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(54) **Title**: CRYSTALLINE FORMS OF DARAPLADIB OXALATE, ADIPATE, SUCCINATE, PHOSPHATE, SULPHATE, FUMARATETARTRATE, NITRATE AND BORATE

(57) **Abstract**: The present invention provides darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, and darapladib borate, their polymorphic forms, processes for their preparation, and pharmaceutical compositions thereof.

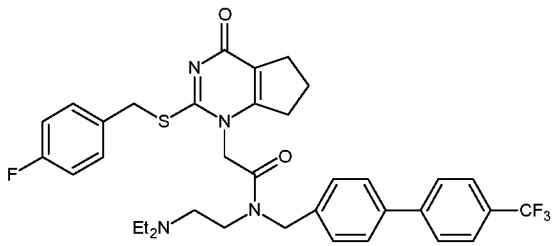
CRYSTALLINE FORMS OF DARAPLADIB OXALATE, ADIPATE, SUCCINATE, PHOSPHATE, SULPHATE, FUMARATE,TARTRATE, NITRATE AND BORATE

Field of the Invention

The present invention provides darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, and darapladib borate, their polymorphic forms, processes for their preparation, and pharmaceutical compositions thereof.

Background of the Invention

Darapladib of Formula A, chemically known as *N*-[2-(diethylamino)ethyl]-2-{2-[(4-fluorobenzyl)sulfanyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-cyclopenta[*d*]pyrimidin-1-yl}-*N*-{[4'-(trifluoromethyl)biphenyl-4-yl]methyl}acetamide is an Lp-PLA_2 inhibitor. Darapladib is known for the treatment of atherosclerosis.



Formula A

PCT Publication No. WO 01/60805 provides darapladib bitartrate and darapladib hydrochloride, and processes for their preparation.

In the pharmaceutical industry there is a constant need to identify critical physicochemical parameters, such as salts and polymorphic forms, which affect the drug's performance and stability.

Since darapladib constitutes an important therapeutic agent, additional salts of darapladib are of value to pharmaceutical science. Thus, there is a need for the development of novel salts of darapladib having improved solubility, stability, bioavailability, and less susceptibility to degradation at lower temperatures.

Summary of the Invention

The present invention provides darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, and darapladib borate.

The present invention provides crystalline forms of darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, and darapladib borate. The present invention further provides processes for the preparation of the above salts of darapladib and their use for the preparation of darapladib free base, or salts, solvates, or polymorphs thereof.

Detailed Description of the Invention

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±10% of the value.

A first aspect of the present invention provides a crystalline form of darapladib oxalate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib oxalate, characterized by: an X-Ray Powder Diffraction (XRPD) pattern as depicted in Figure 1; an XRPD pattern exhibiting interplanar spacing (d) values at 6.52, 5.28, 4.39, 4.26, 4.15, 3.98, 3.49, and 3.42 (Å); an XRPD pattern with characteristic peak values (2θ) at 13.59, 16.79, 20.22, 20.83, 21.41, 22.35, 25.48, and 26.04 ±0.2°; a thermogravimetric analysis (TGA) thermogram as depicted in Figure 2; a differential scanning calorimetry (DSC) thermogram as depicted in Figure 3; a DSC thermogram with a characteristic endothermic peak value at about 175.80°C and an additional endothermic peak at about 221.59°C; or combinations thereof.

The crystalline form of darapladib oxalate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 9.35, 6.99, 5.99, 5.91, 5.09, 4.94, 4.87, 4.78, 4.70, 4.43, 3.89, 3.84, 3.77, 3.66, 3.63, 3.56, 3.38, 3.34, and 3.31 (Å). The crystalline form of darapladib oxalate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 9.45, 12.65, 14.79, 14.99, 17.43, 17.95, 18.22, 18.57, 18.87, 20.04, 22.84, 23.18, 23.60, 24.30, 24.55, 24.99, 26.34, 26.67, and 26.89 ±0.2°.

A second aspect of the present invention provides a crystalline form of darapladib adipate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib adipate, characterized by: an XRPD pattern as depicted in Figure 4; an XRPD pattern exhibiting interplanar spacing (d) values at 4.51, 4.45, 4.02, and 4.01 (Å); an XRPD pattern with characteristic peak values (2θ) at 19.68, 19.98, 22.08, and 22.18 ±0.2°; a TGA thermogram as depicted in Figure 5; a DSC

thermogram as depicted in Figure 6; a DSC thermogram with a characteristic endothermic peak value at about 148.85°C, an additional endothermic peak at about 111.99°C, and an exothermic peak at about 196.04°C; or combinations thereof.

The crystalline form of darapladib adipate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 20.79, 11.04, 10.65, 7.03, 5.77, 5.37, 5.29, 4.74, 4.30, 4.24, and 3.59 (Å). The crystalline form of darapladib adipate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 4.25, 8.01, 8.30, 12.59, 15.35, 16.49, 16.77, 18.72, 20.65, 20.93, and 24.83 ±0.2°.

A third aspect of the present invention provides a crystalline form of darapladib succinate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib succinate, characterized by: an XRPD pattern as depicted in Figure 7; an XRPD pattern exhibiting interplanar spacing (d) values at 20.39, 6.82, 4.55, 4.48, and 4.12 (Å); an XRPD pattern with characteristic peak values (2θ) at 4.33, 12.99, 19.52, 19.81, and 21.56 ±0.2°; a TGA thermogram as depicted in Figure 8; a DSC thermogram as depicted in Figure 9; a DSC thermogram with a characteristic endothermic peak value at about 145.10°C, an additional endothermic peak at about 91.82°C, and an exothermic peak at about 194.05°C; or combinations thereof.

The crystalline form of darapladib succinate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 11.06, 10.25, 5.40, 4.78, 4.39, 4.31, 4.25, 4.19, 4.09, 3.81, 3.69, 3.41, and 2.85 (Å). The crystalline form of darapladib succinate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 7.99, 8.63, 16.41, 18.56, 20.24, 20.59, 20.91, 21.22, 21.71, 23.36, 24.09, 26.10, and 31.43 ±0.2°.

A fourth aspect of the present invention provides a crystalline form of darapladib phosphate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib phosphate, characterized by: an XRPD pattern as depicted in Figure 10; an XRPD pattern exhibiting interplanar spacing (d) values at 14.31, 9.05, 7.99, 4.44, 4.31, 4.23, and 4.07 (Å); an XRPD pattern with characteristic peak values (2θ) at 6.18, 9.77, 11.08, 19.99, 20.59, 21.01, and 21.83 ±0.2°; a TGA thermogram as depicted in Figure 11; a DSC thermogram as depicted in

Figure 12; a DSC thermogram with a characteristic endothermic peak value at about 208.75°C; or combinations thereof.

The crystalline form of darapladib phosphate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 23.90, 16.15, 9.95, 9.47, 6.01, 5.56, 5.33, 5.11, 4.89, 4.75, 4.65, 4.54, 4.17, 3.92, 3.89, 3.77, 3.62, 3.56, 3.49, and 3.37 (Å). The crystalline form of darapladib phosphate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 3.69, 5.47, 8.88, 9.34, 14.74, 15.94, 16.63, 17.35, 18.14, 18.68, 19.09, 19.55, 21.29, 22.67, 22.87, 23.62, 24.56, 24.99, 25.46, and 26.43 ±0.2°.

A fifth aspect of the present invention provides a crystalline form of darapladib sulphate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib sulphate, characterized by: an XRPD pattern as depicted in Figure 13; an XRPD pattern exhibiting interplanar spacing (d) values at 11.37, 5.92, 5.72, 4.44, and 4.21 (Å); an XRPD pattern with characteristic peak values (2θ) at 7.77, 14.98, 15.49, 19.99, and 21.12 ±0.2°; a TGA thermogram as depicted in Figure 14; a DSC thermogram as depicted in Figure 15; a DSC thermogram with a characteristic endothermic peak value at about 193.78°C; or combinations thereof.

The crystalline form of darapladib sulphate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 14.43, 5.54, 4.53, 4.29, 3.98, 3.88, 3.78, 3.43, and 3.01 (Å). The crystalline form of darapladib sulphate can be also characterized by a XRPD pattern with additional characteristic peak values (2θ) at 6.12, 15.99, 19.59, 20.69, 22.36, 22.94, 23.53, 25.97, and 29.64 ±0.2°.

A sixth aspect of the present invention provides a crystalline form of darapladib fumarate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib fumarate, characterized by: an XRPD pattern as depicted in Figure 16; an XRPD pattern exhibiting interplanar spacing (d) values at 15.43, 11.71, 7.73, 5.88, and 3.99 (Å); an XRPD pattern with characteristic peak values (2θ) at 5.73, 7.55, 11.44, 15.06, and 22.23 ±0.2°; a TGA thermogram as depicted in Figure 17; a DSC thermogram as depicted in Figure 18; a DSC thermogram with a characteristic endothermic peak value at about 150.70°C, an additional endothermic peak at about 119.35°C, and an exothermic peak at about 201.91°C; or combinations thereof.

The crystalline form of darapladib fumarate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 8.96, 6.77, 5.17, 5.01, 4.63, 4.49, 4.33, 4.18, 3.88, 3.78, 3.63, 3.49, 3.41, and 3.32 (Å). The crystalline form of darapladib fumarate can be also characterized by a XRPD pattern with additional characteristic peak values (2θ) at 9.87, 13.07, 17.14, 17.69, 19.16, 19.76, 20.52, 21.27, 22.89, 23.53, 24.51, 25.49, 26.10, and 26.83 ±0.2°.

A seventh aspect of the present invention provides a crystalline form of darapladib tartrate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib tartrate, characterized by: an XRPD pattern as depicted in Figure 19; an XRPD pattern exhibiting interplanar spacing (d) values at 16.98, 13.47, 6.38, 6.25, 4.27, 4.11, and 3.55 (Å); an XRPD pattern with characteristic peak values (2θ) at 5.21, 6.56, 13.89, 14.17, 20.78, 21.64, and 25.08 ±0.2°; a TGA thermogram as depicted in Figure 20; a DSC thermogram as depicted in Figure 21; a DSC thermogram with a characteristic endothermic peak value at about 135.10°C and an exothermic peak at about 206.35°C; or combinations thereof.

The crystalline form of darapladib tartrate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 10.58, 7.62, 6.05, 5.26, 5.18, 4.75, 4.69, 4.64, 3.88, 3.34, and 3.16 (Å). The crystalline form of darapladib tartrate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 8.35, 11.62, 14.65, 16.87, 17.13, 18.67, 18.94, 19.13, 22.91, 26.73, and 28.21 ±0.2°.

An eighth aspect of the present invention provides a crystalline form of darapladib nitrate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib nitrate, characterized by: an XRPD pattern as depicted in Figure 22; an XRPD pattern exhibiting interplanar spacing (d) values at 6.59, 5.63, 5.00, 4.31, 4.22, 4.15, and 3.82 (Å); an XRPD pattern with characteristic peak values (2θ) at 13.44, 15.73, 17.73, 20.63, 21.05, 21.39, and 23.29 ±0.2°; a TGA thermogram as depicted in Figure 23; a DSC thermogram as depicted in Figure 24; a DSC thermogram with a characteristic endothermic peak value at about 161.74°C and an additional exothermic peak at about 206.75°C; or combinations thereof.

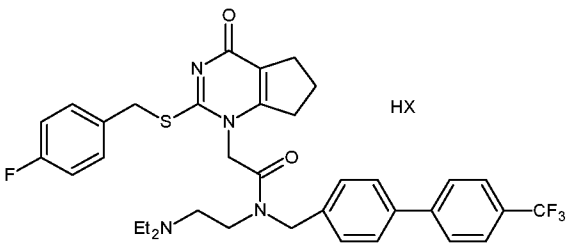
The crystalline form of darapladib nitrate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 14.93, 11.22, 8.64,

7.55, 6.53, 4.68, 4.59, 3.98, 3.89, 3.75, and 3.49 (Å). The crystalline form of darapladib nitrate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 5.92, 7.88, 10.23, 11.72, 13.56, 18.98, 19.35, 22.36, 22.84, 23.72, and 25.53 ±0.2°.

A ninth aspect of the present invention provides darapladib borate. In one embodiment of this aspect, the present invention provides a crystalline form of darapladib borate. The crystalline form of darapladib borate can be characterized by: an XRPD pattern as depicted in Figure 25; an XRPD pattern exhibiting interplanar spacing (d) values at 13.84, 5.06, and 4.67 (Å); an XRPD pattern with characteristic peak values (2θ) at 6.39, 17.54, and 19.02 ±0.2°; a TGA thermogram as depicted in Figure 26; a DSC thermogram as depicted in Figure 27; a DSC thermogram with a characteristic endothermic peak value at about 125.63°C and an additional exothermic peak at about 216.83°C; or combinations thereof.

The crystalline form of darapladib borate may be further characterized by an XRPD pattern with additional interplanar spacing (d) values at 19.71, 6.98, 5.89, 4.1, 4.09, and 4.03 (Å). The crystalline form of darapladib borate can be also characterized by an XRPD pattern with additional characteristic peak values (2θ) at 4.48, 12.69, 15.04, 21.68, and 21.78 ±0.2°.

A tenth aspect of the present invention provides a process for the preparation of a compound of Formula 1



Formula 1

which comprises treating darapladib or salts thereof with HX, wherein HX is selected from the group consisting of oxalic acid, adipic acid, succinic acid, orthophosphoric acid, sulphuric acid, fumaric acid, tartaric acid, nitric acid, and boric acid.

The darapladib or salts thereof used as the starting material may be prepared by any of the methods known in the art, including those described in PCT Publication No. WO 01/60805.

The darapladib or its salts prepared by any of the methods known in the art may be isolated or directly treated with HX.

The darapladib or salts thereof prepared by any of the methods known in the art may be optionally purified prior to treatment with HX to remove foreign particulate matter. Alternatively, they may be treated with activated charcoal in a suitable solvent to remove coloring and other related impurities. The darapladib salt may optionally be converted to darapladib free base before treatment with HX.

Treating darapladib or salts thereof with HX may include adding, dissolving, slurrying, stirring, or a combination thereof. Darapladib or salts thereof may be treated with HX in the presence of a suitable solvent at a suitable temperature.

The term "solvent," as used herein, includes a single solvent or solvent mixtures, including water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, and mixtures thereof.

Examples of esters include ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate. Examples of alkanols include those primary, secondary, and tertiary alcohols having from one to six carbon atoms. Examples of alkanols include methanol, ethanol, *n*-propanol, isopropanol, and butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, and 1,2-dichloroethane. Examples of ketones include acetone and methyl ethyl ketone. Examples of ethers include diethyl ether and tetrahydrofuran. Examples of polar aprotic solvents include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.

Darapladib or salts thereof are treated with HX at a temperature of about 25°C to reflux for a time period sufficient to complete the reaction, preferably for about 10 minutes to about 6 hours.

After completion of the reaction, the compound of Formula 1 can be isolated by a common isolation technique such as cooling, extraction, washing, crystallization,

precipitation, filtration, filtration under vacuum, decantation and centrifugation, or combinations thereof.

An eleventh aspect of the present invention provides the use of a compound of Formula 1 for the preparation of darapladib free base or salts, solvates, or polymorphs thereof.

The compound of Formula 1 may be used for the preparation of darapladib by contacting with a base. The base is selected from the group comprising hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals; ammonia; alkyl amines; hydrazine; and the like. Examples of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals include lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate. Examples of alkyl amines include diethyl amine, triethyl amine, and methyl diethyl amine. Darapladib thus obtained may be converted to salts, solvates, or polymorphs thereof.

A twelfth aspect of the present invention provides a pharmaceutical composition comprising darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, or darapladib borate, and a pharmaceutically acceptable carrier.

A thirteenth aspect of the present invention provides a method of treating atherosclerosis which comprises administering to a patient in need thereof a therapeutically effective amount of darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, or darapladib borate, and a pharmaceutically acceptable carrier.

Brief Description of the Figures

Figure 1 and Figure 1a depict the XRPD of darapladib oxalate and the associated values, respectively, prepared as per Example 1.

Figure 2 depicts the TGA thermogram of darapladib oxalate prepared as per Example 1.

Figure 3 depicts the DSC thermogram of darapladib oxalate prepared as per Example 1.

Figure 4 and Figure 4a depict the XRPD of darapladib adipate and the associated values, respectively, prepared as per Example 2.

Figure 5 depicts the TGA thermogram of darapladib adipate prepared as per Example 2.

Figure 6 depicts the DSC thermogram of darapladib adipate prepared as per Example 2.

Figure 7 and Figure 7a depict the XRPD of darapladib succinate and the associated values, respectively, prepared as per Example 3.

Figure 8 depicts the TGA thermogram of darapladib succinate prepared as per Example 3.

Figure 9 depicts the DSC thermogram of darapladib succinate prepared as per Example 3.

Figure 10 and Figure 10a depict the XRPD of darapladib phosphate and the associated values, respectively, prepared as per Example 4.

Figure 11 depicts the TGA thermogram of darapladib phosphate prepared as per Example 4.

Figure 12 depicts the DSC thermogram of darapladib phosphate prepared as per Example 4.

Figure 13 and Figure 13a depict the XRPD of darapladib sulphate and the associated values, respectively, prepared as per Example 5.

Figure 14 depicts the TGA thermogram of darapladib sulphate prepared as per Example 5.

Figure 15 depicts the DSC thermogram of darapladib sulphate prepared as per Example 5.

Figure 16 and Figure 16a depict the XRPD of darapladib fumarate and the associated values, respectively, prepared as per Example 6.

Figure 17 depicts the TGA thermogram of darapladib fumarate prepared as per Example 6.

Figure 18 depicts the DSC thermogram of darapladib fumarate prepared as per Example 6.

Figure 19 and Figure 19a depict the XRPD of darapladib tartrate and the associated values, respectively, prepared as per Example 7.

Figure 20 depicts the TGA thermogram of darapladib tartrate prepared as per Example 7.

Figure 21 depicts the DSC thermogram of darapladib tartrate prepared as per Example 7.

Figure 22 and Figure 22a depict the XRPD of darapladib nitrate and the associated values, respectively, prepared as per Example 8.

Figure 23 depicts the TGA thermogram of darapladib nitrate prepared as per Example 8.

Figure 24 depicts the DSC thermogram of darapladib nitrate prepared as per Example 8.

Figure 25 and Figure 25a depict the XRPD of darapladib borate and the associated values, respectively, prepared as per Example 9.

Figure 26 depicts the TGA thermogram of darapladib borate prepared as per Example 9.

Figure 27 depicts the DSC thermogram of darapladib borate prepared as per Example 9.

The XRPD of the samples were determined by using a PANalytical®; Mode: X'Pert PRO; Detector: X'celerator®; Scan Range: 3-40°2 theta; Step size: 0.02°; CuKα radiation at 45kV; Time per step: 40 seconds.

The DSC thermogram of the samples was determined by using a Mettler Toledo® DSC 821; Rate of heating: 10°C/minute, from 30°C to 300°C; Nitrogen flow rate: 20 mL per minute.

The TGA thermogram of the samples was determined by using a TA Instruments® Q500; Rate of heating: 10°C/minute from 30°C to 300°C.

While the present invention has been described in terms of its specific aspects, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be within the scope of the present invention.

EXAMPLES

Example 1: Preparation of darapladib oxalate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of oxalic acid (2.25 g oxalic acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 30 minutes at 20°C to 25°C. Methanol (120 mL) was charged to the reaction mixture at 20°C to 25°C, then the reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 14 g

Example 2: Preparation of darapladib adipate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of adipic acid (3.62 g adipic acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 30 minutes at 20°C to 25°C. Methanol (75 mL) was charged to the reaction mixture at 20°C to 25°C, then the reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 11.2 g

Example 3: Preparation of darapladib succinate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of succinic acid (2.95 g succinic acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was heated to 60°C. The reaction mixture was gradually cooled to 20°C to 25°C over 45 minutes. The reaction mixture was further cooled to 5°C to 10°C, then the reaction mixture was stirred at 5°C to 10°C for 3 hours. The reaction mixture was filtered at 5°C to 10°C. The wet solid obtained was washed

with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 5 g

Example 4: Preparation of darapladib phosphate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of orthophosphoric acid (2.43 g orthophosphoric acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 30 minutes at 20°C to 25°C. Methanol (75 mL) was charged to the reaction mixture at 20°C to 25°C, then the reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 15.8 g

Example 5: Preparation of darapladib sulphate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of sulphuric acid (2.43 g sulphuric acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 60 minutes at 20°C to 25°C, then was cooled to 10°C. Methanol (45 mL) was charged to the reaction mixture, then the temperature was raised to 20°C. The reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 10 g

Example 6: Preparation of darapladib fumarate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of fumaric acid (2.87 g fumaric acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 30 minutes at 20°C to 25°C. The reaction mixture was heated to 60°C. The reaction mixture was gradually cooled to 20°C to 25°C over 45 minutes. Methanol (30 mL) was charged to the reaction mixture at 20°C to 25°C, then the reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol

(30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 11 g

Example 7: Preparation of darapladib tartrate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of tartaric acid (3.72 g tartaric acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 30 minutes at 20°C to 25°C. Methanol (45 mL) was charged to the reaction mixture at 20°C to 25°C, then the reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 10.5 g

Tartrate content: 17.1% w/w

Example 8: Preparation of darapladib nitrate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of nitric acid (1.56 g nitric acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was heated to 60°C. The reaction mixture was gradually cooled to 20°C to 25°C over 45 minutes. The reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 10 g

Example 9: Preparation of darapladib borate

Darapladib (15 g) and methanol (30 mL) were combined at 20°C to 25°C. A methanolic solution of boric acid (1.55 g boric acid in 75 mL methanol) was charged at 20°C to 25°C. The reaction mixture was stirred for 30 minutes at 20°C to 25°C. Methanol (30 mL) was charged to the reaction mixture at 20°C to 25°C, then the reaction mixture was stirred at 20°C to 25°C for 3 hours. The reaction mixture was filtered at 20°C

to 25°C. The wet solid obtained was washed with methanol (30 mL). The wet solid was suck dried for 15 minutes and then dried under vacuum at 45°C to 50°C for overnight to obtain the title compound.

Yield: 7.5 g

CLAIMS:

1. A crystalline form of darapladib oxalate characterized by an XRPD pattern substantially as depicted in Figure 1.

2. A crystalline form of darapladib oxalate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 6.52, 5.28, 4.39, 4.26, 4.15, 3.98, 3.49, and 3.42 (Å).

3. A crystalline form of darapladib oxalate characterized by an XRPD pattern with characteristic peak values (2θ) at about 13.59, 16.79, 20.22, 20.83, 21.41, 22.35, 25.48, and 26.04 ±0.2°.

4. A crystalline form of darapladib oxalate characterized by a TGA thermogram substantially as depicted in Figure 2.

5. A crystalline form of darapladib oxalate characterized by a DSC thermogram substantially as depicted in Figure 3.

6. A crystalline form of darapladib oxalate characterized by a DSC thermogram with a characteristic endothermic peak value at about 175.80°C and an additional endothermic peak at about 221.59°C.

7. A crystalline form of darapladib adipate characterized by an XRPD pattern substantially as depicted in Figure 4.

8. A crystalline form of darapladib adipate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 4.51, 4.45, 4.02, and 4.01 (Å).

9. A crystalline form of darapladib adipate characterized by an XRPD pattern with characteristic peak values (2θ) at about 19.68, 19.98, 22.08, and 22.18 ±0.2°.

10. A crystalline form of darapladib adipate characterized by a TGA thermogram as depicted in Figure 5.

11. A crystalline form of darapladib adipate characterized by a DSC thermogram substantially as depicted in Figure 6.

12. A crystalline form of darapladib adipate characterized by a DSC thermogram with a characteristic endothermic peak value at about 148.85°C, an additional endothermic peak at about 111.99°C, and an exothermic peak at about 196.04°C.

13. A crystalline form of darapladib succinate characterized by an XRPD pattern substantially as depicted in Figure 7.

14. A crystalline form of darapladib succinate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 20.39, 6.82, 4.55, 4.48, and 4.12 (Å).

15. A crystalline form of darapladib succinate characterized by an XRPD pattern with characteristic peak values (2θ) at about 4.33, 12.99, 19.52, 19.81, and 21.56 ±0.2°.

16. A crystalline form of darapladib succinate characterized by a TGA thermogram substantially as depicted in Figure 8.

17. A crystalline form of darapladib succinate characterized by a DSC thermogram substantially as depicted in Figure 9.

18. A crystalline form of darapladib succinate characterized by a DSC thermogram with a characteristic endothermic peak value at about 145.10°C, an additional endothermic peak at about 91.82°C, and an exothermic peak at about 194.05°C.

19. A crystalline form of darapladib phosphate characterized by an XRPD pattern substantially as depicted in Figure 10.

20. A crystalline form of darapladib phosphate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 14.31, 9.05, 7.99, 4.44, 4.31, 4.23, and 4.07 (Å).

21. A crystalline form of darapladib phosphate characterized by an XRPD pattern with characteristic peak values (2θ) at about 6.18, 9.77, 11.08, 19.99, 20.59, 21.01, and 21.83 ±0.2°.

22. A crystalline form of darapladib phosphate characterized by a TGA thermogram substantially as depicted in Figure 11.

23. A crystalline form of darapladib phosphate characterized by a DSC thermogram substantially as depicted in Figure 12.

24. A crystalline form of darapladib phosphate characterized by a DSC thermogram with a characteristic endothermic peak value at about 208.75°C.

25. A crystalline form of darapladib sulphate characterized by an XRPD pattern substantially as depicted in Figure 13.

26. A crystalline form of darapladib sulphate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 11.37, 5.92, 5.72, 4.44, and 4.21 (Å).

27. A crystalline form of darapladib sulphate characterized by an XRPD pattern with characteristic peak values (2θ) at about 7.77, 14.98, 15.49, 19.99, and 21.12 ±0.2°.

28. A crystalline form of darapladib sulphate characterized by a TGA thermogram substantially as depicted in Figure 14.

29. A crystalline form of darapladib sulphate characterized by a DSC thermogram substantially as depicted in Figure 15.

30. A crystalline form of darapladib sulphate characterized by a DSC thermogram with a characteristic endothermic peak value at about 193.78°C.

31. A crystalline form of darapladib fumarate characterized by an XRPD pattern substantially as depicted in Figure 16.

32. A crystalline form of darapladib fumarate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 15.43, 11.71, 7.73, 5.88, and 3.99 (Å).

33. A crystalline form of darapladib fumarate characterized by an XRPD pattern with characteristic peak values (2θ) at about 5.73, 7.55, 11.44, 15.06, and 22.23 ±0.2°.

34. A crystalline form of darapladib fumarate characterized by a TGA thermogram substantially as depicted in Figure 17.

35. A crystalline form of darapladib fumarate characterized by a DSC thermogram substantially as depicted in Figure 18.

36. A crystalline form of darapladib fumarate characterized by a DSC thermogram with a characteristic endothermic peak value at about 150.70°C, an additional endothermic peak at about 119.35°C, and an exothermic peak at about 201.91°C.

37. A crystalline form of darapladib tartrate characterized by an XRPD pattern substantially as depicted in Figure 19.

38. A crystalline form of darapladib tartrate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 16.98, 13.47, 6.38, 6.25, 4.27, 4.11, and 3.55 (Å).

39. A crystalline form of darapladib tartrate characterized by an XRPD pattern with characteristic peak values (2θ) at about 5.21, 6.56, 13.89, 14.17, 20.78, 21.64, and 25.08 ±0.2°.

40. A crystalline form of darapladib tartrate characterized by a TGA thermogram substantially as depicted in Figure 20.

41. A crystalline form of darapladib tartrate characterized by a DSC thermogram substantially as depicted in Figure 21.

42. A crystalline form of darapladib tartrate characterized by a DSC thermogram with a characteristic endothermic peak value at about 135.10°C and an exothermic peak at about 206.35°C.

43. A crystalline form of darapladib nitrate characterized by an XRPD pattern substantially as depicted in Figure 22.

44. A crystalline form of darapladib nitrate characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 6.59, 5.63, 5.00, 4.31, 4.22, 4.15, and 3.82 (Å).

45. A crystalline form of darapladib nitrate characterized by an XRPD pattern with characteristic peak values (2θ) at about 13.44, 15.73, 17.73, 20.63, 21.05, 21.39, and 23.29 ±0.2°.

46. A crystalline form of darapladib nitrate characterized by a TGA thermogram substantially as depicted in Figure 23.

47. A crystalline form of darapladib nitrate characterized by a DSC thermogram substantially as depicted in Figure 24.

48. A crystalline form of darapladib nitrate characterized by a DSC thermogram with a characteristic endothermic peak value at about 161.74°C and an additional exothermic peak at about 206.75°C.

49. Darapladib borate.

50. The darapladib borate of claim 49, in a crystalline form.

51. The darapladib borate of claim 49, characterized by an XRPD pattern substantially as depicted in Figure 25.

52. The darapladib borate of claim 49, characterized by an XRPD pattern exhibiting interplanar spacing (d) values at about 13.84, 5.06, and 4.67 (Å).

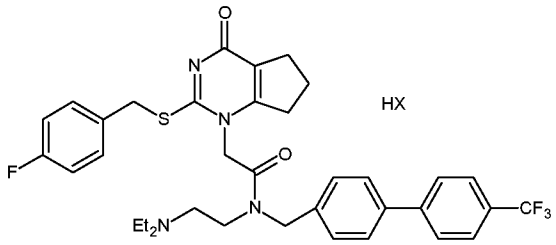
53. The darapladib borate of claim 49, characterized by an XRPD pattern with characteristic peak values (2θ) at about 6.39, 17.54, and 19.02 ±0.2°.

54. The darapladib borate of claim 49, characterized by a TGA thermogram substantially as depicted in Figure 26.

55. The darapladib borate of claim 49, characterized by a DSC thermogram substantially as depicted in Figure 27.

56. The darapladib borate of claim 49, characterized by a DSC thermogram with a characteristic endothermic peak value at about 125.63°C and an additional exothermic peak at about 216.83°C.

57. A process for the preparation of a compound of Formula 1



Formula 1

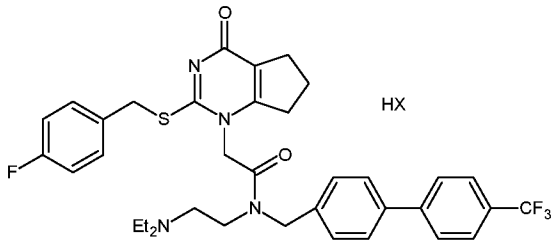
which comprises treating darapladib with HX, wherein HX is selected from the group consisting of oxalic acid, adipic acid, succinic acid, orthophosphoric acid, sulphuric acid, fumaric acid, tartaric acid, nitric acid, and boric acid.

58. The process according to claim 57, wherein the darapladib is treated with HX in the presence of a solvent.

59. The process according to claim 58, wherein the solvent is selected from the group comprising water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, and mixtures thereof.

60. The process according to claim 57, wherein the reaction is carried out at a temperature of about 25°C to reflux.

61. A process for the preparation of darapladib free base, or salts, solvates, or polymorphs thereof, comprising contacting the compound of Formula 1 with a base



Formula 1

wherein HX is selected from the group consisting of oxalic acid, adipic acid, succinic acid, orthophosphoric acid, sulphuric acid, fumaric acid, tartaric acid, nitric acid, and boric acid.

62. A pharmaceutical composition comprising darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, or darapladib borate, and a pharmaceutically acceptable carrier

63. A method of treating atherosclerosis which comprises administering to a patient in need thereof a therapeutically effective amount of darapladib oxalate, darapladib adipate, darapladib succinate, darapladib phosphate, darapladib sulphate, darapladib fumarate, darapladib tartrate, darapladib nitrate, or darapladib borate, and a pharmaceutically acceptable carrier.

FIGURE 1: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB OXALATE

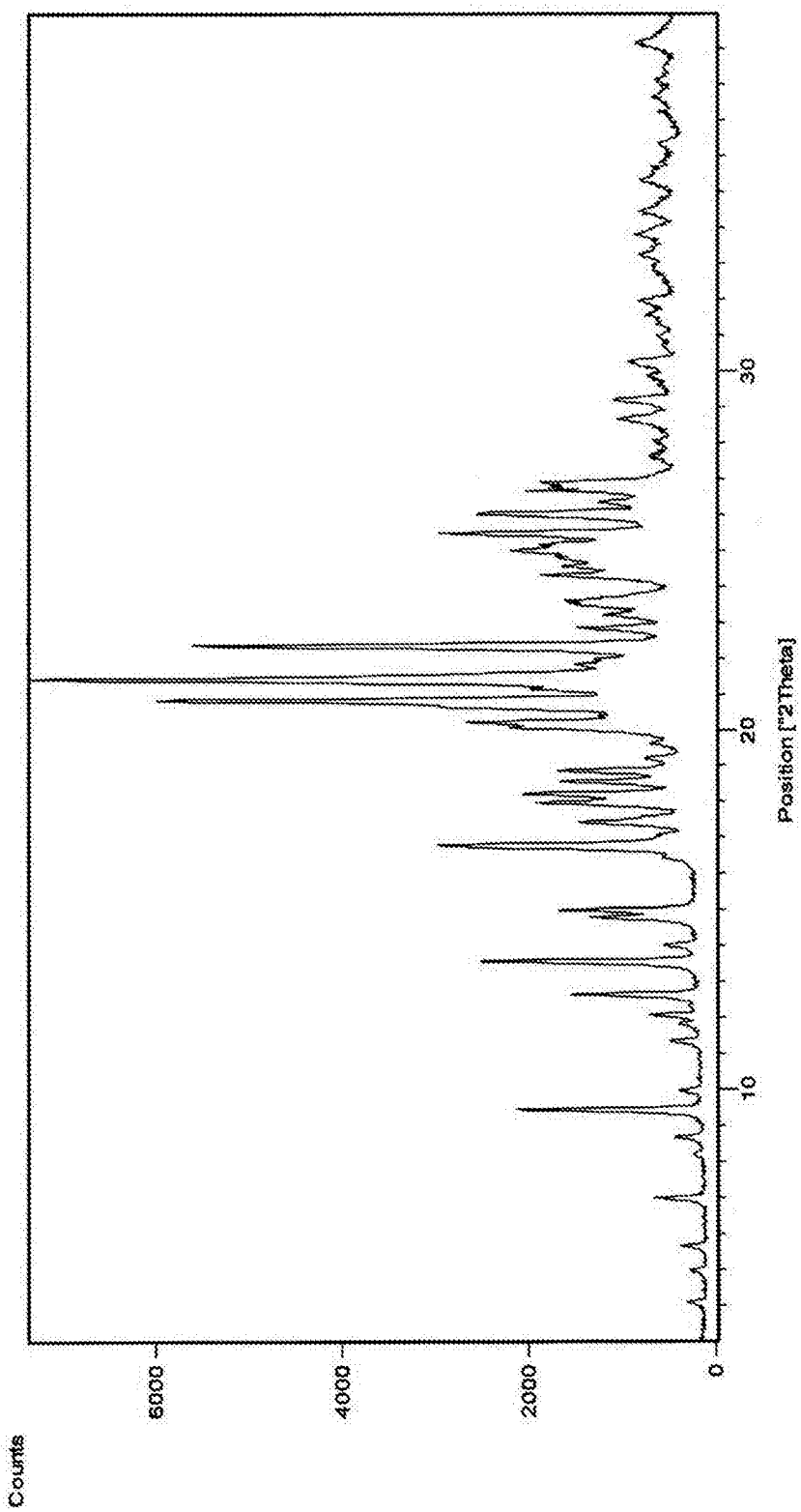
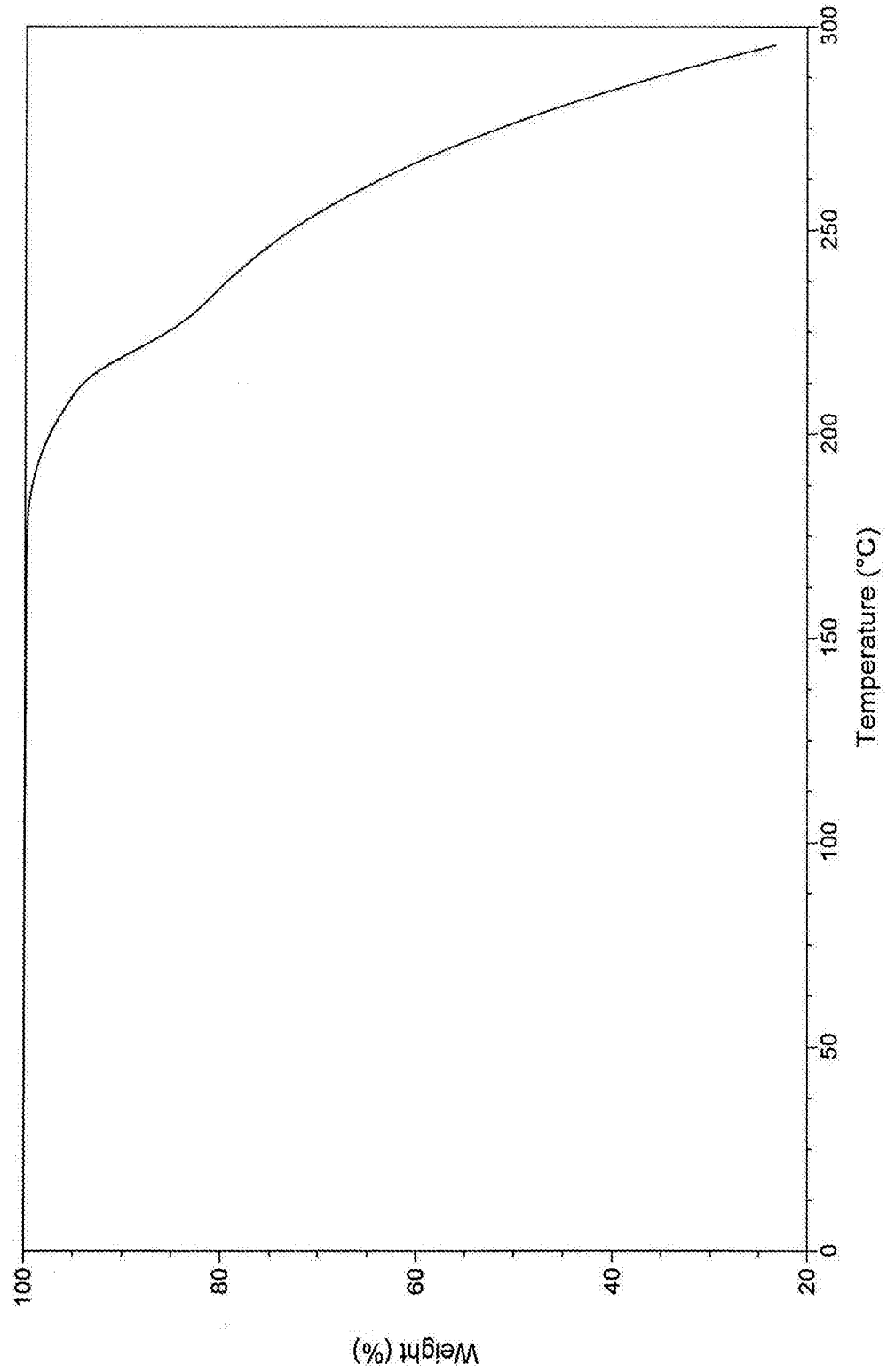


FIGURE 1a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]	Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
4.09	21.57	2.83	20.83	4.26	80.40
4.99	17.69	2.08	21.41	4.15	100.00
5.67	15.59	3.16	22.35	3.98	74.56
7.00	12.62	7.53	22.84	3.89	18.92
8.19	10.78	1.67	23.18	3.84	14.03
8.69	10.18	4.34	23.60	3.77	20.07
9.45	9.35	27.51	24.30	3.66	22.77
9.98	8.86	3.59	24.55	3.63	20.81
11.35	7.79	5.01	24.99	3.56	28.76
11.82	7.49	3.72	25.48	3.49	39.68
12.09	7.32	8.23	26.04	3.42	33.18
12.65	6.99	19.32	26.34	3.38	15.55
13.59	6.52	32.83	26.67	3.34	23.72
14.05	6.30	5.38	26.89	3.31	23.45
14.79	5.99	16.29	27.61	3.23	7.89
14.99	5.91	21.46	28.67	3.11	12.41
16.79	5.28	39.16	29.22	3.06	12.95
17.43	5.09	18.63	30.28	2.95	11.07
17.95	4.94	23.23	31.55	2.84	8.07
18.22	4.87	26.31	31.97	2.79	9.25
18.57	4.78	21.38	33.23	2.69	9.41
18.87	4.70	22.08	33.78	2.65	10.09
19.21	4.62	8.94	34.44	2.60	9.25
19.62	4.53	7.88	35.31	2.54	9.34
20.04	4.43	27.44	36.33	2.47	6.71
20.22	4.39	35.54	37.67	2.39	7.33
20.61	4.31	37.37	39.19	2.29	9.92

FIGURE 2: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB OXALATE



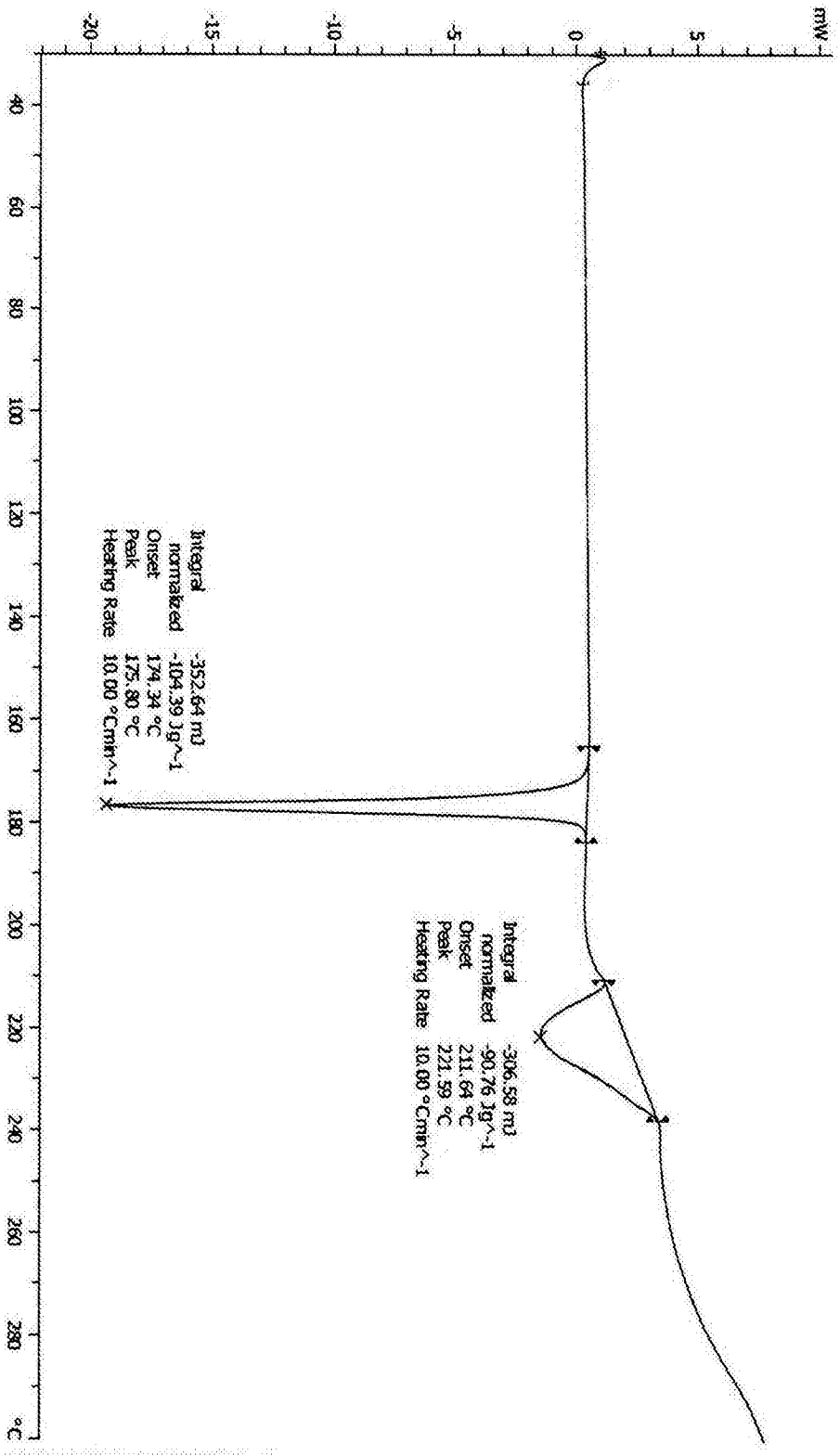


FIGURE 3: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB OXALATE

FIGURE 4: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB ADIPATE

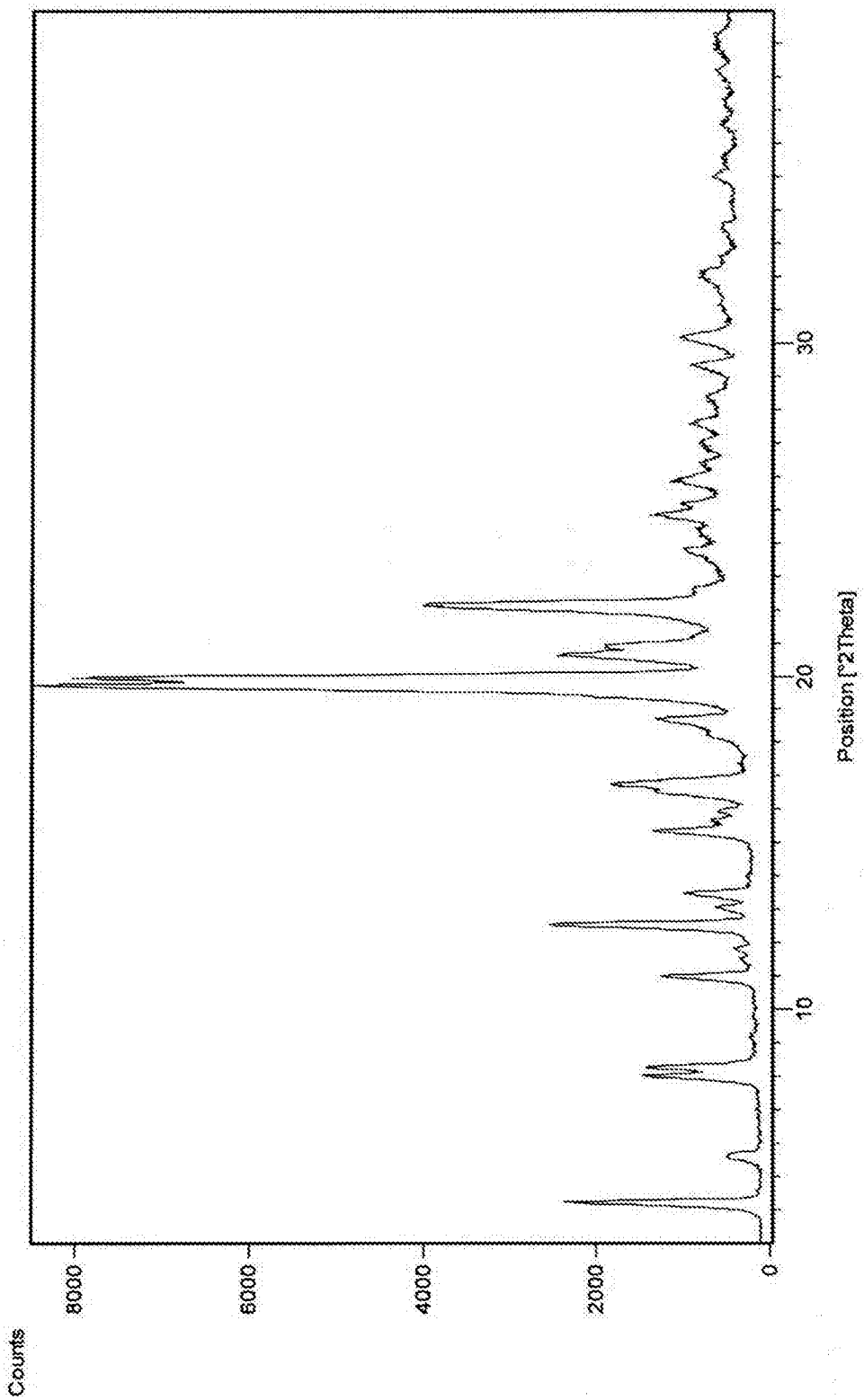


FIGURE 4a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
4.25	20.79	27.56
5.70	15.49	3.96
8.01	11.04	16.21
8.30	10.65	14.71
9.16	9.65	0.84
11.03	8.02	12.34
11.82	7.49	2.71
12,59	7.03	26.71
13.07	6.77	5.11
13.49	6.56	9.90
15.35	5.77	14.35
15.97	5.55	4.50
16.49	5.37	13.71
16.77	5.29	20.07
18.72	4.74	13.51
19.68	4.51	100.00
19.98	4.45	92.94
20.65	4.30	26.39
20.93	4.24	20.16
22.08	4.02	44.93
22.18	4.01	44.87
23.80	3.74	8.43
24.41	3.65	6.48
24.83	3.59	12.97
25.18	3.54	8.83
25.88	3.44	9.34
26.99	3.30	5.59
27.63	3.23	6.44
28.40	3.14	4.65
29.35	3.04	6.63
30.22	2.96	7.70
32.11	2.79	4.97
33.56	2.67	1.71
35.02	2.56	2.75
36.57	2.46	1.35
37.23	2.42	0.96
38.17	2.36	1.87

FIGURE 5: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB ADIPATE

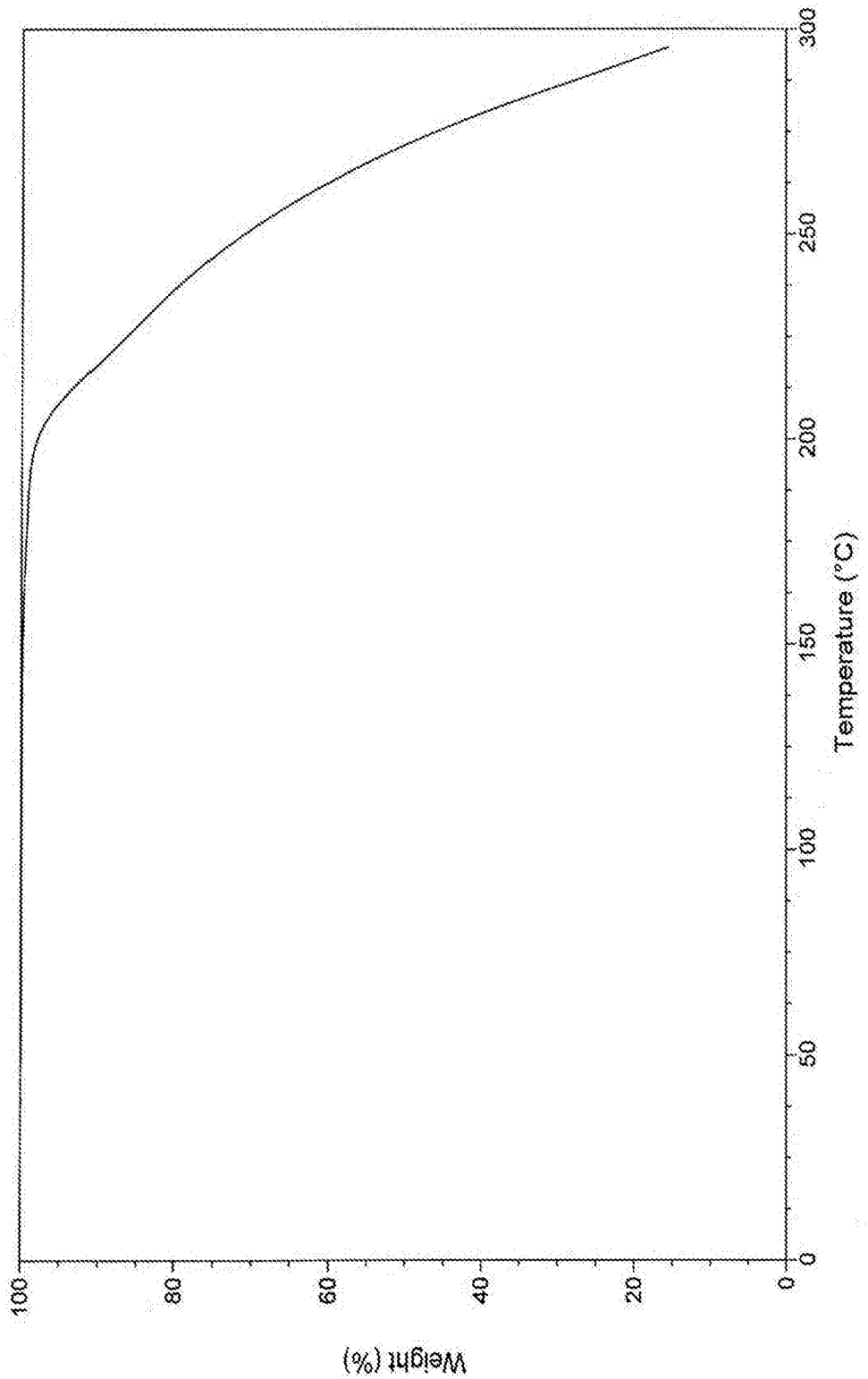


FIGURE 6: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB ADIPATE

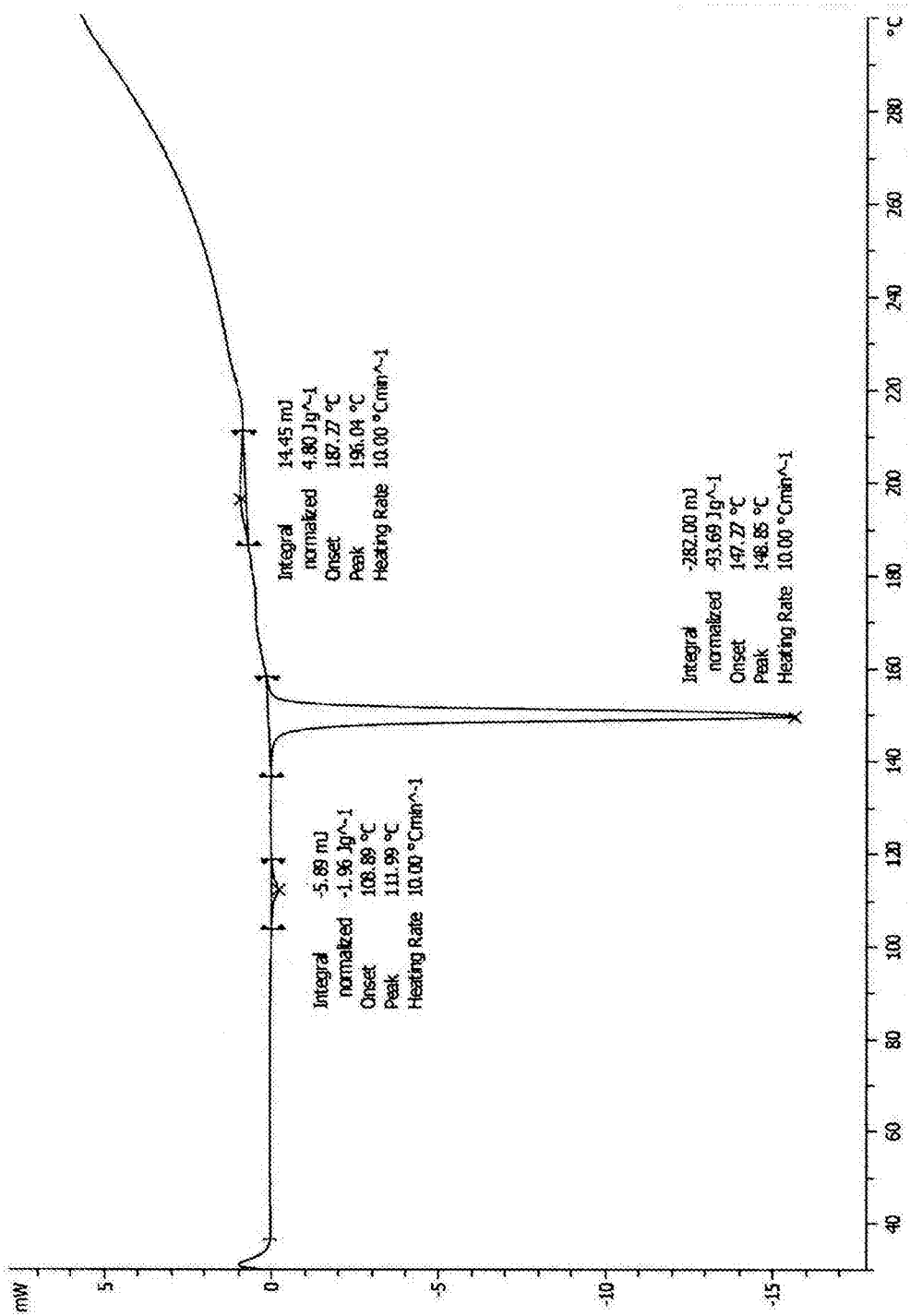


FIGURE 7: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB SUCCINATE

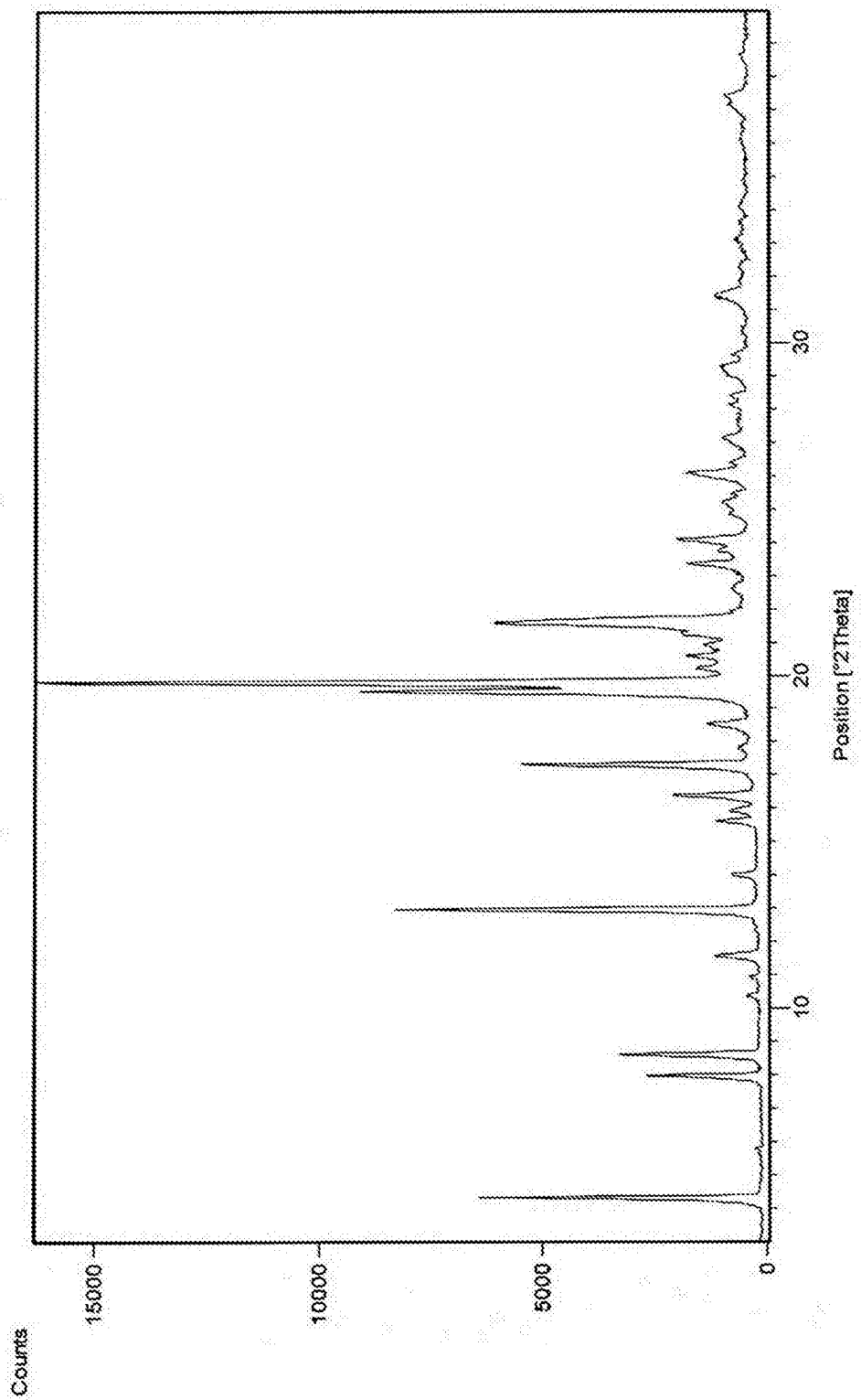


FIGURE 7a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]	Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
4.33	20.39	38.82	21.71	4.09	24.82
5.78	15.29	0.90	22.62	3.93	2.88
7.99	11.06	15.60	23.36	3.81	9.70
8.63	10.25	19.66	23.75	3.75	4.74
10.37	8.53	1.75	24.09	3.69	10.63
10.95	8.08	1.37	24.84	3.58	3.18
11.57	7.65	5.93	25.21	3.53	4.27
12.99	6.82	49.31	26.10	3.41	8.89
14.03	6.31	3.65	26.40	3.38	2.84
15.63	5.67	5.72	27.15	3.29	3.94
15.92	5.57	3.69	28.12	3.17	2.85
16.41	5.40	11.95	28.42	3.14	2.98
17.33	5.11	32.94	29.32	3.05	3.95
17.79	4.98	2.48	29.66	3.01	2.29
18.56	4.78	6.41	31.43	2.85	5.02
19.52	4.55	55.77	32.39	2.76	1.28
19.81	4.48	100.00	33.13	2.70	1.71
20.24	4.39	7.93	34.13	2.63	1.31
20.59	4.31	9.56	36.08	2.49	0.88
20.91	4.25	7.14	37.45	2.40	3.38
21.22	4.19	10.13	38.59	2.33	0.78
21.56	4.12	35.68			

FIGURE 8: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB SUCCINATE

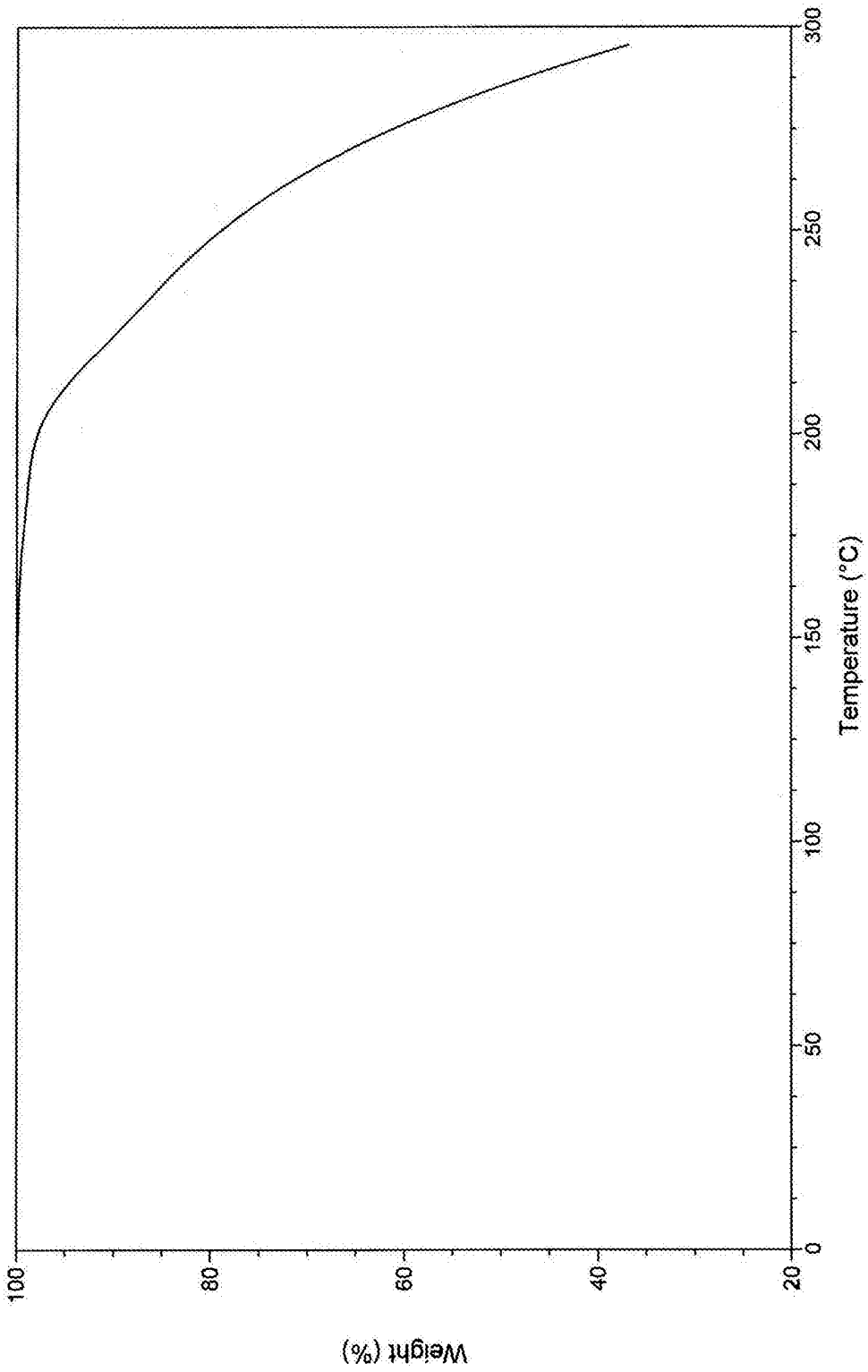


FIGURE 9: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB SUCCINATE

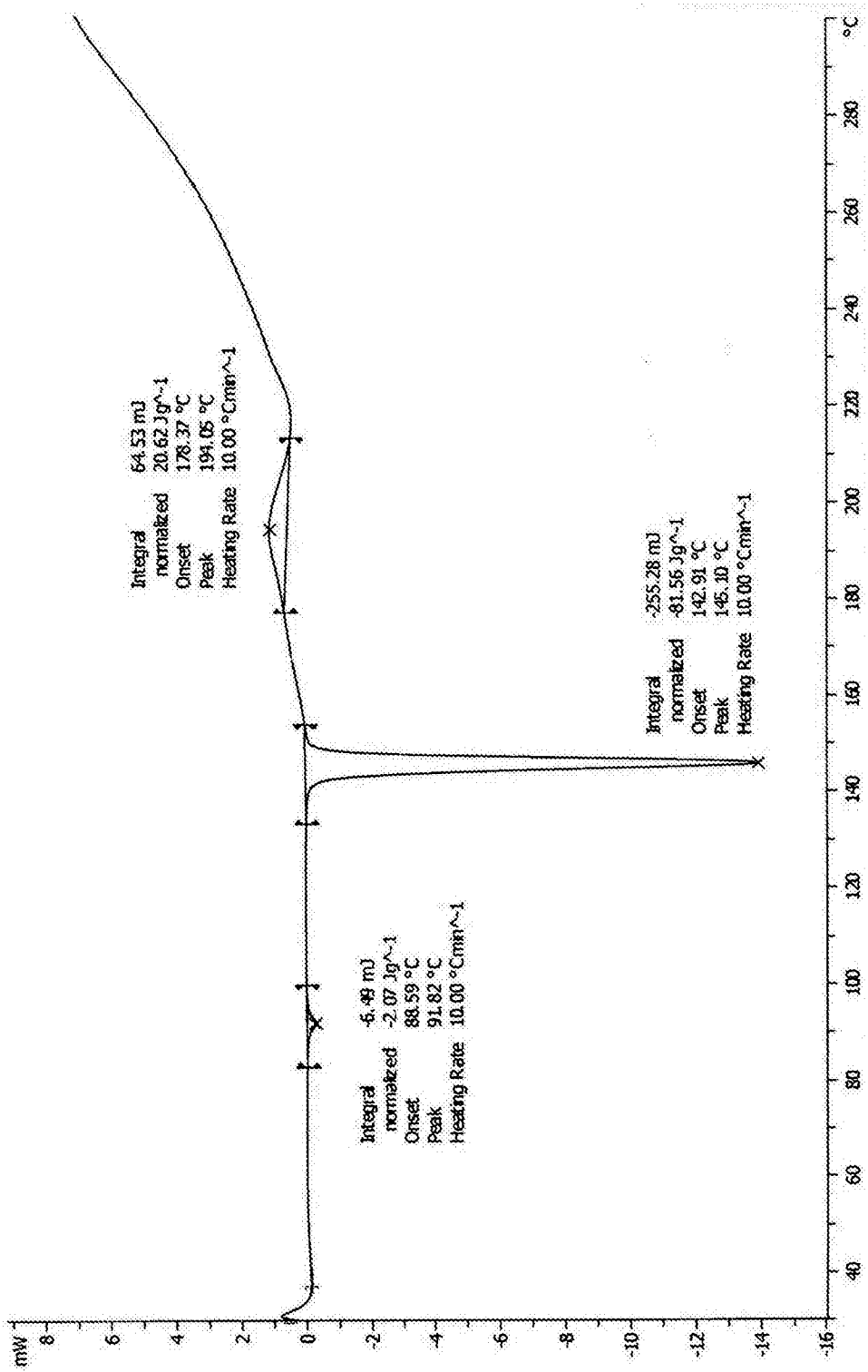


FIGURE 10: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB PHOSPHATE

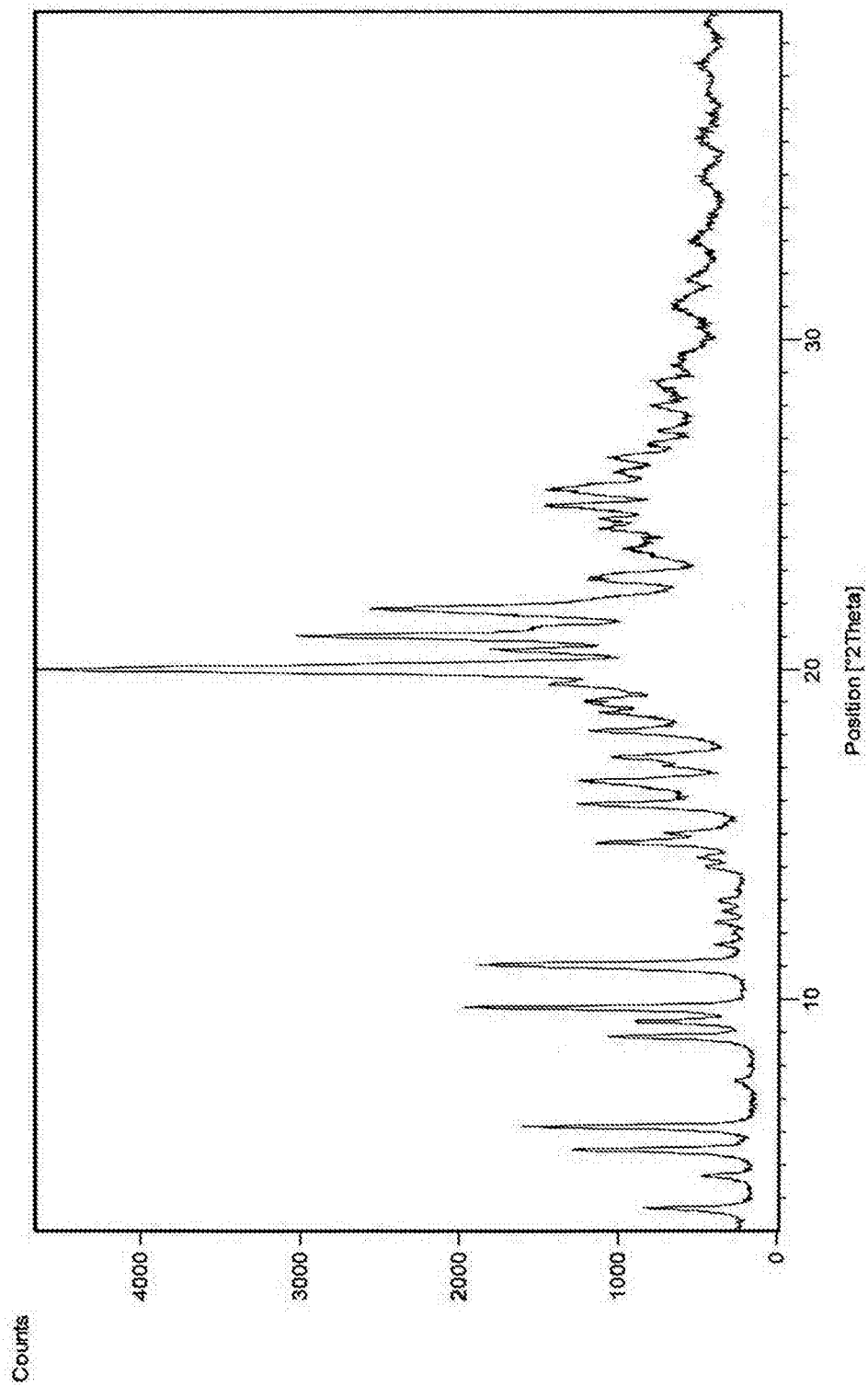


FIGURE 10a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]	Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
3.69	23.90	15.43	19.55	4.54	26.56
4.69	18.83	6.10	19.99	4.44	100.00
5.47	16.15	25.10	20.59	4.31	35.11
6.18	14.31	30.38	21.01	4.23	62.94
7.55	11.69	2.38	21.29	4.17	27.88
8.88	9.95	19.96	21.83	4.07	52.12
9.34	9.47	16.27	22.67	3.92	18.95
9.77	9.05	39.05	22.87	3.89	18.52
11.08	7.99	35.19	23.62	3.77	14.63
11.66	7.59	4.12	24.56	3.62	18.65
12.34	7.17	4.28	24.99	3.56	25.27
12.67	6.99	3.28	25.46	3.49	25.45
12.98	6.82	3.59	26.43	3.37	16.42
13.98	6.34	5.07	26.82	3.32	11.18
14.31	6.19	6.39	27.23	3.28	9.86
14.74	6.01	21.33	27.99	3.19	10.43
15.04	5.89	10.91	28.75	3.11	9.80
15.94	5.56	23.10	30.99	2.89	7.03
16.63	5.33	23.27	31.84	2.81	5.14
17.35	5.11	18.69	32.96	2.72	4.18
18.14	4.89	21.56	35.08	2.56	2.21
18.68	4.75	19.34	36.10	2.49	2.38
19.09	4.65	20.64	38.42	2.34	1.97

FIGURE 11: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB PHOSPHATE

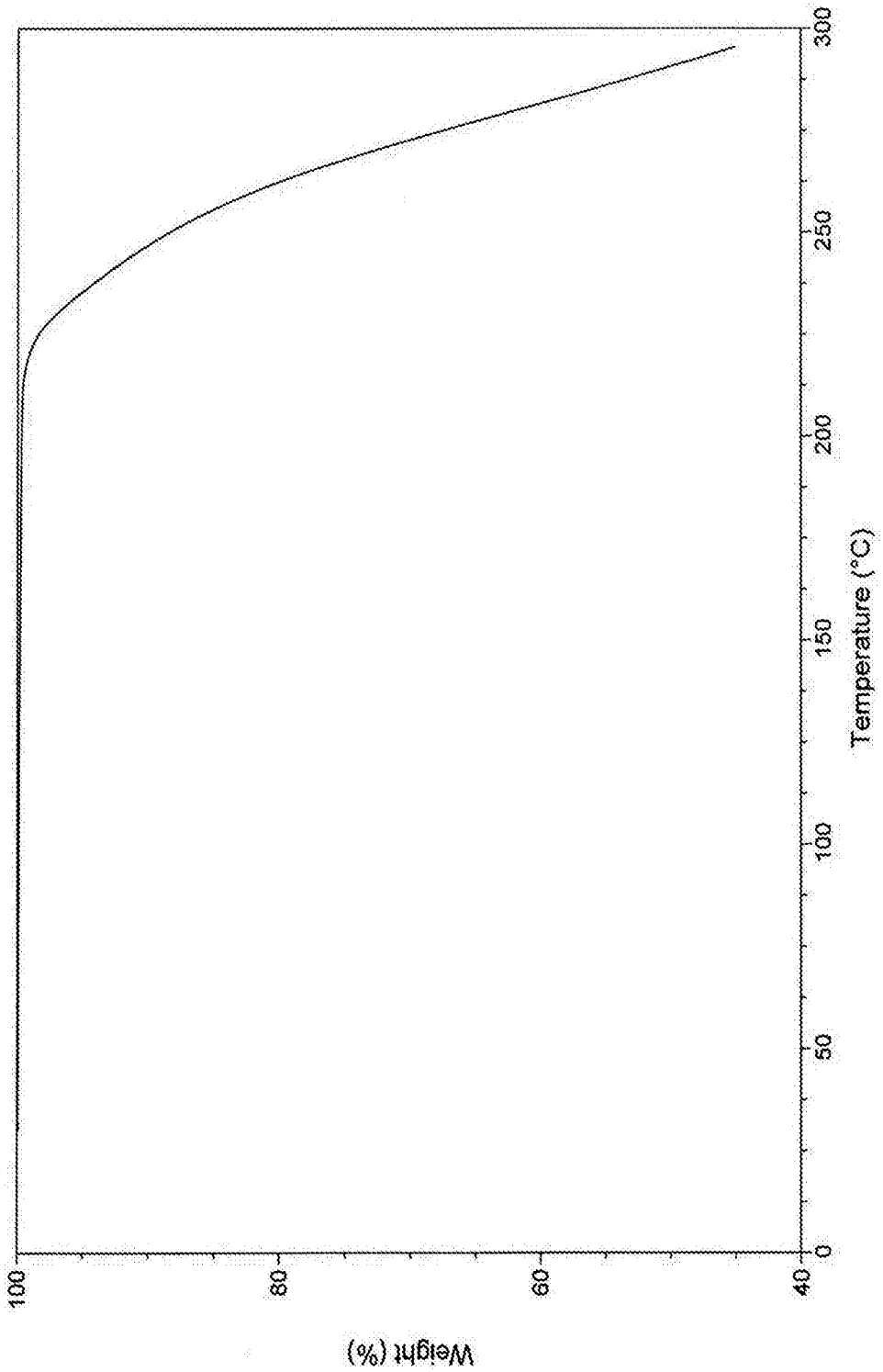


FIGURE 12: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB PHOSPHATE

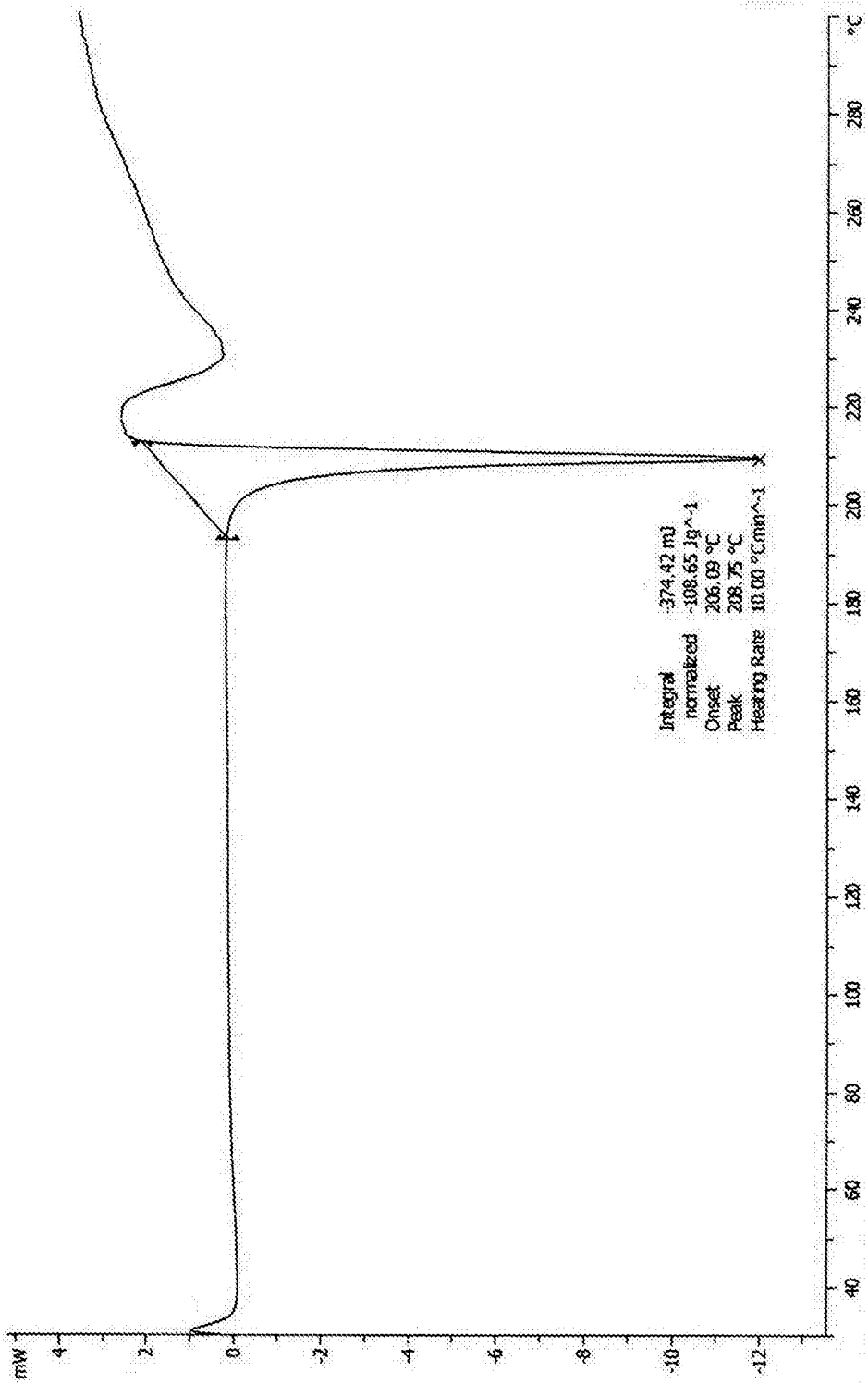


FIGURE 13: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB SULPHATE

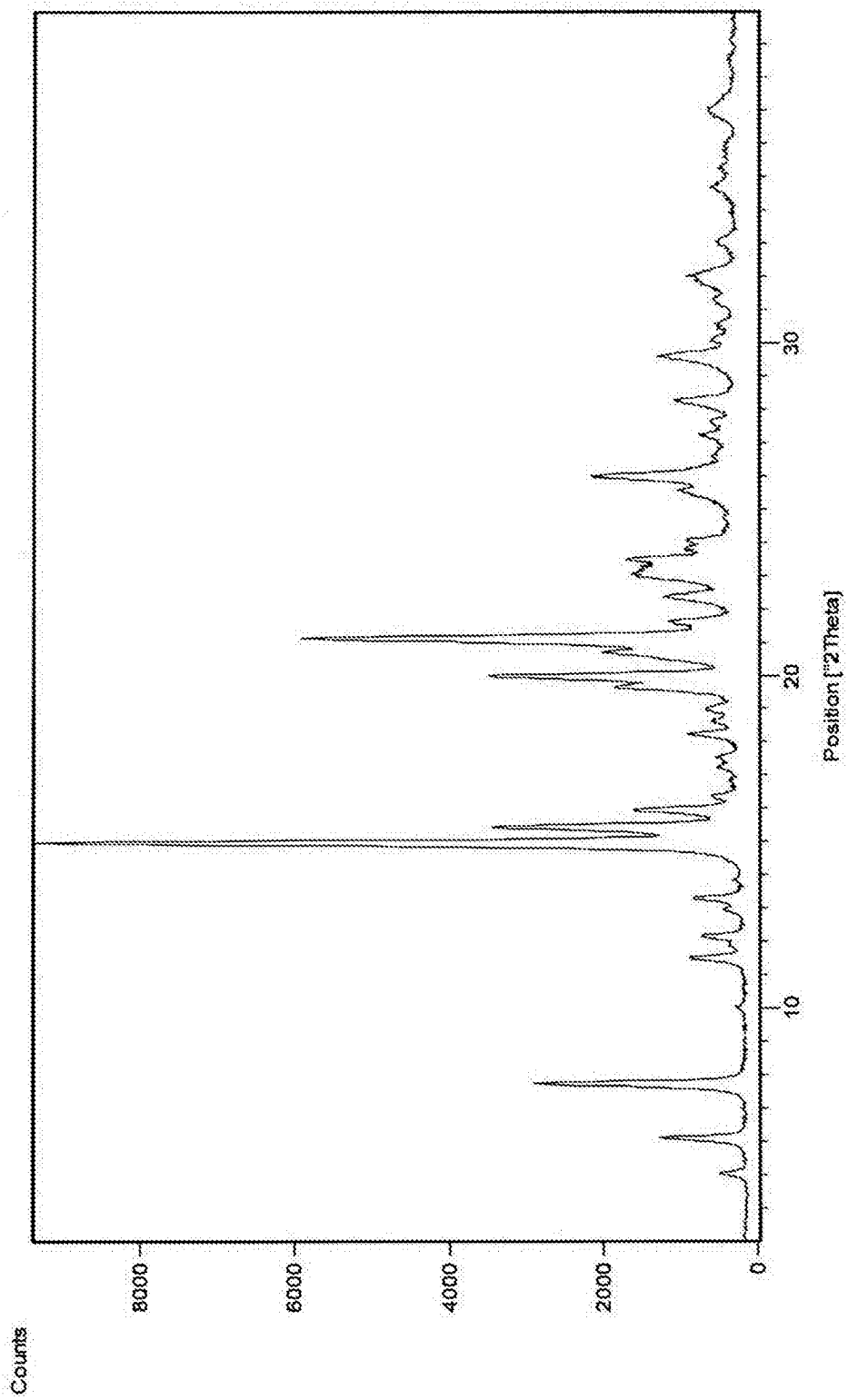


FIGURE 13a

Position [^{o} 2θ]	d-spacing (Å)	Relative Intensity [%]	Position [^{o} 2θ]	d-spacing (Å)	Relative Intensity [%]
5.03	17.56	3.91	21.12	4.21	62.38
6.12	14.43	12.09	21.64	4.11	9.50
7.77	11.37	28.48	22.36	3.98	10.43
10.00	8.84	1.02	22.94	3.88	12.97
11.54	7.67	7.57	23.53	3.78	14.40
12.18	7.27	5.89	24.06	3.69	7.30
12.95	6.84	2.56	25.55	3.49	8.27
13.34	6.64	6.63	25.97	3.43	20.76
14.98	5.92	100.00	27.22	3.28	4.92
15.49	5.72	30.81	27.66	3.23	3.60
15.99	5.54	14.11	28.27	3.16	8.46
16.35	5.42	3.92	29.64	3.01	9.65
17.23	5.15	3.24	30.08	2.97	3.38
17.55	5.05	3.23	30.58	2.92	2.77
18.23	4.87	7.52	31.26	2.86	2.93
18.62	4.77	3.86	32.03	2.79	6.26
18.98	4.68	4.71	33.06	2.71	2.29
19.59	4.53	16.65	34.68	2.59	2.96
19.99	4.44	35.66	36.98	2.43	3.23
20.69	4.29	19.33			

FIGURE 14: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB SULPHATE

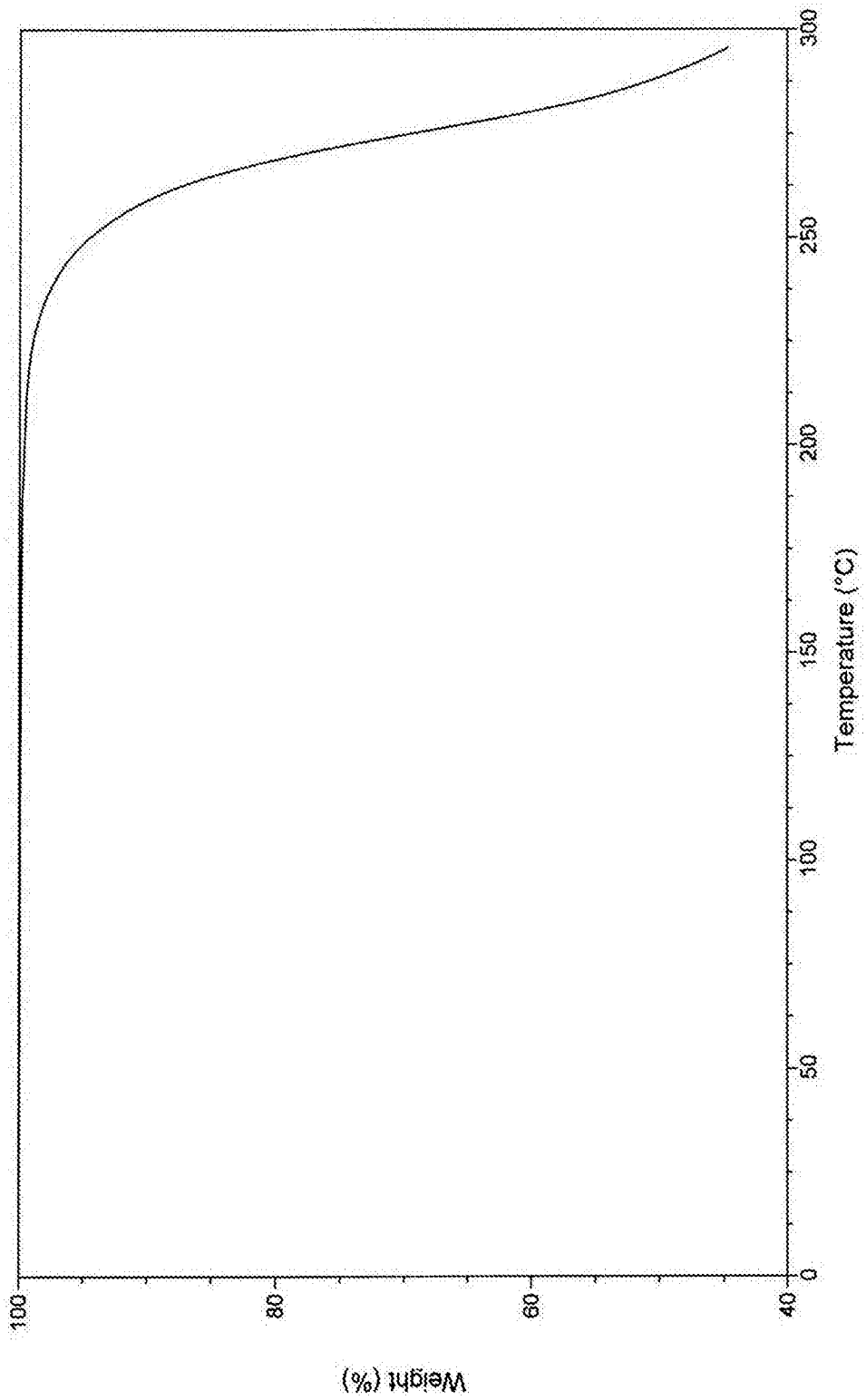


FIGURE 15: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB SULPHATE

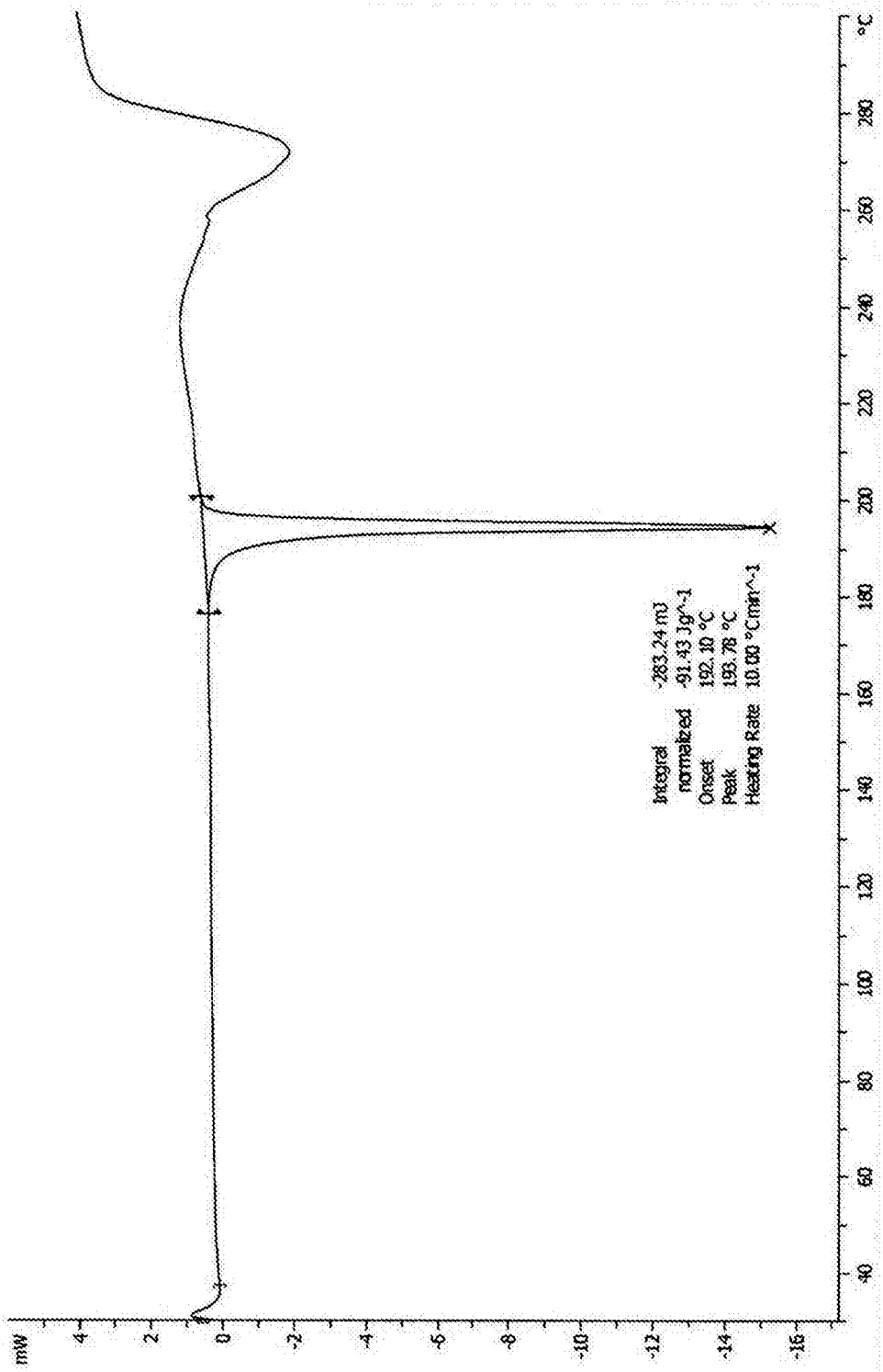


FIGURE 16: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB FUMARATE

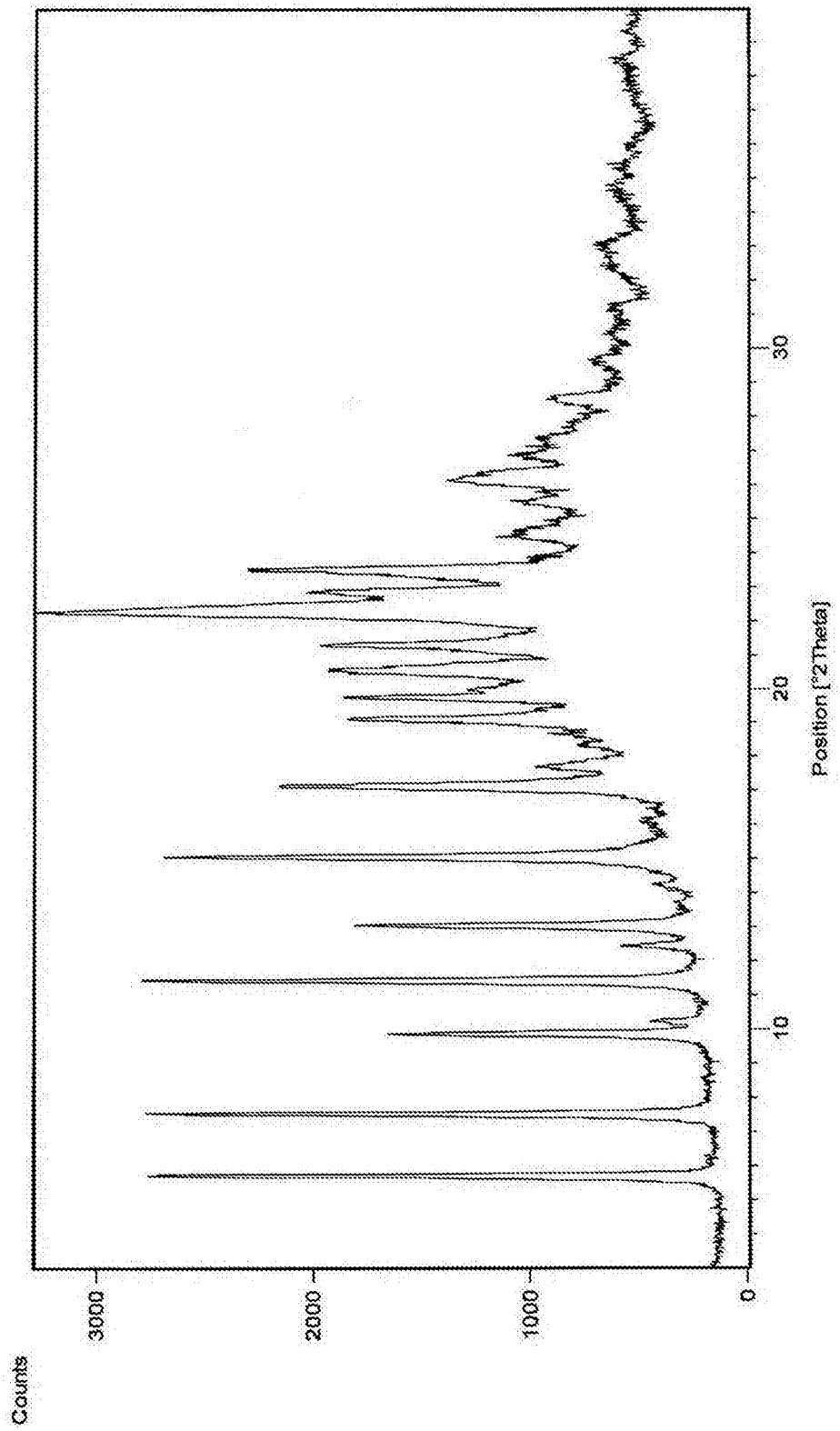


FIGURE 16a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
5.73	15.43	93.79
7.55	11.71	90.44
9.87	8.96	52.46
10.23	8.65	8.77
11.44	7.73	93.03
12.44	7.12	12.93
13.07	6.77	55.36
14.22	6.23	5.61
15.06	5.88	86.45
17.14	5.17	67.00
17.69	5.01	23.08
19.16	4.63	50.00
19.76	4.49	54.14
20.52	4.33	55.46
21.27	4.18	57.52
22.23	3.99	100.00
22.89	3.88	56.50
23.53	3.78	65.23
24.51	3.63	23.63
25.49	3.49	21.99
26.10	3.41	33.70
26.83	3.32	21.97
28.53	3.13	16.06
29.71	3.01	7.94
31.14	2.87	4.12
33.05	2.71	5.35
38.49	2.34	3.14

FIGURE 17: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB FUMARATE

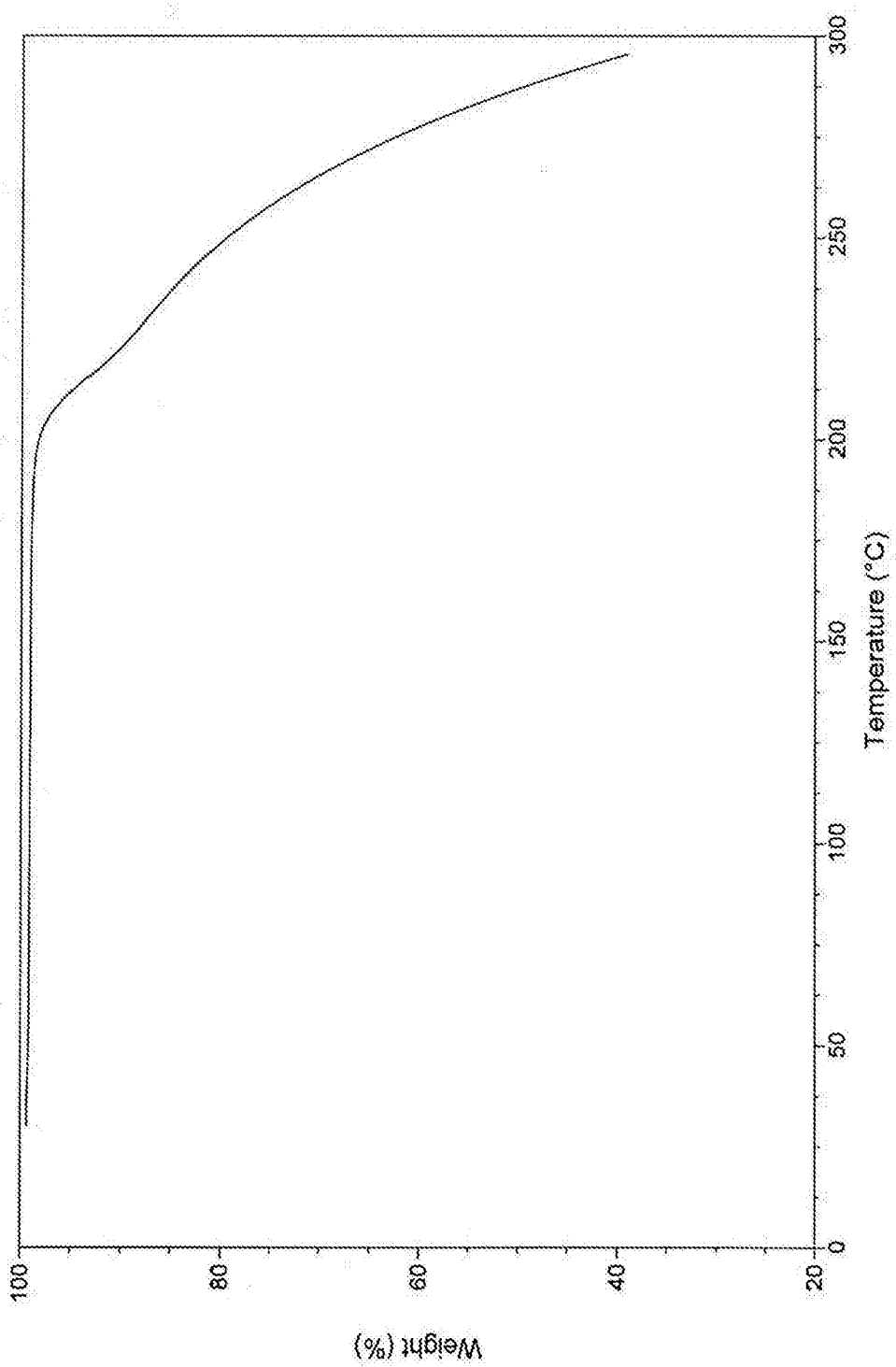


FIGURE 18: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB FUMARATE

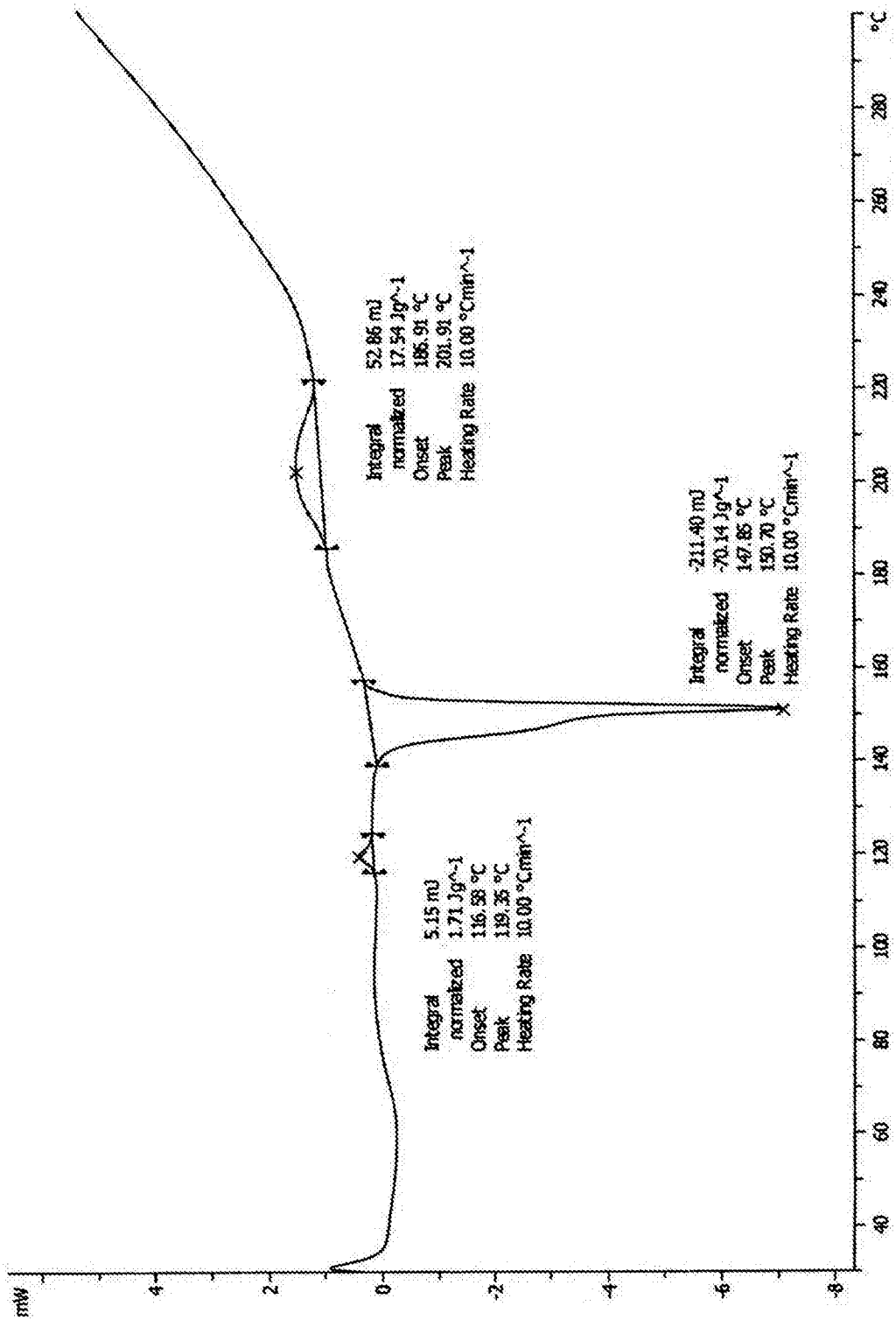


FIGURE 19: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB TARTRATE

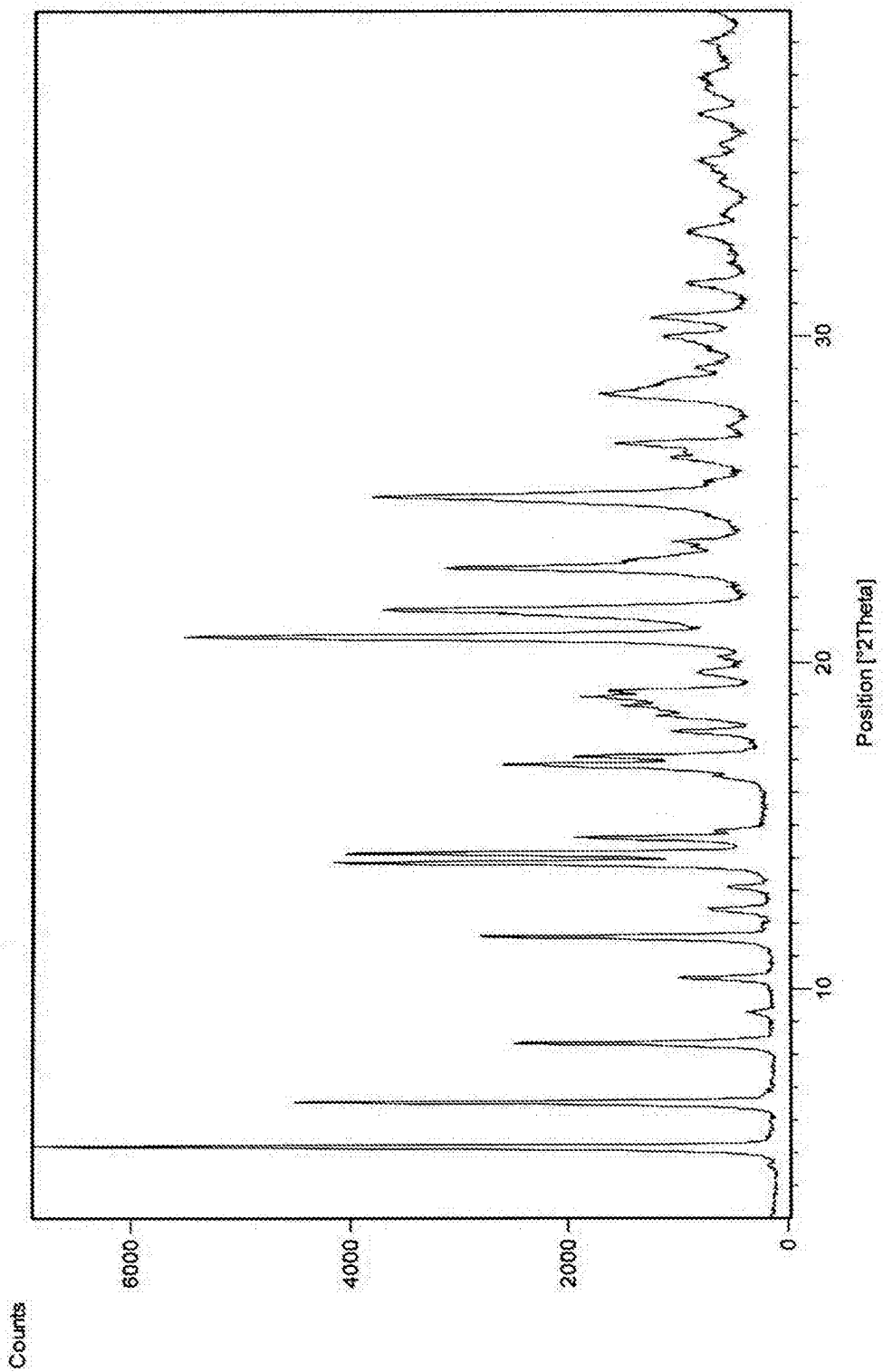


FIGURE 19a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]	Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
5.21	16.98	100.00	21.64	4.11	53.27
6.56	13.47	66.06	22.91	3.88	45.27
8.35	10.58	34.72	23.71	3.75	13.38
9.28	9.53	3.59	25.08	3.55	55.19
10.36	8.54	12.99	26.25	3.40	14.08
11.62	7.62	40.61	26.73	3.34	21.19
12.47	7.09	7.83	27.23	3.27	6.22
13.15	6.73	6.74	28.21	3.16	23.62
13.89	6.38	59.57	28.67	3.11	14.35
14.17	6.25	58.14	29.08	3.07	10.91
14.65	6.05	27.96	30.03	2.98	14.11
14.85	5.97	8.13	30.59	2.92	16.57
16.47	5.38	7.59	31.63	2.83	12.16
16.87	5.26	37.46	33.29	2.69	11.15
17.13	5.18	26.81	33.76	2.65	6.95
17.90	4.95	12.78	34.67	2.59	7.51
18.34	4.84	15.09	35.42	2.53	10.07
18.67	4.75	21.03	35.90	2.50	7.69
18.94	4.69	26.76	36.79	2.44	10.26
19.13	4.64	22.88	37.53	2.39	9.19
19.72	4.50	10.30	37.98	2.37	9.77
20.17	4.40	7.62	39.01	2.31	9.32
20.78	4.27	81.04			

FIGURE 20: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB TARTRATE

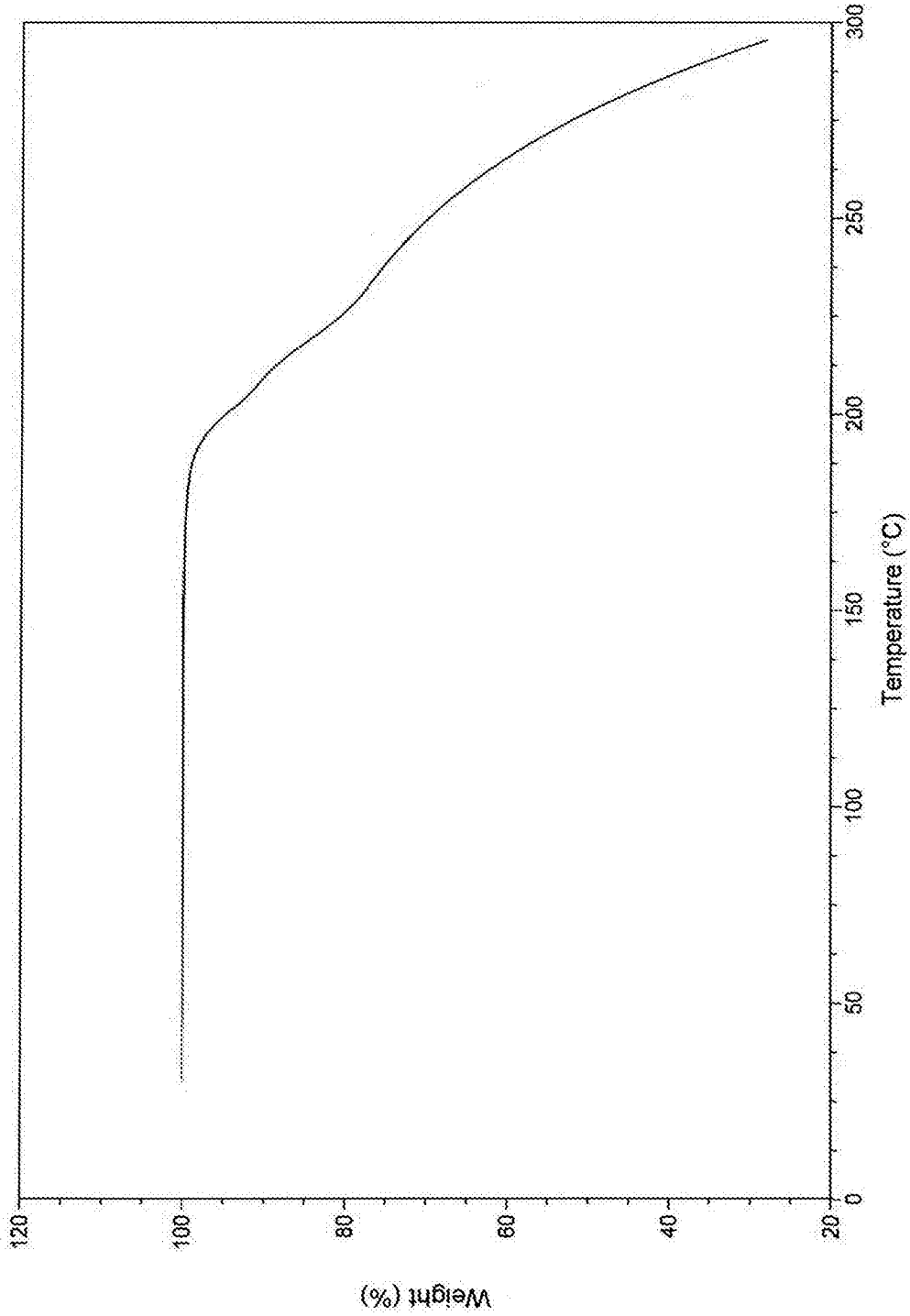


FIGURE 21: DSC OF DARAPLADIB TARTRATE

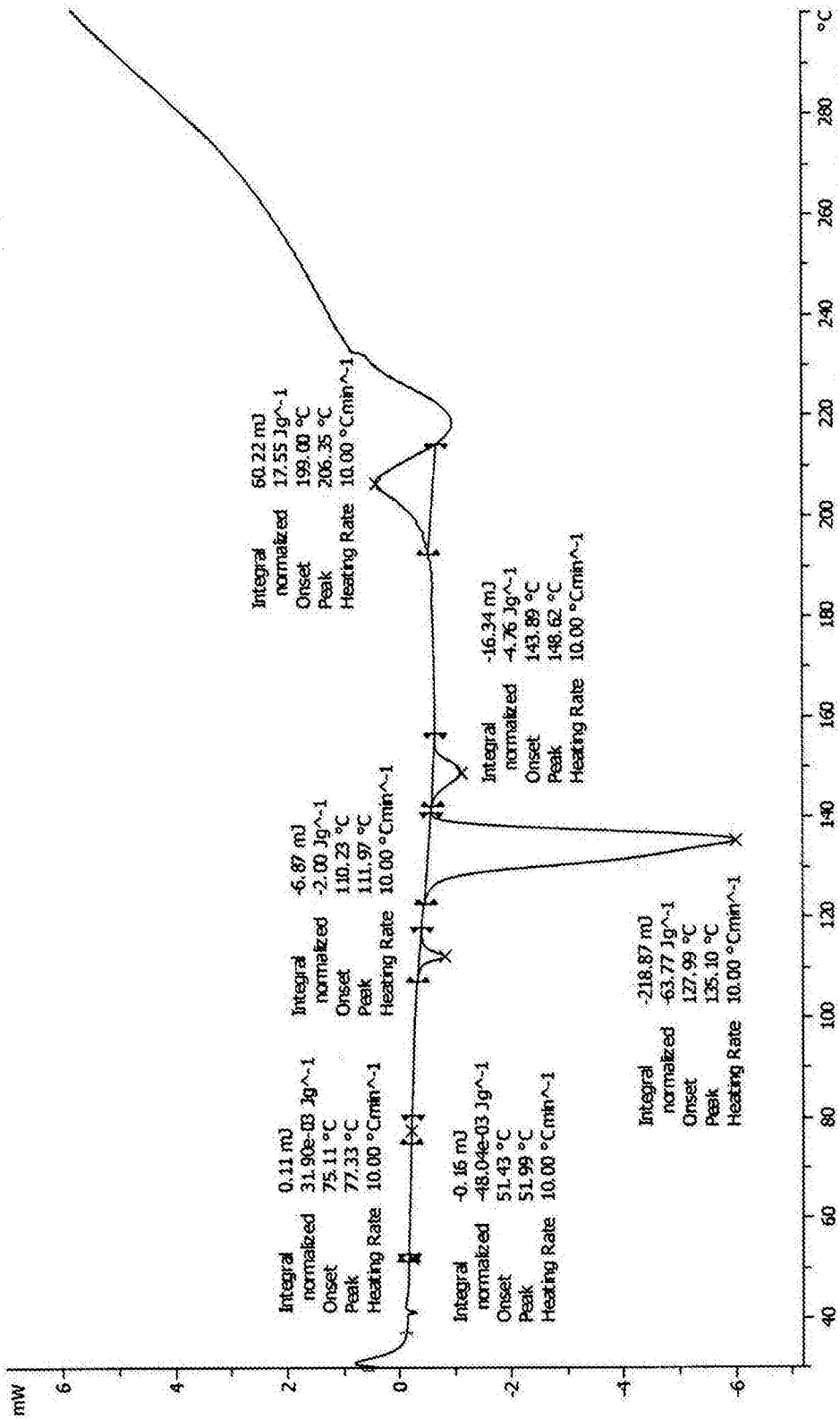


FIGURE 22: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB NITRATE

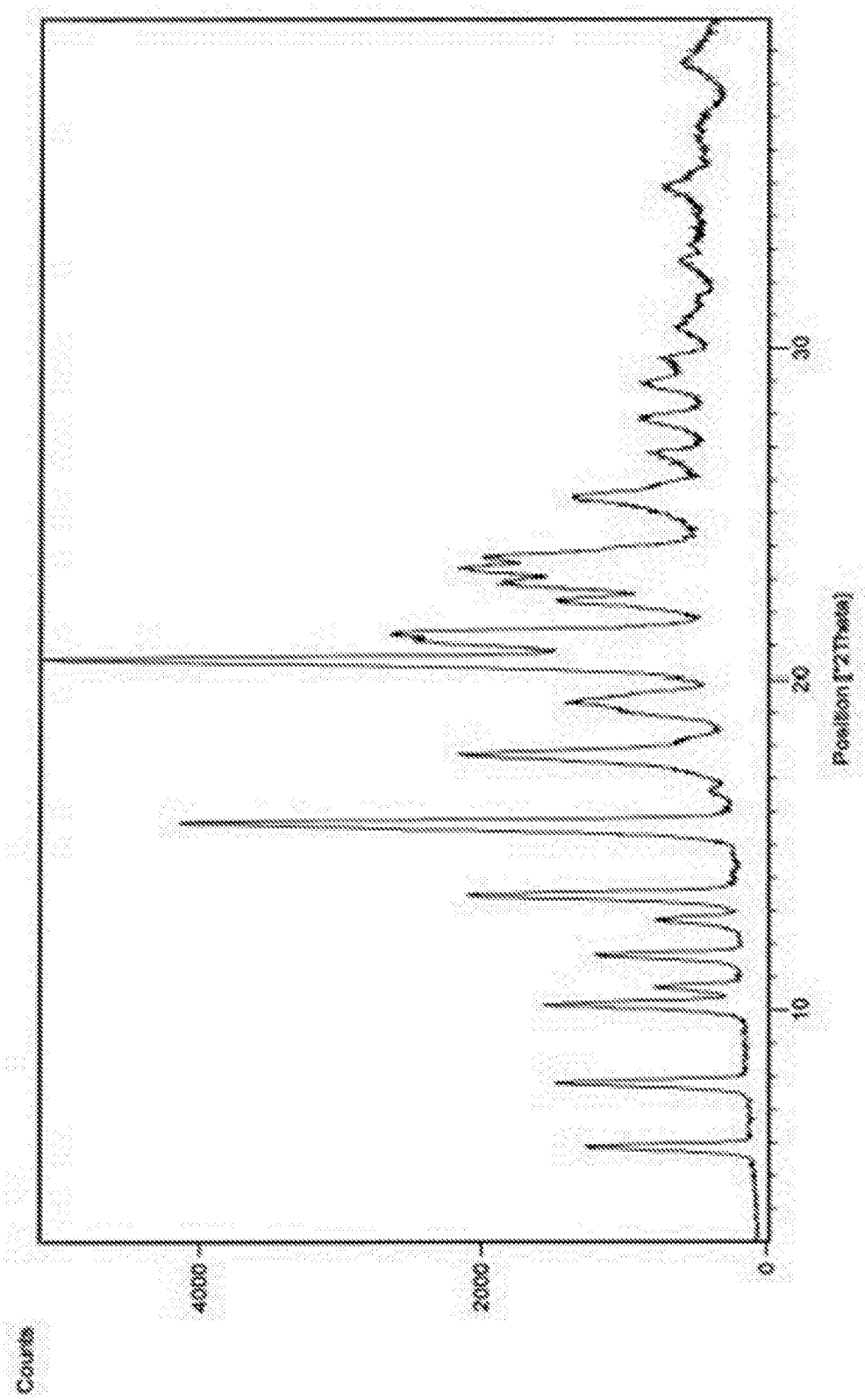


FIGURE 22a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]	Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
5.92	14.93	27.29	21.39	4.15	59.27
7.88	11.22	25.04	22.36	3.98	32.26
10.23	8.64	28.79	22.84	3.89	40.73
10.72	8.25	15.20	23.29	3.82	46.83
11.72	7.55	24.04	23.72	3.75	42.83
12.82	6.91	13.75	25.53	3.49	29.03
13.44	6.59	45.64	26.85	3.32	16.44
13.56	6.53	40.93	27.81	3.21	18.61
15.73	5.63	83.53	28.89	3.09	17.93
16.63	5.33	6.89	29.72	3.01	14.60
17.73	5.00	47.15	30.59	2.92	12.79
18.98	4.68	19.22	32.67	2.74	12.29
19.35	4.59	29.61	34.98	2.57	14.02
20.63	4.31	100.00	36.73	2.45	9.04
21.05	4.22	51.28	38.60	2.33	11.55

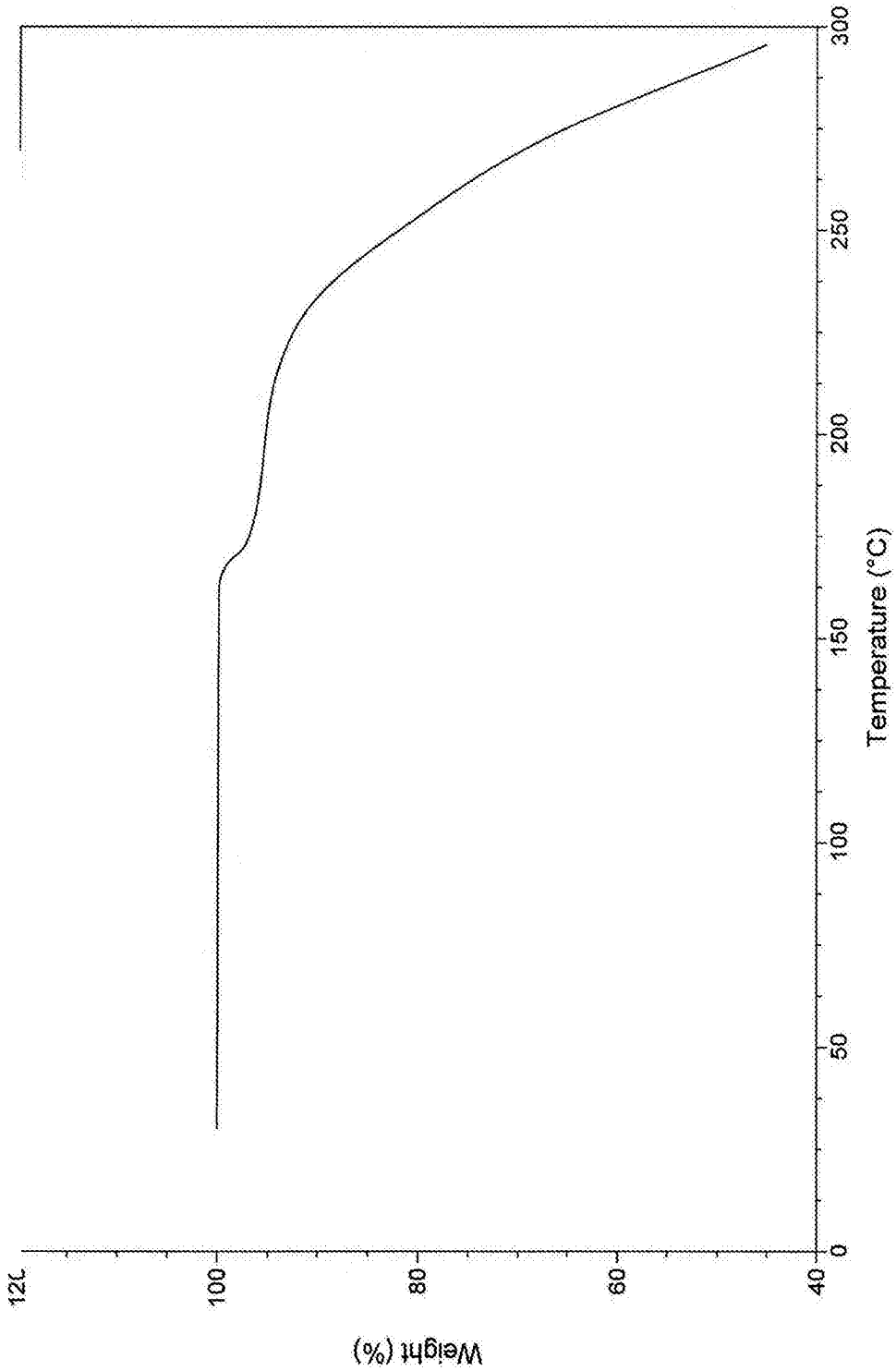


FIGURE 23: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB NITRATE

FIGURE 24: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB NITRATE

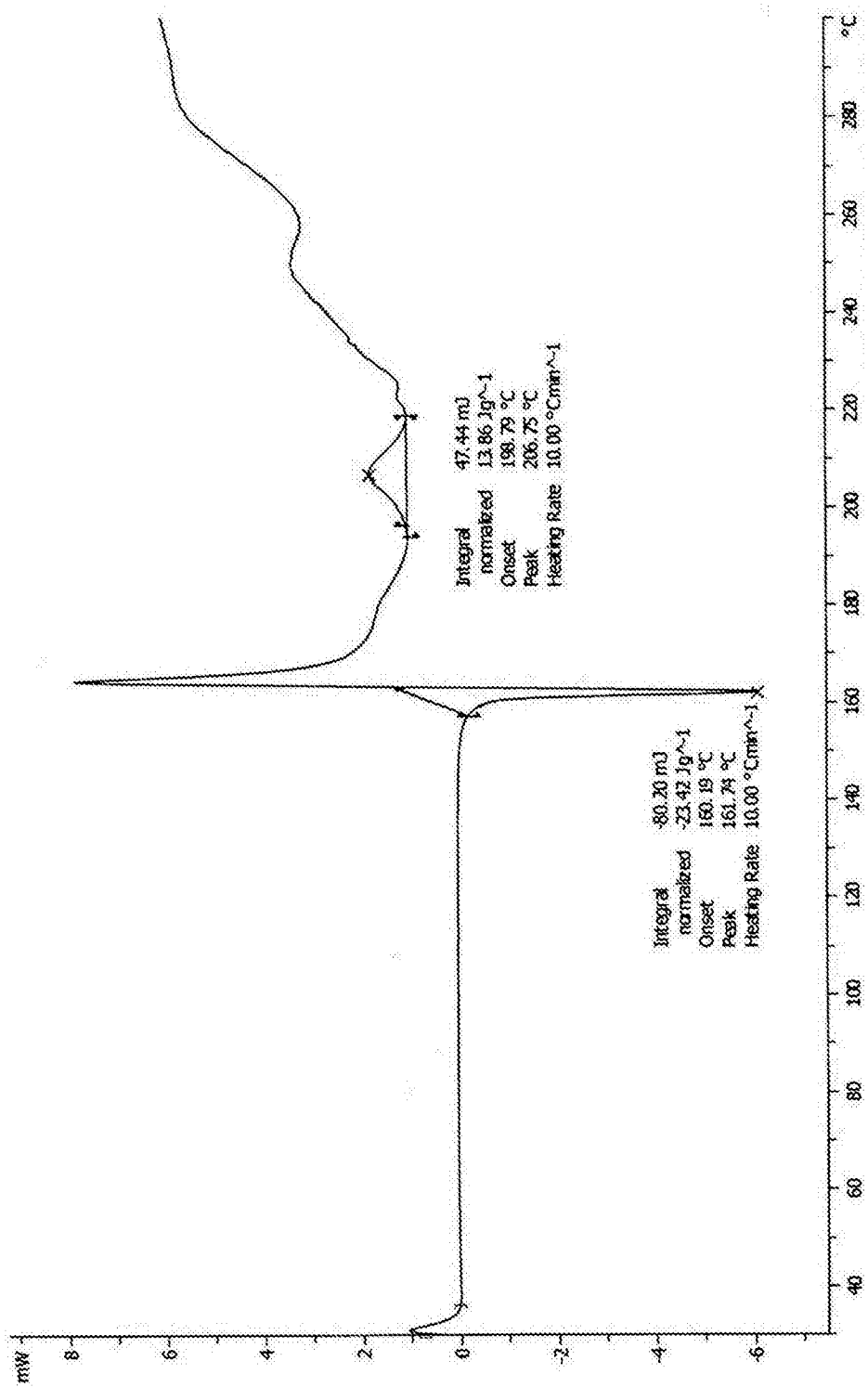


FIGURE 25: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF DARAPLADIB BORATE

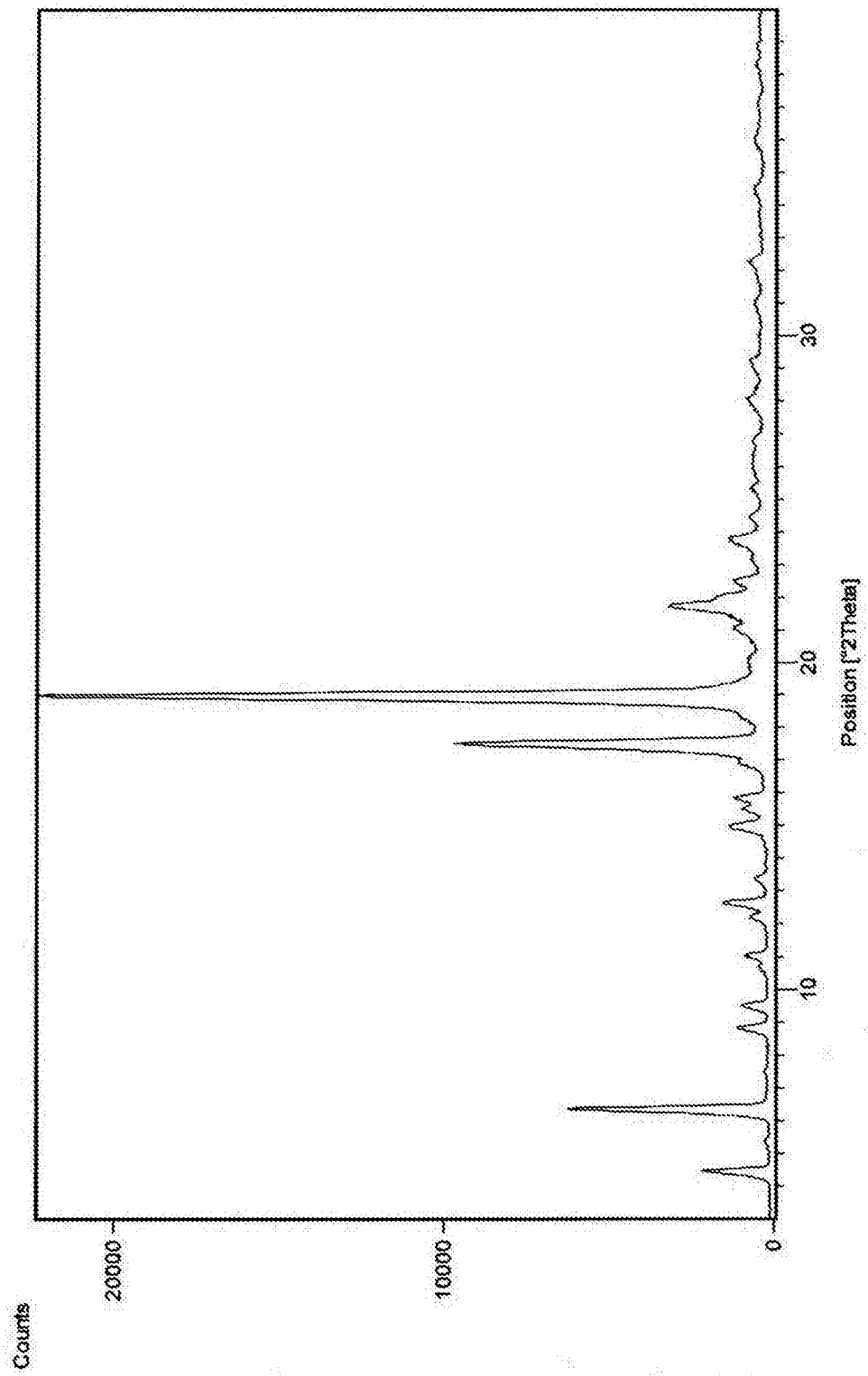


FIGURE 25a

Position [°2θ]	d-spacing (Å)	Relative Intensity [%]
4.48	19.71	9.59
5.40	16.36	0.65
6.39	13.84	28.73
7.47	11.83	0.60
8.88	9.96	4.00
9.52	9.29	4.00
10.68	8.28	1.49
11.07	7.99	3.19
12.16	7.28	2.24
12.69	6.98	5.84
13.38	6.62	1.90
15.04	5.89	5.04
15.49	5.72	3.44
15.87	5.58	4.58
16.91	5.24	4.07
17.54	5.06	43.62
19.02	4.67	100.00
20.21	4.39	2.25
21.05	4.22	4.57
21.68	4.10	13.92
21.78	4.09	13.41
22.05	4.03	6.64
22.52	3.94	4.49
23.83	3.73	4.85
24.45	3.64	2.13
25.36	3.51	1.83
26.05	3.42	1.72
26.88	3.31	1.42
28.09	3.17	2.36
29.24	3.05	1.83
30.97	2.89	1.26
32.27	2.77	1.88
34.51	2.59	1.13
36.03	2.49	1.04
37.16	2.42	0.49
38.31	2.35	0.56

FIGURE 26: THERMOGRAVIMETRIC ANALYSIS (TGA) OF DARAPLADIB BORATE

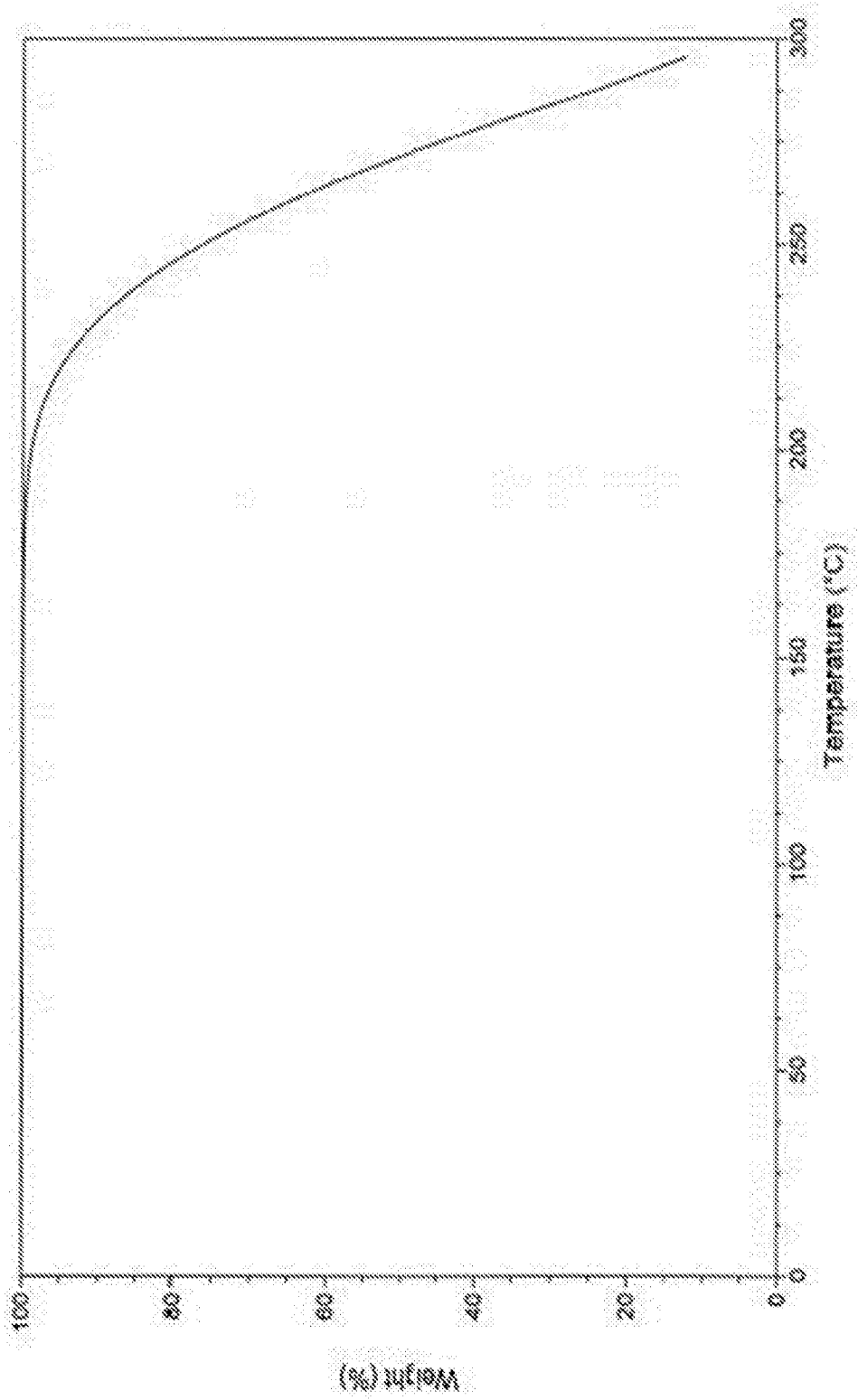
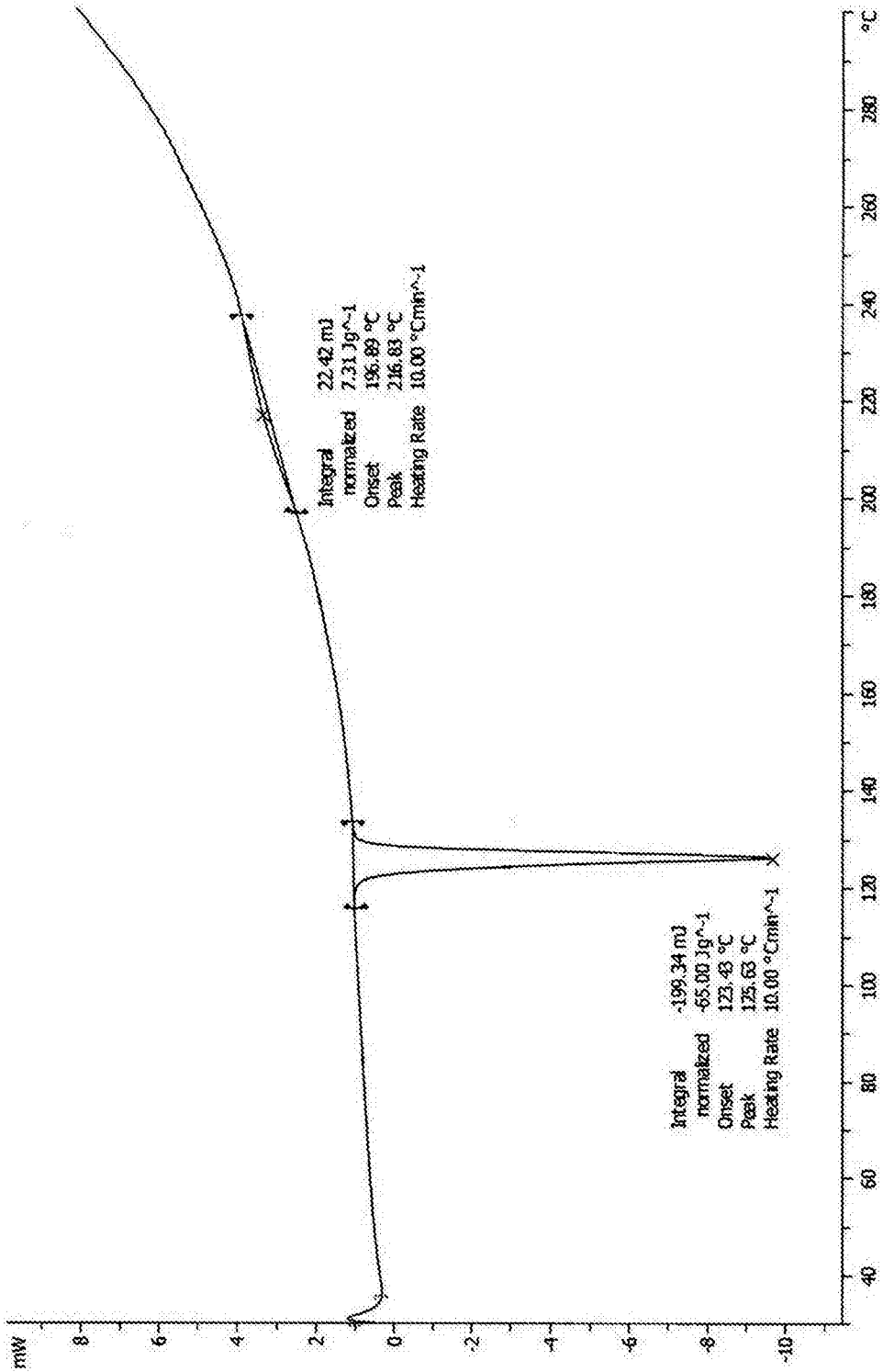


FIGURE 27: DIFFERENTIAL SCANNING CALORIMETRY (DSC) OF DARAPLADIB BORATE



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/050284

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/56 A61K31/517 A61P9/10
ADD.

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)
C07D

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)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/60805 A1 (SMITHKLINE BEECHAM PLC [GB]) 23 August 2001 (2001-08-23) page 30 - page 31; examples 3a-3c claim 23 page 6, line 10 - line 14 -----	1-36, 43-48, 57-63

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2015	15/05/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cortés, José

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/050284

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:

see additional sheet

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 an 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.:

1-36, 43-48(completely); 57-63(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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-36, 43-48(completely); 57-63(partially)

   A crystalline form of darapladib oxalate, adipate, succinate, phosphate, sulphate, fumarate or nitrate

   ---

2. claims: 37-42(completely); 57-63(partially)

   A crystalline form of darapladib tartrate

   ---

3. claims: 49-56(completely); 57-63(partially)

   Darapladib borate

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/050284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0160805 A1	23-08-2001	AR 030190 A1	13-08-2003
		AT 333446 T	15-08-2006
		AT 437862 T	15-08-2009
		AU 3546601 A	27-08-2001
		AU 2001235466 B2	22-04-2004
		BG 66014 B1	29-10-2010
		BG 107034 A	30-04-2003
		BR 0108396 A	11-03-2003
		CA 2400554 A1	23-08-2001
		CN 1418199 A	14-05-2003
		CO 5271661 A1	30-04-2003
		CY 1109484 T1	13-08-2014
		CZ 20022768 A3	14-05-2003
		DE 60121550 T2	21-06-2007
		DK 1263740 T3	13-11-2006
		DK 1686119 T3	09-11-2009
		EP 1263740 A1	11-12-2002
		EP 1686119 A1	02-08-2006
		ES 2267714 T3	16-03-2007
		ES 2330552 T3	11-12-2009
		GC 0000221 A	29-03-2006
		HK 1053466 A1	09-02-2007
		HU 0204410 A2	28-05-2003
		IL 151236 A	11-02-2009
		JP 4095804 B2	04-06-2008
		JP 2003523335 A	05-08-2003
		KR 20030011772 A	11-02-2003
		MX PA02008062 A	29-11-2002
		MY 135732 A	30-06-2008
		NO 20023828 A	30-09-2002
		NZ 520752 A	26-03-2004
		PL 357382 A1	26-07-2004
		PT 1263740 E	30-11-2006
		PT 1686119 E	06-10-2009
		SI 1263740 T1	31-12-2006
		SI 1686119 T1	31-12-2009
		SK 11772002 A3	04-02-2003
		TW 550259 B	01-09-2003
		US 6649619 B1	18-11-2003
		US 2002103213 A1	01-08-2002
		US 2004097525 A1	20-05-2004
		US 2007123549 A1	31-05-2007
		US 2007155762 A1	05-07-2007
		US 2009118313 A1	07-05-2009
		US 2009170877 A1	02-07-2009
		US 2010144765 A1	10-06-2010
		US 2012172378 A1	05-07-2012
		US 2015045375 A1	12-02-2015
		WO 0160805 A1	23-08-2001