(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 March 2019 (14.03.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/047989 A2

(51) International Patent Classification:
Not classified

(21) International Application Number:
PCT/CZ2018/000040

(22) International Filing Date:
31 August 2018 (31.08.2018)

(25) Filing Language: Czech

(26) Publication Language: English

(30) Priority Data:
PUV 2017-34072 05 September 2017 (05.09.2017) CZ

(71) Applicant: **ZENTIVA, K.S.** [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).

(72) Inventors: **SLAVIKOVA, Marketa**; Letecka 482, 252 66 Libcice nad Vltavou (CZ). **ZEZULA, Josef**; Dobroutov 27, 588 13 Polna (CZ). **CERNY, Josef**; Smetackova 1407, 274 01 Slany (CZ). **DAMMER, Ondrej**; Novotneho 975, 253 01 Hostivice (CZ). **SIMEK, Michal**; Na Vysluni 818/3, 337 01 Jindrichuv Hradec (CZ).

(74) Agent: **JIROTKOVA, Ivana** et al.; Rott, Ruzicka & Guttmann, Vinohradska 37, 120 00 Praha 2 (CZ).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: CRYSTALLINE FORMS OF (3α,5β,6α,7α)-6-ETHYL-3,7-DIHYDROXYCHOLAN-24-IC ACID

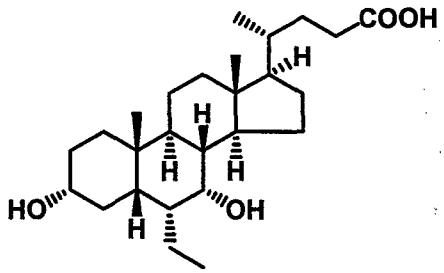
(57) Abstract: Crystalline form J-1 and J-2 of obeticholic acid, whereas crystalline form J-1 shows characteristic reflections in an X-ray powder record using CuKα radiation: 6.3; 9.4; 12.2; 14.4; 16.5 and 19.0 ± 0.2° 2-theta and crystalline form J-2 shows characteristic reflections in an X- ray powder record using CuKα radiation: 6.3; 8.9; 10.8; 15.8; 16.5; 18.4 and 20.3 ± 0.2° 2-theta.

WO 2019/047989 A2

Crystalline forms of (3α,5β,6α,7α)-6–ethyl-3,7-dihydroxycholan-24-ic acid

Field of the Invention

The invention is based on crystalline forms of obeticholic acids (I), chemical name (3α,5β,6α,7α)6-ethyl-3,7-dihydroxycholan-24-ic acid and a pharmaceutical composition containing crystalline forms of obeticholic acid.



(I)

Background Art

Obeticholic acid is a semi-synthetic bile acid analog with an agonistic effect on the farnesoid X receptor (FXR). It is designed for the treatment of liver diseases, e.g. primary biliary cirrhosis (PBC), nonalcoholic steatohepatitis (NASH) or primary sclerosing cholangitis (PSC).

Obeticholic acid was first mentioned in the patent application WO2002072598. It was isolated via column chromatography, and no physicochemical characterization of the solid form was mentioned here. Two patent applications WO2006122977 and US20090062526 followed, dealing with a synthesis of obeticholic acid.

Another published patent application WO2013192097 describes two solid forms of obeticholic acid: crystalline form C and amorphous form 1. It describes preparation of crystalline form C and subsequently its reprecipitation to amorphous form 1. The said patent application also mentions other crystalline forms of obeticholic acid, which however are not suitable for use in the pharmaceutical industry for various reasons.

Crystalline form A of obeticholic acid was described in patent application WO2016107575.

Crystalline forms I-2 and I-3 were described in patent application WO2017008773.

Another crystalline form identified as I was described in patent application CN105175473.

The method of preparation of amorphous form of obeticholic acid is described in patent application CN105085597.

Another crystalline form of obeticholic acid was described in application CN105985395.

Solid forms I and II of obeticholic acid are also described in patent application CN105777836.

Another crystalline form is described in patent application CN105859814.

Crystalline form marked α is described in patent application CN105859818.

Many pharmaceutical solid compounds may exist in different crystalline forms which are considered to be polymorphs, or they may exist in the form of hydrates/solvates. Individual solid forms have different physicochemical characteristics such as melting temperature, solubility, dissolution rate and bioavailability. To distinguish individual solid phases of a compound, several solid-state analytic methods can be used, e.g. the X-ray powder diffraction (XRPD), solid-state nuclear magnetic resonance (NMR), Raman spectroscopy as well as thermoanalytical techniques, e.g. differential scanning calorimetry (DSC).

Discovering novel solid forms (polymorphs, solvates and hydrates) of an active pharmaceutical ingredient offers an opportunity to select a suitable modification with desirable physicochemical characteristics and processability, and to improve the characteristics of the pharmaceutical product.

Disclosure of the Invention

The subject of the invention comprises crystalline forms of obeticholic acid marked as J-1 and J-2.

The subject of the invention comprises crystalline form J-1 of obeticholic acid, showing characteristic reflections in a radiographic (X-ray) powder record using CuKα radiation: 6.3;

9.4; 12.2; 14.4; 16.5 and 19.0 ± 0.2° 2-theta. In some embodiments, obeticholic acid crystalline form J-1 is characterized with the following other reflections in an X-ray powder record: 4.3; 5.1; 7.5; 8.8; 10.3 and 11.8; ± 0.2° 2-theta.

Another subject of the invention comprises crystalline form J-2 of obeticholic acid, showing characteristic reflections in a (X-ray) powder record using CuKα radiation: 6.3; 8.9; 10.8; 15.8; 16.5; 18.4 and 20.3 ± 0.2° 2-theta. In some embodiments, obeticholic acid crystalline form J-2 is characterized with the following other reflections in an X-ray powder record: 3.1; 4.1; 12.4 and 18.4 ± 0.2° 2-theta.

These forms are advantageous, particularly in terms of removal of process impurities from the raw API and getting of a chemically stable form.

Brief description of the Drawings

Fig. 1: XRPD record of crystalline form J-1 of obeticholic acid
Fig. 2: DSC record of crystalline form J-1 of obeticholic acid
Fig. 3: XRPD record of crystalline form J-2 of obeticholic acid
Fig. 4: DSC record of crystalline form J-2 of obeticholic acid

Detailed description of the invention

In a effort to find crystalline forms of obeticholic acid having the required characteristics, various solvents and their combinations were tested. The selected examples of solvents (*i*-PrOH - isopropanol, AcOH - acetic acid, MeOH - methanol) are presented in Table 1. In some cases, the known form I-2 (WO2017008773) were prepared with success, and in addition, two novel forms named J-1 and J-2 were prepared as well. Form J-1 crystallized surprisingly well from methylisobutylketone (MIBK), as well as from a mixture of *n*-butyl acetate (*n*-BuOAc) and acetonitrile (MeCN), whereas form J-2 was obtained from acetone and combinations of cyclopentylmethylether (CPME) or isopropyl acetate (i-PrOAc) with cyclohexane.

Table 1: Screening of crystallization solvents

Sample	Scale (g)	Solvents (total volume in ml)	Result	XRPD Form	Yield
A	0.29	i-PrOH (0.6)	solution		
B	0.24	MIBK (0.8)	crystals	**J-1**	**49%**
C	0.25	CPME (0.4)	solution		
D	0.21	AcOH (0.2)	solution		
E	0.21	MeOH (0.4)	solution		
F	0.23	Heptane-*i*-PrOAc (1+1)	crystals	I-2	63%
G	0.23	Acetone (0.6)	crystals	**J-2**	**55%**
H	0.22	Water-Acetone (0.6+1)	enamel		
I	0.23	n-pentanol (0.4)	solution		
J	0.21	CPME-Heptane (0.6+0.6)	crystals	I-2	67%
K	0.26	CPME-Cyclohexane (0.6+0.6)	crystals	**J-2**	**55%**
L	1.5	MIBK (10)	crystals	**J-1**	**50%**
M	1.67	CPME-Cyclohexane (10+10)	crystals	**J-2**	**77%**
N	1.5	*i*-PrOAc-Cyclohexane (5+10)	crystals	**J-2**	**83%**
O	30	*n*-BuOAc-MeCN (45+45)	crystals	**J-1**	**91%**

Through polymorphic screening of amorphous obeticholic acid suspension and a range of 50 solvents and their combinations, forms G (according to WO2013192097), I-2, J-1, J-2 and amorphous form were also obtained. Selected examples are presented in Table 2. Experiments were made of 50 mg of obeticholic acid and a relevant solvent; the suspension was agitated for 2 weeks in repeated cycles for 12 hours at a temperature of 50 °C and for 12 hours at a temperature of 27 °C.

Table 2: Polymorphic screening of a suspension of amorphous obeticholic acid

Solvent	Boiling point at °C	Form
acetonitrile	81.6	**G**
butyl acetate	126	**I-2**

2-butanone	80	**J-2**
chloroform	58	**I-2**
ethyl acetate	77.1	**J-2**
methyl isobutyl ketone	116	**J-1**
toluene	110.6	**J-2**
xylene	136	**I-2**
heptane	98.4	**I-2**
isopropyl acetate	89	**J-2**
n-propyl acetate	102	**I-2**
isobutyl acetate	118	**J-1**
water	100	**amorph**
anisole	153.8	**J-2**

X-ray powder record of crystalline form J-1 of obeticholic acid is presented in **Figure 1**. Characteristic diffractions using radiation CuKα are 6.3; 9.4; 12.2; 14.4; 16.5 and 19.0 ± 0.2° 2-theta. Form J-1 also shows the following characteristic reflections: 4.3; 5.1; 7.5; 8.8; 10.3 and 11.8; ± 0.2° 2-theta. Diffraction peaks with relative intensity higher than 1% are presented in **Table 3.**

Table 3: XRPD - characteristic diffraction peaks of form J-1 of obeticholic acid

Pos. [°2Th.]	Interplanar distance [Å] [Å]=0.1nm	Rel. intensity [%]
3.11	28.395	15.2
4.29	20.600	29.7
5.08	17.377	44.5
6.27	14.088	100.0
7.48	11.815	53.9
8.34	10.598	13.0
8.84	9.999	36.0
9.39	9.413	89.5
9.97	8.865	58.9

10.32	8.568	43.8
11.18	7.905	38.1
11.44	7.726	28.5
11.80	7.494	33.0
12.22	7.239	95.4
12.63	7.005	60.1
13.09	6.758	9.1
13.59	6.508	12.0
14.36	6.162	62.0
14.85	5.961	56.9
15.21	5.822	25.5
15.73	5.629	58.9
16.50	5.367	76.6
17.70	5.008	28.9
18.62	4.762	24.7
19.04	4.657	41.7
19.51	4.545	25.6
20.02	4.431	10.2
20.69	4.289	11.2
21.13	4.201	20.0
22.21	3.999	6.1
24.81	3.586	7.2
25.94	3.432	7.9
26.83	3.320	6.3

Differential scanning calorimetry (DSC) was used to measure the melting point of the crystalline form of form J-1 of obeticholic acid 92.5 °C (**Fig. 2**).

X-ray powder record of crystalline form J-2 of obeticholic acid is presented in **Figure 3**. Characteristic diffractions using radiation CuKα are 6.3; 8.9; 10.8; 15.8; 16.5 and 18.4 ± 20.3° 0.2 2-theta. Form J-2 also shows the following characteristic reflections: 3.1; 4.1; 12.4 and 18.4 ± 0.2° 2-theta. Diffraction peaks with relative intensity higher than 1% are presented in **Table 4**.

Table 4: XRPD - characteristic diffraction peaks of form J-2

Pos. [°2Th.]	Interplanar distance [Å] [Å]=0.1nm	Rel. intensity [%]
3.09	28.528	34.0
4.05	21.802	35.7
4.58	19.276	12.6
6.25	14.120	97.3
7.82	11.298	39.8
8.18	10.804	50.8
8.89	9.939	75.5
9.41	9.393	68.4
9.78	9.035	21.3
10.82	8.173	56.7
12.37	7.148	41.6
12.64	6.999	35.5
13.25	6.676	9.1
14.15	6.253	13.9
15.84	5.589	93.6
16.49	5.372	100.0
17.03	5.202	28.0
17.67	5.015	15.4
18.42	4.812	36.6
18.84	4.707	29.3
20.27	4.378	19.3
20.69	4.289	8.4
21.10	4.207	8.6
21.65	4.102	7.4
22.88	3.884	5.5
24.39	3.647	9.4
24.90	3.574	7.0
25.88	3.440	5.8

26.69	3.337	5.1

Differential scanning calorimetry (DSC) was used to measure the melting point of the crystalline form of form J-2 of obeticholic acid 78.6 °C (**Fig. 4**).

Crystalline form J-1 of obeticholic acid according to the submitted invention is prepared by dissolving obeticholic acid in a solvent which is methyl isobutyl ketone or a mixture of solvents which are *n*-butyl acetate and acetonitrile at an increased temperature from 50 °C to the boiling point of the solvent or the mixture of solvents and following cooling of the produced solution to a temperature ranging from -10 °C to 40 °C. Crystallized form J-1 is then isolated using known techniques.

Crystalline form J-2 of obeticholic acid according to the submitted invention is prepared by dissolving of obeticholic acid in a solvent which is cyclopentyl methyl ether, isopropyl acetate or acetone at an increased temperature from 60 °C to the boiling point of the solvent, or another solvent is added as an antisolvent, e.g. cyclohexane or *n*-heptane. The produced solution is cooled to a temperature ranging from -10 °C to 40 °C. Crystallized form J-2 is then isolated using known techniques.

The amorphous form of obeticholic acid can be prepared from both forms, J-1 as well as J-2, through a procedure comprising the following steps:

a/ conversion of the crystalline form J-1 or crystalline form J-2 of obeticholic acid to its salt;

b/ addition of acid;

c/ isolation of produced precipitate of the amorphous for through filtration.

The crystalline form of obeticholic acid can be advantageously converted in step a/ to ammonium or sodium salt. In step b/, hydrochloric acid or phosphoric acid is advantageously added.

Crystalline forms of obeticholic acid J-1 and J-2 according to the submitted invention can be used for preparation of obeticholic acid with chemical purity higher than 99.80% according to HPLC (High Performance Liquid Chromatography).

Crystalline forms of obeticholic acid J-1 and J-2 according to the submitted invention can be subsequently used for preparation of a pharmaceutical composition.

Another subject of the invention is a pharmaceutical composition containing crystalline form J-1 or crystalline form J-2 of obeticholic acid and at least one pharmaceutically acceptable excipient. In some embodiments at least one pharmaceutically acceptable excipient is selected out of the group including lactose, microcrystalline cellulose, carboxymethyl starch sodium salt and magnesium stearate. In some embodiments, the pharmaceutical composition is in the form of tablet.

The invention is clarified in more detail in the following embodiment examples. These examples, which illustrate preparation of crystalline forms of obeticholic acid, have exclusively an illustrative character and do not restrict the scope of the invention in any respect.

Examples

Unless stated otherwise, the starting obeticholic acid was used in crystalline form I-2 prepared according to patent application WO2017008773.

Example 1

Obeticholic acid (1.5 g) was dissolved while boiling in methyl isobutyl ketone (10 ml), and the produced solution, while being stirred, was gradually cooled to a laboratory temperature of approx. 23 °C. Suspension was then stirred at that temperature for 24 hours. The crystalline product was isolated through filtration and dried via sucking of air on a frit for 24 hours. 0.75 g (50% yield) of crystalline form J-1 of obeticholic acid was obhtained. XRPD in Fig. 1, melting point 92.5 °C, content of methyl isobutyl ketone 8.0% (determined by gas chromatography (GC)).

Example 2

Obeticholic acid (0.227 g) was dissolved while boiling in acetone (0.6 ml), and the produced solution, while being stirred, was gradually cooled to a laboratory temperature of approx. 23 °C. Thick suspension was then stirred at that temperature for 24 hours. The crystalline

product was isolated through filtration and dried via sucking of air on a frit for 24 hours. 0.124 g (55% yield) of crystalline form J-2 was obtained.

Example 3

Obeticholic acid (1.67 g) was, while boiling, dissolved in cyclopentyl methyl ether (10 ml), cooled to approx. 80 C, then cyclohexane was slowly added (10 ml) while the mixture was stirred. The produced solution was gradually cooled to the laboratory temperature of approx. 23°C and the suspension was stirred at this temperature for 22 hours. The crystalline product was isolated through filtration and dried via sucking of air on a frit. 1.29 g of crystalline form J-2 of obeticholic acid was obtained (yield 77%). XRPD in Fig. 3, melting point 78.6 °C, content of cyclopentyl methylether 5.56%, cyclohexane 3.8% (GC).

Example 4

Obeticholic acid (1.5 g) was, while boiling, dissolved in isopropyl acetate (5 ml), then cyclohexane was slowly added (10 ml) while the mixture was stirred. The produced solution was gradually cooled to the laboratory temperature of approx. 23 °C and the suspension was stirred at this temperature for 22 hours. The crystalline product was isolated through filtration and dried via sucking of air on a frit for 24 hours, and then in a vacuum drier at 50 °C/180 mbar for 3 days. 1.24 g (83% yield) of crystalline form J-2 of obeticholic acid was obtained. Content of isopropyl acetate 0.05%, cyclohexane 3.3% (GC).

Example 5

Obeticholic acid (300 mg, HPLC 95.83%) was dissolved at 80 °C in methyl isobutyl ketone (0.5 ml), and the solution, while being stirred and slightly cooled to a temperature of approx. 60 °C, was inoculated with crystals of form J-1 (approx. 5 mg) and left stirred to cool to a laboratory temperature of approx. 23 °C. Suspension was then stirred at that temperature for 16 hours. The crystalline product was isolated through filtration and dried via sucking of air on a frit for 2 hours, and then in a vacuum drier at 40 °C/200 mbar for 16 hours. Crystalline form J-1 of obeticholic acid was obtained (246 mg, yield 82%) of HPLC purity 99.38%. XRPD in Fig. 1, content of methyl isobutyl ketone 8.5% (GC).

Example 6

Obeticholic acid (30 g, HPLC 99.54%, content of chenoxydeoxycholic acid 0.32%) was dissolved at 53 °C in a mixture of butyl acetate (45 ml) and acetonitrile (45 ml), and the solution was stirred at that temperature for 30 minutes. Then the solution was cooled to the temperature of 40 °C and stirred at that temperature for 1 hour. The produced suspension was then cooled slowly along 5 hours to the temperature of -10 °C, ant at that temperature it was stirred for 16 hours. The crystalline product was isolated through filtration and the obtained white crystals were dried in a vacuum drier at 40 °C/200 mbar for 16 hours. Crystalline form J-1 of obeticholic acid (27.35 g, yield 91.2%) of HPLC purity 99.74%, content of chenoxydeoxycholic acid 0.17%.

Example 7

Obeticholic acid (form J-1, 3.0 g; 7.14 mmol; HPLC 99.48%) was stirred up in demineralized water (60 ml) and the suspension was heated to 40 °C. At that temperature, 25% aqueous solution of ammonium hydroxide (1.35 ml) was added and the produced solution was stirred for 40 minutes and filtered. The solution was cooled to a temperature of 5 °C and at that temperature diluted phosphoric acid was dripped in during 30 minutes (1 ml of 85% of phosphoric acid + 1.5 ml of demineralized water). The suspension was stirred for 2 hours while being cooled, than it was filtered and washed through with water (approx. 60 ml). Obtained amorphous obeticholic acid was dried for 16 hours in a vacuum drier at 40 °C/180 mbar. Amorphous obeticholic acid was obtained (2.874 g, yield 95.8%)of HPLC purity 99.91%, content of methyl isobutyl ketone 790 ppm (GC), content of water 4%.

List of analytic methods

Measuring parameters of XRPD: The diffractograms were measured using an X'PERT PRO MPD PANalytical diffractometer with graphite monochromator; used radiation CuKα (λ = 1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ. Measurements were carried out with a flat powder sample applied on an Si plate. For the setting of the primary optical system programmable divergence slits with the irradiated sample area of 10 mm, 0.02 rad Soller slits and a ¼° anti-dispersion slit were used.

For the setting of the secondary optical system an X'Celerator detector with the maximum opening of the detection slot, 0.02 rad Soller slits and a 5.0 mm anti-dispersion slit were used.

Records of differential scanning calorimetry (DSC) were measured with a DSC instrument Pyris 1 made by Perkin Elmer Company. The charge of the sample in a standard Al pot was 3-4 mg and the heating rate was 10 °C/min. The used temperature program consists of 1 stabilization minute at 50 °C and then of heating up to 250 °C at the heating rate of 10°C/min. As the carrier gas, 4.0 N_2 was used at the flow of 20 ml / min.

Determination of chemical/optical purity by HPLC:
Column XSelect CSH C18, (2.5 μm, l = 150 mm, I.D. 3.0 mm), temperature 60 °C,
Mobile phase A: 1.0 ml of 70% wt perchloric acid dissolved in 1000 ml of water,
mobile phase B: acetonitrile, linear gradient according to the table below, flow-rate 0.7 ml/min,
detection at 195 nm.

Table 5: HPLC gradient

Time [min]	Mobile phase A [% V/V]	Mobile phase B [% V/V]
0	65	35
10	25	75
11	25	75
12	65	35
15	65	35

Residual solvents were determined through **gas chromatography (GC)** according to the method *Ph.Eur. 2.2.28.*

CLAIMS

1. Crystalline form J-1 and J-2 of obeticholic acid, whereas crystalline form J-1 shows characteristic reflections in an X-ray powder record using CuKα radiation: 6.3; 9.4; 12.2; 14.4; 16.5 and 19.0 ± 0.2° 2-theta and crystalline form J-2 shows characteristic reflections in an X-ray powder record using CuKα radiation: 6.3; 8.9; 10.8; 15.8; 16.5; 18.4 and 20.3 ± 0.2° 2-theta.

2. Crystalline form J-1 of obeticholic acid according to Claim 1, characterized by the following other reflections in an X-ray powder record: 4.3; 5.1; 7.5; 8.8; 10.3 and 11.8; ± 0.2° 2-theta.

3. Crystalline form J-1 of obeticholic acid according to Claims 1 and 2, characterized by a differential scanning calorimetric curve with the melting point at 92.5 °C.

4. Crystalline form J-2 of obeticholic acid according to Claim 1, characterized by the following other reflections in an X-ray powder record: 3.1; 4.1; 12.4 and 18.4 ± 0.2° 2-theta.

5. Crystalline form J-2 of obeticholic acid according to Claims 1 and 4, characterized by a differential scanning calorimetric curve with the melting point at 78.6 °C.

6. The pharmaceutical composition characteristic with containing crystalline form J-1 and/or J-2 of obeticholic acid according to any of the claims 1 to 5 and at least one pharmaceutically acceptable excipient.

Drawings

Fig. 1:

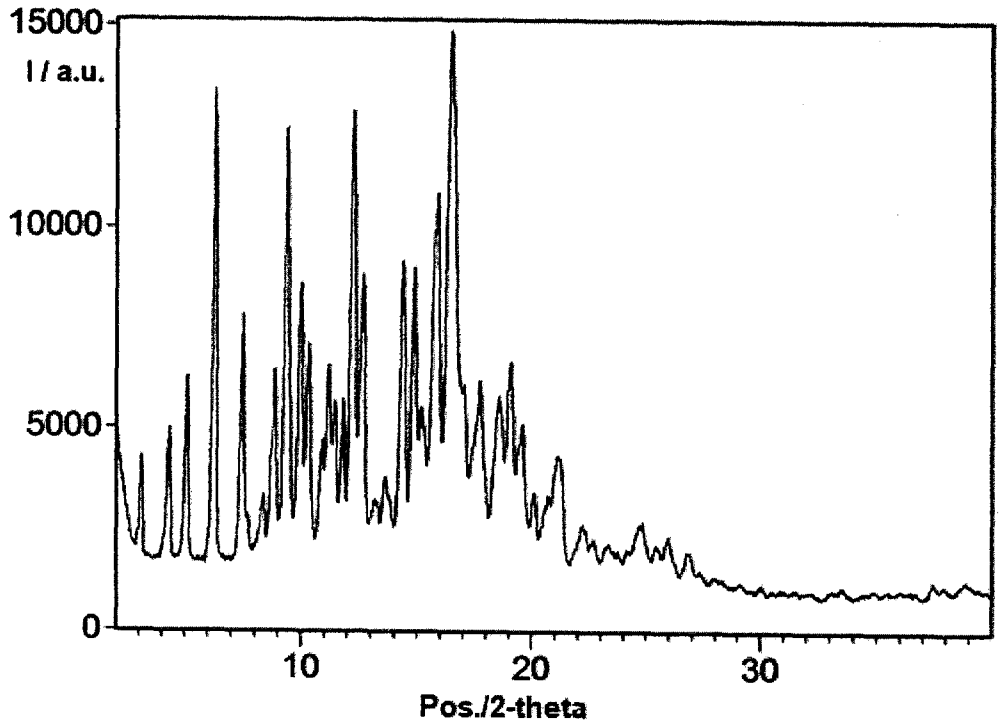


Fig. 2:

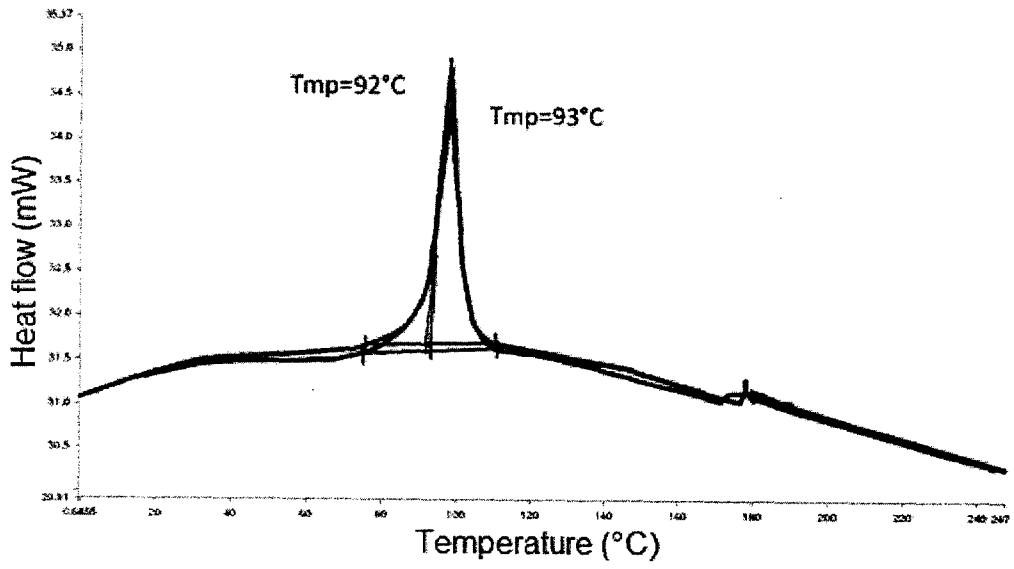


Fig. 3:

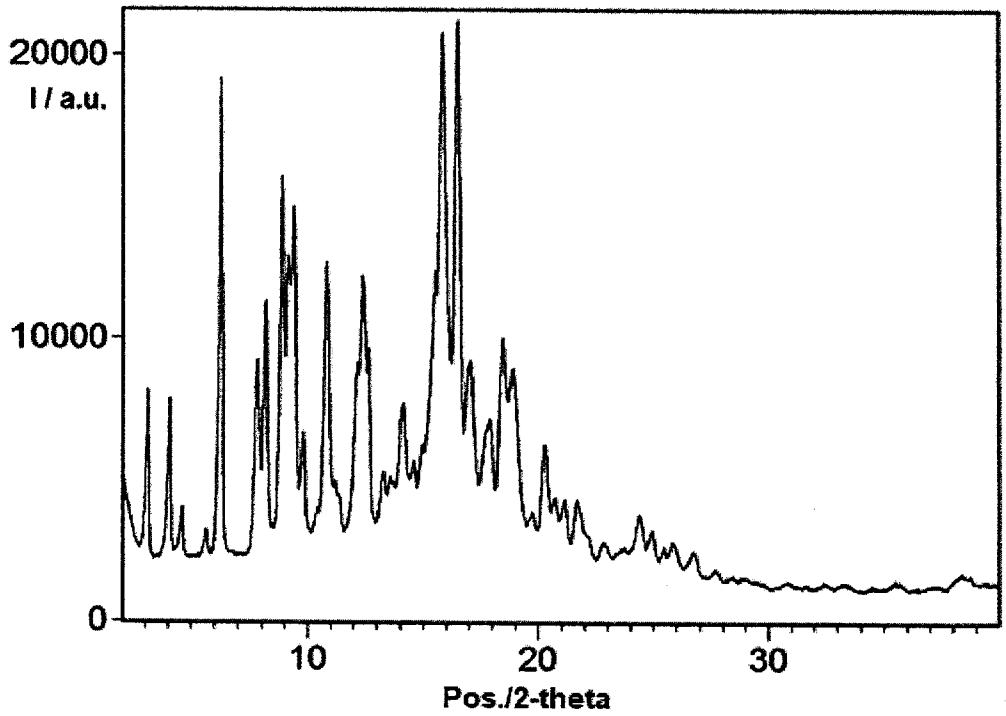
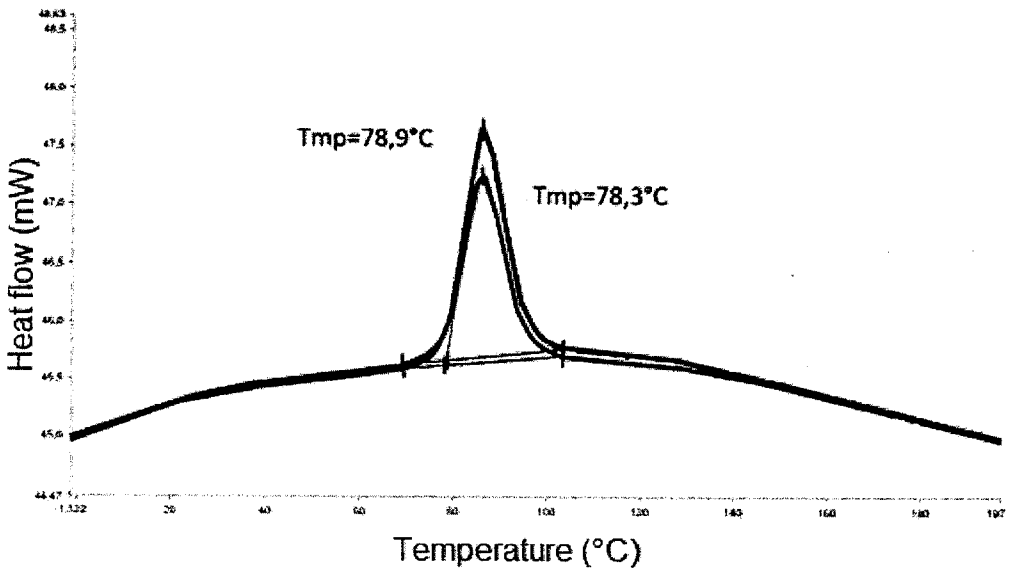

20000
I / a.u.
10000
0
10
20
30
Pos./2-theta

Fig. 4:


Tmp=78,9°C
Tmp=78,3°C
Heat flow (mW)
Temperature (°C)