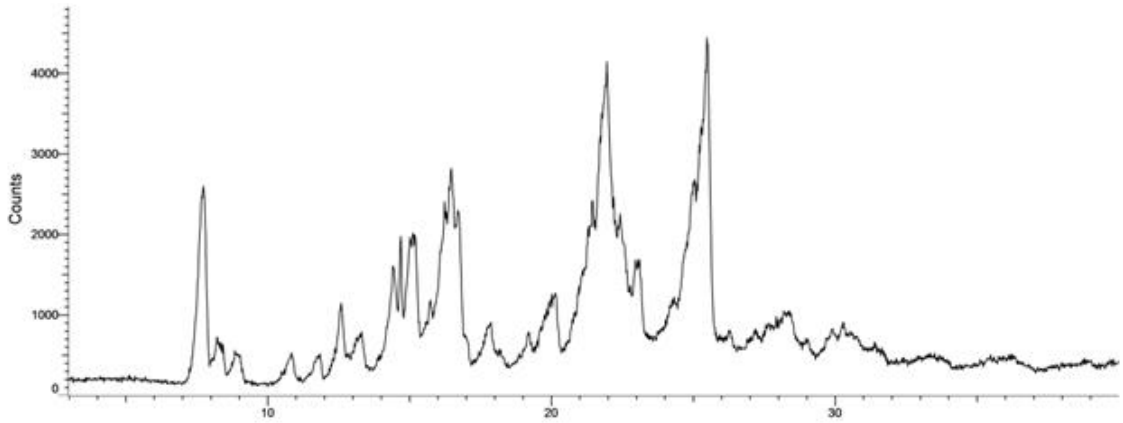
2-Theta-Scale
Figure-6



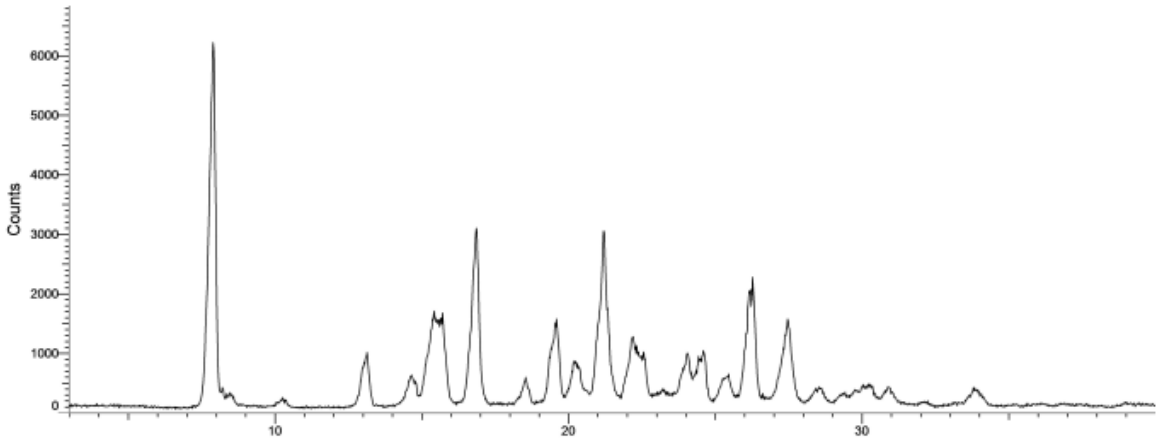
2-Theta-Scale
Figure-7



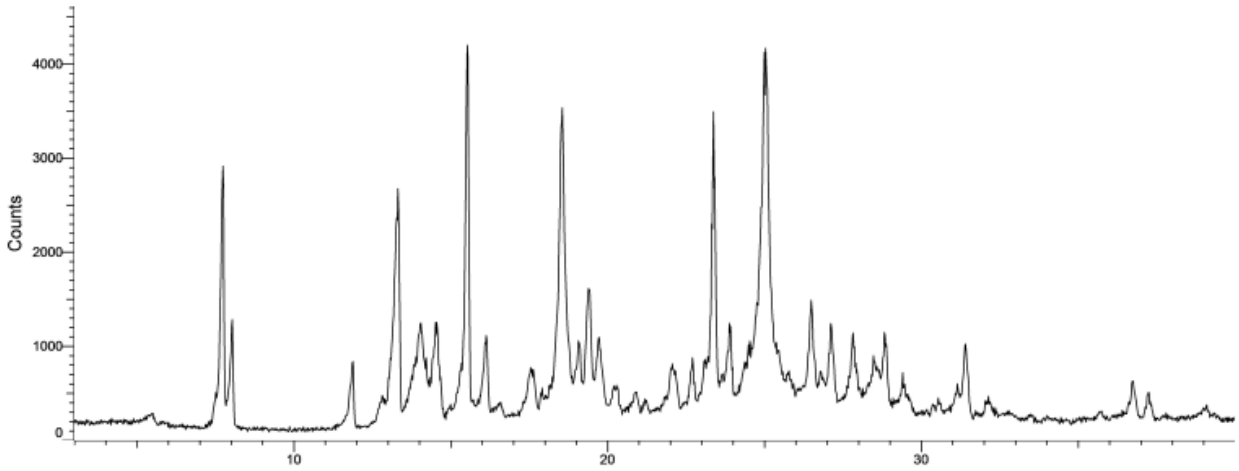
2-Theta-Scale
Figure-8



2-Theta-Scale
Figure-9



2-Theta-Scale
Figure-10



2-Theta-Scale
Figure-11

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