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Solid State Form Of Salcaprozate Sodium And Process For Preparation Thereof

Anonymous

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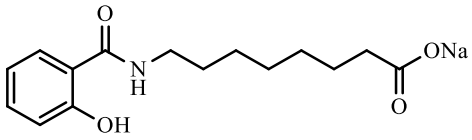
The present invention provides solid state form of Salcaprozate sodium represented by the following structural formula-1a and process for preparation thereof.



Formula-1a

Sodium 8-(2-hydroxybenzamido)octanoate (commonly known as Salcaprozate sodium or SNAC) and its process for preparation is described in US5650386A.

Salcaprozate sodium is used for facilitating the delivery of various active pharmaceuticals ingredients like Semaglutide.

The present inventors have developed crystalline polymorph of Salcaprozate sodium and process for its preparation.

The present invention provides crystalline polymorph of sodium 8-(2-hydroxy benzamido)octanoate compound of formula-1a. The crystalline polymorph of compound of formula-1a of the present invention is characterized by its PXRD pattern having peaks at about 6.7, 11.5 and 18.2 ± 0.2° of 2-theta values.

The crystalline polymorph of compound of formula-1a of the present invention is further characterized by its PXRD pattern having peaks at about 9.6, 13.2, 16.1, 16.2, 16.8, 19.5, 20.4, 21.7, 22.2, 23.3, 24.8 and 28.0 ± 0.2° of 2-theta values.

The crystalline polymorph of compound of formula-1a of the present invention is further characterized by its PXRD pattern as illustrated in figure-1.

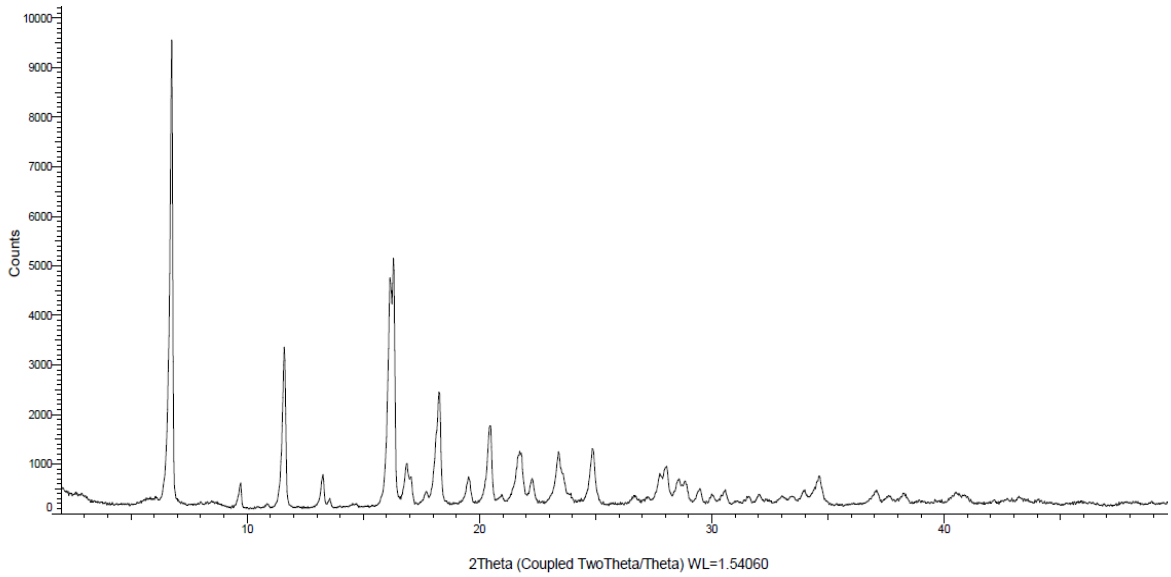


Figure-1: PXRD pattern of crystalline polymorph of Salcaprozate sodium.

The crystalline polymorph of Salcaprozate sodium of the present invention is prepared by the process as described in the present invention.

The present invention further provides a process for the preparation of crystalline polymorph of sodium 8-(2-hydroxy benzamido)octanoate compound of formula-1a characterized by its PXRD pattern having peaks at about 6.7, 11.5 and 18.2 ± 0.2° of 2-theta values, comprising;

a) providing a mixture of 8-(2-hydroxybenzamido)octanoic acid compound of formula-1 and a sodium source in a solvent or mixture of solvents,
b) obtaining crystalline polymorph of compound of formula-1a characterized by its PXRD pattern having peaks at about 6.7, 11.5 and 18.2 ± 0.2° of 2-theta values.

The sodium source in step-a) is NaOH; and the solvent is selected from isopropyl alcohol, water or mixtures thereof;

Obtaining crystalline polymorph of compound of formula-1a in step-b) is carried out by heating the reaction mixture of step-a) to a temperature ranging from about 35°C to reflux temperature of the solvent used followed by cooling the solution to a temperature ranging from about 20-30°C.

The process of step-b) may further comprises, adding isopropyl alcohol to the mixture at about 20-30°C, cooling the mixture to about 0-10°C.

A preferred embodiment of the present invention provides a process for the preparation of crystalline polymorph of sodium 8-(2-hydroxy benzamido)octanoate compound of formula-1a characterized by its PXRD pattern having peaks at about 6.7, 11.5 and 18.2 ± 0.2° of 2-theta values, comprising;

a) providing a mixture of 8-(2-hydroxybenzamido)octanoic acid compound of formula-1, NaOH, water and isopropyl alcohol,
b) heating the mixture to about 45-50°C,
c) cooling the solution to about 20-30°C,
d) obtaining crystalline polymorph of compound of formula-1a characterized by its PXRD pattern having peaks at about 6.7, 11.5 and 18.2 ± 0.2° of 2-theta values.

The crystalline polymorph of Salcaprozate sodium 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 Salcaprozate sodium is present in the composition in particular polymorphic form mentioned.

An aspect of the present invention provides the use of crystalline polymorph of Salcaprozate sodium of the present invention for the preparation of various pharmaceutical formulations.

The other aspect of the present invention provides a pharmaceutical composition comprising an active ingredient (for example Semaglutide) and crystalline polymorph of Salcaprozate sodium of the present invention.

Another aspect of the present invention provides a method of treating or preventing a disease in a patient comprising administering to the said patient a finished dosage form comprising an active ingredient (for example Semaglutide) and crystalline polymorph of Salcaprozate sodium of the present invention.

The crystalline polymorph of compound of formula-1a produced by the process of the present invention may have particle size distribution of D_{90} less than about 400 µm, preferably less than about 300 µm, more preferably less than about 200 µm.

In one aspect of the present invention, the crystalline polymorph of compound of formula-1a may have particle size distribution of D_{90} less than about 100 µm, preferably less than about 50 µm.

The 8-(2-hydroxybenzamido)octanoic acid (Compound of formula-1) which is used as input in example-1 of the present invention can be prepared by any of the processes known in the art or it can be synthesized by the process as described in the present invention.

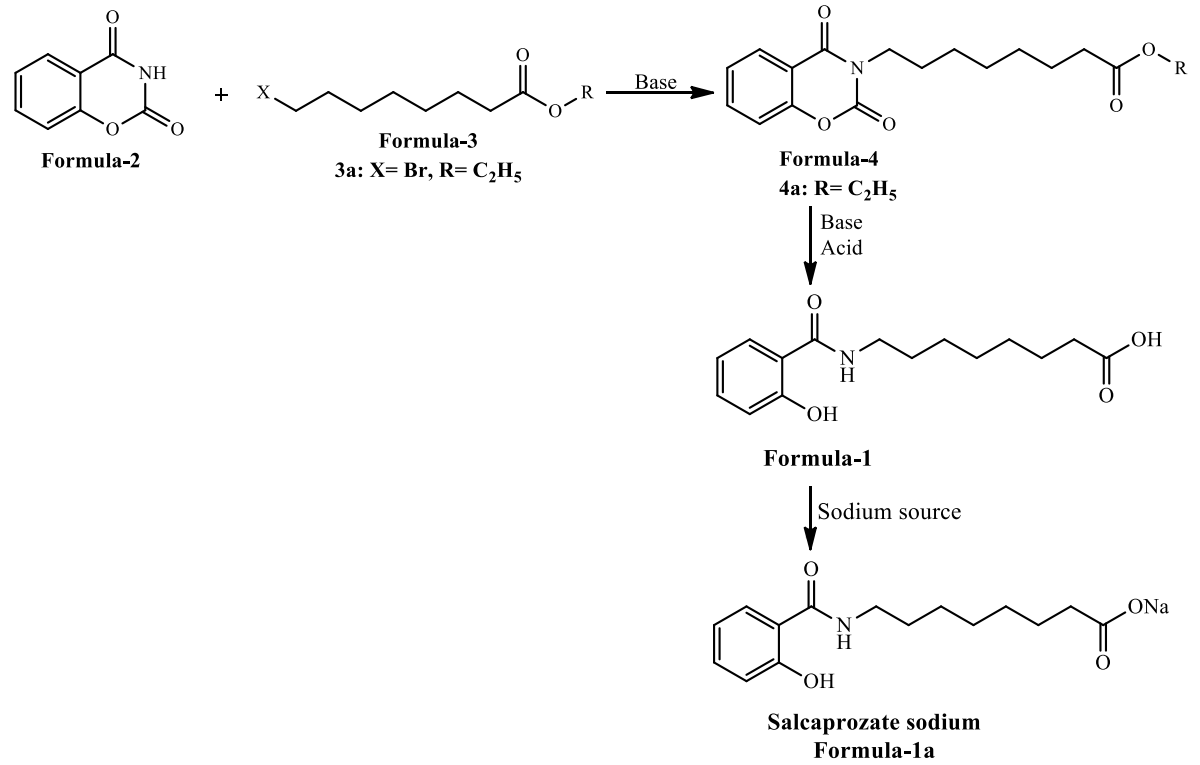
The crystalline compound of formula-1a produced by the process of the present invention can be further micronized or milled to get desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction includes 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/micronization may be performed before drying or after drying of the product.

P-XRD Method of Analysis:

The PXRD analysis of compound of formula-1a of the present invention was carried out by using BRUKER/D8 ADVANCE diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

Salcaprozate sodium of the present invention is prepared by the following synthetic scheme;

Scheme-I:



In the above scheme, 'X' represents halogens such as Cl, Br and I; 'R' represents C_1-C_6 straight chain or branched chain alkyl groups for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, pentyl, hexyl etc.,

Examples:

Example-1: Preparation of ethyl 8-(2,4-dioxo-2H-benzo[e][1,3]oxazin-3(4H)-yl) octanoate (Formula-4a)

A mixture of 2H-benzo[e][1,3]oxazine-2,4(3H)-dione compound of formula-2 (100 gm), ethyl 8-bromooctanoate compound of formula-3a (184.75 gm), sodium carbonate (77.91 gm) and dimethylformamide (400 ml) was heated to 70-75°C and stirred the reaction mixture for 5 hr at the same temperature. Reduced the temperature of the reaction mixture to 40-45°C, filtered through hyflow bed and washed the hyflow bed with isopropyl alcohol. Cooled the filtrate to 15-20°C, water (200 ml) was added to it and stirred the mixture for 1 hr at the same temperature. Filtered the solid, washed with water and suck dried the material.

n-Heptane (600 ml) was added to the obtained compound at 25-30°C. Heated the mixture to 45-50°C and stirred for 45 min at the same temperature. Cooled the mixture to 25-30°C and stirred for 3 hr at the same temperature. Filtered the solid, washed the material with n-heptane and dried to get the title compound.
Yield: 170 gm.

Example-2: Preparation of 8-(2-hydroxybenzamido)octanoic acid (Formula-1)

Nitrogen gas was bubbled into water (500 ml) at 25-30°C. Heated the water to 100°C and stirred for 2 hr at the same temperature. Cooled the water to 25-30°C. Sodium hydroxide (95.84 gm) followed by ethyl 8-(2,4-dioxo-2H-benzo[e][1,3]oxazin-3(4H)-yl)octanoate compound of formula-4a (200 gm) were added to water at 25-30°C. Heated the reaction mixture to 75-80°C and stirred for 2 hr at the same temperature. Cooled the reaction mixture to 25-30°C and slowly acidified it by using aqueous hydrochloric acid solution (240 ml of conc.HCl in 360 ml of water). Heated the reaction mixture to 60-65°C and stirred for 45 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 45 min at the same temperature. Filtered the solid, washed with water and dried to get the title compound.
Yield: 148.3 gm; M.R: 117.4-118.6°C.

Example-3: Preparation of crystalline polymorph of Salcaprozate sodium (Formula-1a)

A mixture of 8-(2-hydroxybenzamido)octanoic acid compound of formula-1 (100 gm), sodium hydroxide (14.6 gm), water (60 ml) and isopropyl alcohol (400 ml) was stirred for 30 min at 25-30°C. Heated the reaction mixture to 45-50°C and stirred for 30 min at the same temperature. Filtered the solution to make it particle free and washed with aqueous isopropyl alcohol. Cooled the solution to 20-30°C and stirred for 10 hr at the same temperature. Isopropyl alcohol (400 ml) was slowly added to the obtained mixture at 20-30°C. Cooled the mixture to 0-10°C and stirred for 10 hr at the same temperature. Filtered the solid, washed with isopropyl alcohol and dried to get the title compound.
The PXRD pattern of the obtained compound is shown in figure-1.
Yield: 106.4 gm.