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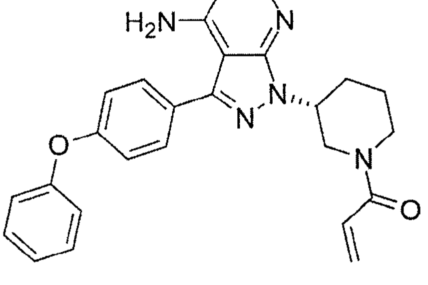
(54) Title: SOLID FORMS OF IBRUTINIB



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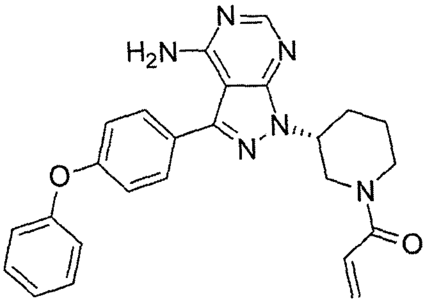
(57) Abstract: The invention relates to a solid form of 1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H- pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one of formula I and to preparation methods of crystalline particles with variable morphology. Crystalline form C of ibrutinib free base with the primary particle size smaller than or equal to 120 μm, the ratio of the primary particle size to the cluster size being at least 1:5 and the clusters having the minimum size of 150 μm.

Solid forms of ibrutinib

Field of the Invention

The invention relates to a solid form of 1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one of formula I,



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known as ibrutinib, and to preparation methods of crystalline particles with variable morphology.

Background Art

1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one, which is known as ibrutinib (CAS no. 936563-96-1) and belongs to the group of kinase inhibitors that can be used for the treatment of lymphomas. Under the trade name Imbruvica, Ibrutinib was approved by The Food and Drug Administration (FDA) for the treatment of centrocytic lymphoma.

Preparation of this molecule and its isolation with the use of chromatography was described in the patent document WO2008/039218. Preparation of crystalline forms of ibrutinib in a solvated or non-solvated form was described in the patent documents WO 2013/184572, CN 103694241 and WO 2015/145415. Use of ibrutinib in the treatment of lymphomas together with other pharmaceutically active ingredients was described in the patent document WO 2013/113841 and the patent document WO 2013/155347, which also mentions pharmaceutically acceptable salts of this drug without any further description or production example. Besides preparation methods, the patent document WO 2013/184572 deals with the pharmaceutical composition of crystalline and solvated forms of ibrutinib for oral administration and mentions pharmaceutically acceptable salts of this drug without any further description or production example. Further use of ibrutinib for the treatment of cancer, inflammatory and autoimmune diseases, together with a description of pharmaceutical compositions mentioning its pharmaceutically acceptable salts without their further description or production example is mentioned in the patent document WO2014/004707.

The solubility of crystalline form A of the free base of ibrutinib in water is very low, even if aqueous solutions with different pH are used. It is clear that novel solid forms of this active pharmaceutical ingredient are necessary for the preparation of a drug form with higher solubility and biological availability.

Disclosure of the Invention

The dissolution rate of crystalline form C of ibrutinib free base in a solution having pH 2 is $0.052\ \mathrm{mg \cdot min^{-1} \cdot cm^{-2}}$, while the dissolution rate of the thermodynamically most stable form A of ibrutinib free base is $0.017\ \mathrm{mg \cdot min^{-1} \cdot cm^{-2}}$ under identical conditions. The object of the invention is preparation of a crystalline solid form of ibrutinib (form C) with a variable size of the primary particles and their clusters. The morphology of particles is governed by the process parameters during crystallization. Crystalline form C of ibrutinib free base can be prepared from a methanolic solution by crystallization when through a change of process parameters (solution saturation, temperature, cooling rate, inoculation temperature), crystalline form C of ibrutinib free base can be prepared in a yield of > 90% with controlled morphology and the size of primary particles from 5 μm to 120 μm. The crystallization yield of ibrutinib form C described in the patent application WO 2008/039218 is 70% with the primary particle size of about 35 μm.

The morphology and size of the primary particles of crystalline form C of ibrutinib free base also significantly influences filterability of the suspension during production. We have found out that in the case of crystalline form C of ibrutinib free base with the primary particle size of 120 μm and the cluster size of ≤ 600 μm the filtration time is approximately three times shorter than in the case of preparation of crystalline form C of ibrutinib free base according to the procedure described in the patent application WO2008/039218, when the size of primary particles was ≤ 35 μm. A larger size of the primary particles and clusters also enables easier handling after filtration of the product and faster achievement of a constant weight during product drying. The prepared crystalline forms C of ibrutinib free base have suitable physicochemical properties for use in pharmacy and formulation of new drug forms.

Brief description of the Drawings

Figure 1. Raman spectra of a) crystalline form A of ibrutinib (according to Example 1); b) suspension of ibrutinib in methanol after 15 min at 25°C; suspension of ibrutinib in methanol after 48 hours at 25°C; d) crystalline form F of ibrutinib (according to example 3); e) crystalline form of ibrutinib after filtering and drying of the product for 16 hours at 40°C and the pressure of 13 kPa; f) crystalline form C of ibrutinib (according to Example 2)

Figure 2. SEM image of crystalline form A of ibrutinib free base (according to Example 1)

Figure 3. X-ray powder pattern of crystalline form A of ibrutinib free base (according to Example 1)

Figure 4. SEM image of crystalline form C of ibrutinib free base (according to Example 2)

Figure 5. X-ray powder pattern of crystalline form C of ibrutinib free base (according to Example 2)

Figure 6. SEM image of crystalline form C of ibrutinib free base (according to Example 4)

Figure 7. SEM image of crystalline form C of ibrutinib free base (according to Example 5)

Figure 8. SEM image of crystalline form C of ibrutinib free base (according to Example 6)

Figure 9. SEM image of crystalline form C of ibrutinib free base (according to Example 7)

Detailed description of the Invention

Biological availability of active pharmaceutical ingredients greatly depends on whether a crystalline or amorphous product is obtained. An amorphous product is usually more readily soluble, it cannot often be obtained in the required quality and it is also often unstable. Conversely, compared to the amorphous form, a crystalline product is often stable, its required purity is easier to achieve and it dissolves more slowly. The problem may be solved by crystalline forms of active pharmaceutical ingredients with a lower melting point than the corresponding thermodynamically most stable crystalline form, when such crystal arrangement guarantees higher solubility of the crystalline form.

The size of the primary particles and morphology of clusters can be controlled by the process parameters of crystallization as solution saturation, temperature, cooling rate, inoculation temperature.

The size of the primary particles and clusters influences the filtering rate of the suspension during preparation and the time of achievement of a constant weight during product drying.

This product provides a preparation method of crystalline form C of ibrutinib free base in high yields, when the obtained crystalline forms exhibit higher solubility than in the case of the thermodynamically most stable crystalline form A of ibrutinib free base.

The object of the invention is a preparation method of a crystalline solid form of ibrutinib (form C) with a variable size of the primary particles and their clusters. Crystalline form C of ibrutinib free base can be prepared from a methanolic solution by crystallization or from a suspension. The preparation method of form C of ibrutinib free base comprises dissolution of ibrutinib at a concentration of 10 mg/ml to 260 mg/ml at 60°C or at a concentration of 90 mg/ml to 260 mg/ml at 60°C. The solution is cooled down at a rate of 0.1°C/min to 3°C/min, preferably 0.1°C/min to 1°C/min. The solution is inoculated at a temperature from 45°C to 0°C.

The preparation method of form C of ibrutinib free base consists in that ibrutinib is obtained by crystallization of a solution produced by dissolution of ibrutinib in methanol at the concentration of 90 mg/ml at 60°C, the solution is cooled down at the rate of 0.3°C/min until the temperature 0°C is achieved, the solution is inoculated by addition of 2% of crystalline form C of ibrutinib free base at 25°C, the solid fraction is obtained by filtering and drying of the filter cake at 40°C and the pressure of 20 kPa; drying being applied until a constant product weight is achieved.

The size of the primary particles and morphology of clusters can be controlled by the process parameters of crystallization as solution saturation, temperature, cooling rate, inoculation temperature.

The size of the primary particles and clusters influences the filtering rate of the suspension during preparation and the time of achievement of a constant weight during product drying.

Within the invention, crystalline form C of ibrutinib free base with the primary particle size of ≤ 120 μm is preferred, the ratio of the primary particle size to the cluster size being at least 1:5 and the cluster size being at least 150 μm, and the particles prepared this way were prepared in a high yield, with good filterability and workability in the powder state as well as a short time to achieve a constant weight during product drying.

Preparation of this molecule and its isolation with the use of chromatography was described in the patent document WO2008/039218. Preparation of crystalline forms of ibrutinib in a solvated or non-solvated form was described in the patent documents WO2013/184572, CN 103694241 and WO 2015/145415. Crystalline forms A, C (morphology I) and F of ibrutinib free base were prepared according to the procedure disclosed in the patent application WO2013/184572.

It was found out that crystalline form C of ibrutinib can be prepared by suspending or recrystallization of forms A, B or their mixtures in methanol (see tab. 1).

Table 1: Polymorphic transformation of crystalline forms of ibrutinib in a methanolic suspension (3 weeks at 35°C)

Initial crystalline form or mixture of crystalline forms of ibrutinib	Final crystalline form after filtering and drying (XRPD)
Form A	Form C
Form B	Form C
Form A + Form B	Form C
Form A + Form C	Form C
Form B + Form C	Form C
Form A + Form B + Form C	Form C

Raman spectroscopy showed that during the preparation of crystalline form C of ibrutinib, crystalline form F of ibrutinib, which is described in the patent application WO2008/039218 as a methanol solvate, is first produced and its desolvation provides crystalline form C, see the Raman spectra in Figure 1.

The characteristic diffraction peaks of crystalline form A of ibrutinib free base with the use of CuKα radiation are: 5.7; 13.6; 16.1; 18.9; 21.3 and 21.6 ± 0.1° 2-theta. The melting point of crystalline form A of ibrutinib free base is 154°C according to DSC. An image of the morphology and size of the particles from the SEM is shown in Figure 2. A powder material with the primary particle size (max. Feret) of ≤ 15 μm without the presence of clusters at 80% crystallization yield was obtained by a reproduction of the procedure disclosed in the patent application (WO2013/184572). An example of the X-ray powder pattern is shown in Figure 3.

The characteristic diffraction peaks of crystalline form C of ibrutinib free base with the use of CuKα radiation are: 7.0; 14.0; 15.7; 18.2; 19.1; 19.5; 20.3; 22.1; 22.9 ± 0.1° 2-theta. The melting point of crystalline form C of ibrutinib free base is 134°C according to DSC. An image of the morphology and size of the primary particles from the SEM is shown in Figure 4. A powder material with the primary particle size (max. Feret) of ≤ 35 μm without the presence of clusters at 70% crystallization yield was obtained by a reproduction of the procedure disclosed in the patent application (WO2008/039218). An example of the X-ray powder pattern is shown in Figure 5.

Figure no. 6 shows an image of the morphology and size of the primary particles and a cluster of crystalline form C of ibrutinib from the SEM. The particles were prepared according to the procedure described in Example 4. Figure no. 7 shows an image of the morphology and size of the primary particles and a cluster of crystalline form C of ibrutinib from the SEM. The particles were prepared according to the procedure described in Example 5. Figure no. 8 shows an image of the morphology and size of the primary particles and a cluster of crystalline form C of ibrutinib from the SEM. The particles were prepared according to the procedure described in Example 6. Figure no. 9 shows an image of the morphology and size of the primary particles and a cluster of crystalline form C of ibrutinib from the SEM. The particles were prepared according to the procedure described in Example 7.

The prepared particles of crystalline ibrutinib of form C showed a different resistance during filtration depending on the size of the primary particles or clusters (see Tab. 2).

Table 2: Resistance of the prepared particles of crystalline ibrutinib of form C during filtration

morphology	primary particle size (max. Feret)	cluster size (max. Feret)	filtration time
I	≤ 35 μm	individual particles	169 s
II	≤ 5 μm	≤ 150 μm	24 s
III	≤ 30 μm	≤ 300 μm	82 s
IV	≤ 20 μm	≤ 100 μm	181 s
V	≤ 120 μm	≤ 600 μm	55 s

The invention is clarified in a more detailed way using the embodiment examples below. These examples, which illustrate the preparation of the novel solid forms of ibrutinib in accordance with the invention, only have an illustrative character and do not restrict the scope of the invention in any respect.

Experimental part

X-ray powder diffraction

The diffractograms were obtained using an X'PERT PRO MPD PANalytical powder diffractometer, used radiation CuKα (λ=1.542 Å), excitation voltage: 45 kV, anodic current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ at the dwell time at a reflection of 0.5 s, the measurement was carried out with a flat sample with the area/thickness of 10/0.5 mm. For the correction of the primary array 0.02 rad Soller slits, a 10mm mask and a 1/4° fixed anti-dispersion slit were used. The irradiated area of the sample is 10 mm, programmable divergence slits were used. For the correction of the secondary array 0.02 rad Soller slits and a 5.0 anti-dispersion slit were used.

Differential Scanning Calorimetry (DSC)

The melting points of the solid forms of ibrutinib were measured with the Discovery DSC device made by TA Instruments. The sample charge in a standard Al pot (40 μL) was in the range of 4-5 mg and the heating rate was 5°C/min. The temperature program that was used consists of 1 min of stabilization at the temperature of 0°C and then of heating up to 220°C at the heating rate of 5°C/min (Amplitude = 0.8°C and Period = 60 s). As the carrier gas 5.0 N2 was used at the flow of 50 ml/min.

Scanning Electron Microscope (SEM)

The electron microscope images were obtained using a MIRA II device, Tescan, Czech Republic, 2006. As the cathode, W fiber with the applied voltage of 7 kV was used with a YAG scintillation detector positioned in the optical axis under the pole piece of the objective (BSE). The measurement was carried out under high vacuum. The sample was applied onto a carbon tape and plated with Pt in a vacuum sprayer before the measurement.

Determining the dissolution rate using the true dissolution method

The dissolution rate was measured using an Agilent 708-DS dissolution device. Disks for true dissolution with the surface area available for dissolution of 0.125 cm^2 were prepared using a Specac press. The pressing time was 30 seconds under the pressure of 1 ton. The dissolution was carried out in 500 ml of a solution with pH 2 (10 mM HCl) at the constant speed of 100 rpm. Samples were extracted in 5-minute intervals and the concentration of dissolved ibrutinib was determined with an Agilent Cary 60 UV/Vis spectrophotometer at the wavelength of 274 nm.

Raman spectroscopy

The Raman spectra were measured using a Bruker RFS 100/S device. Wavelength of the laser radiation source 1064 nm. The measurements were carried with the accumulation of 64 scans with the resolution of 4 cm^{-1}.

Measurement of the resistance of prepared particles during filtration

The filtration rate was determined by measuring the flow time of the solvent through the prepared filter cake. The filter cake was prepared by weighing of the corresponding quantity of dried particles of crystalline ibrutinib after the preparation of the sample. The weighed particles were washed with 20 ml of water on frit of defined dimensions. The filter cake prepared this way was characterized by measurement of the height and the filtration resistance was determined by measurement of the flow time of 25 ml of water. All the samples were measured under identical conditions.

Examples

Example 1

Preparation of ibrutinib of form A.

The free base of ibrutinib (Form A) was prepared in accordance with the procedure mentioned in the patent (WO2008/039218). An image of the morphology and size of the particles from the SEM is shown in Figure 2. An example of the X-ray powder pattern is shown in Figure 3.

Example 2

Preparation of ibrutinib of form C (morphology I)

The free base of ibrutinib (Form C) was prepared in accordance with the procedure mentioned in the patent (WO2008/039218). An image of the morphology and size of the particles from the SEM is shown in Figure 4. An example of the X-ray powder pattern is shown in Figure 5.

Example 3

Preparation of ibrutinib of form F.

The free base of ibrutinib (Form F) was prepared in accordance with the procedure mentioned in the patent (WO2008/039218).

Example 4

Preparation of ibrutinib of form C (morphology II)

1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (4 g, 9.08 mmol) was put in a reactor and this charge was suspended in 61 ml of methanol. Being stirred (250 rpm), the obtained suspension was heated up to 60°C for 10 min. The solution obtained this way was then cooled down at a rate of 3°C/min to the temperature of 5°C and subsequently aftercooled at the rate of 0.3°C/min to -7°C. At the temperature of 0°C, the solution was inoculated with 5% of the crystalline form C of ibrutinib prepared in Example 1. The obtained suspension was filtered and the solid fraction was dried in a vacuum drier at the temperature of 40°C and pressure of 13 kPa. A solid crystalline product of ibrutinib (Form C) was obtained. An image of the prepared product from the SEM is shown in figure 6. This way, particles were prepared with generally spherical clusters with the size of ≤ 150 μm and the primary particle size of ≤ 5 μm. Crystallization yield 3.91 g (93%).

Example 5

Preparation of ibrutinib of form C (morphology III)

1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (4.1 g, 9.31 mmol) was put in a reactor, 50 ml of methanol being added. Being stirred (125 rpm), the obtained suspension was heated up to 60°C for 10 min. The solution obtained this way was then cooled down at a rate of 3°C/min to the temperature of 40°C and subsequently aftercooled at the rate of 1°C/min to -7°C. At the temperature of 35°C, the solution was inoculated with 5% of the crystalline form C of ibrutinib prepared in Example 1. The obtained suspension was filtered and the solid fraction was dried in a vacuum drier at the temperature of 40°C and pressure of 13 kPa. A solid crystalline product of ibrutinib (Form C) was obtained. An image of the prepared product from the SEM is shown in figure 7. This way, particles were prepared with generally spherical clusters with the size of ≤ 300 μm and the primary particle size of ≤ 30 μm. Crystallization yield 4.05 g (94%).

Example 6

Preparation of ibrutinib of form C (morphology IV)

1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (4 g, 9.08 mmol) was put in a reactor, 50 ml of methanol being added. Being stirred (65 rpm), the obtained suspension was heated up to 60°C for 10 min. The solution obtained this way was then cooled down at a rate of 1°C/min to the temperature of 40°C and subsequently aftercooled at the rate of 1°C/min to -7°C. At the temperature of 35°C, the solution was inoculated with 5% of the crystalline form C of ibrutinib prepared in Example 1. The obtained suspension was filtered and the solid fraction was dried in a vacuum drier at the temperature of 40°C and pressure of 13 kPa. A solid crystalline product of ibrutinib (Form C) was obtained. An image of the prepared product from the SEM is shown in figure 8. This way, particles were prepared with generally spherical clusters with the size of ≤ 100 μm and the primary particle size of ≤ 20 μm. Crystallization yield 3.95 g (94%).

Example 7

Preparation of ibrutinib of form C (morphology V)

1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (4 g, 9.08 mmol) was put in a reactor, 50 ml of methanol being added. Being stirred (250 rpm), the obtained suspension was heated up to 60°C for 10 min. The solution obtained this way was then cooled down at a rate of 0.333°C/min to the temperature of 0°C. At the temperature of 25°C, the solution was inoculated with 5% of the crystalline form C of ibrutinib prepared in Example 1. The obtained suspension was left to be stirred for 24 hours at 0°C and subsequently the suspension was filtered and the solid fraction was dried in a vacuum drier at the temperature of 40°C and pressure of 13 kPa. A solid crystalline product of ibrutinib (Form C) was obtained. An image of the prepared product from the SEM is shown in figure 9. This way, particles were prepared with generally spherical clusters with the size of $\leq$ 600 μm and the primary particle size of $\leq$ 120 μm. Crystallization yield 3.78 g (90%).

Claims

1. A method for preparing crystalline form C of ibrutinib free base, characterized in that it is prepared by crystallization from methanol.

2. The method for preparing crystalline form C of ibrutinib free base according to claim 1, characterized in that it is prepared from a suspension of ibrutinib, ibrutinib being dissolved at a concentration of 10 mg/ml to 260 mg/ml at 60°C.

3. The method for preparing crystalline form C of ibrutinib free base according to claim 2, characterized in that ibrutinib is dissolved at a concentration of 90 mg/ml to 260 mg/ml at 60°C.

4. The method for preparing crystalline form C of ibrutinib free base according to claims 1 or 3, characterized in that the solution is cooled down at a rate of 0.1°C/min to 3°C/min.

5. The method for preparing crystalline form C of ibrutinib free base according to claim 4, characterized in that the solution is cooled down at a rate of 0.1°C/min to 1°C/min.

6. The method for preparing crystalline form C of ibrutinib free base according to claims 1 or 2 or 3, characterized in that the solution is inoculated at a temperature from 45°C to 0°C.

7. The method for preparing form C of ibrutinib free base according to claims 1 or 2 or 3 or 6, characterized in that ibrutinib is obtained by crystallization of a solution produced by dissolution of ibrutinib in methanol at the concentration of 90 mg/ml at 60°C, the solution is cooled down at the rate of 0.3°C/min until 0°C is achieved, the solution is inoculated by addition of 2% of crystalline form C of ibrutinib free base at 25°C, the solid fraction is obtained by filtering and drying of the filter cake at 40°C and the pressure of 20 kPa; drying being applied until a constant product weight is achieved.

8. Crystalline form C of ibrutinib free base, consisting of clusters, the ratio of the primary particle size to the cluster size being at least 1:5 and the cluster size being at least 150 μm.

9. Crystalline form C of ibrutinib free base, obtainable according to claim 7.

10. Crystalline form C of ibrutinib free base, prepared according to claim 7, consisting of clusters, the ratio of the primary particle size to the cluster size being at least 1:5 and the cluster size being at least 150 μm.

Drawings

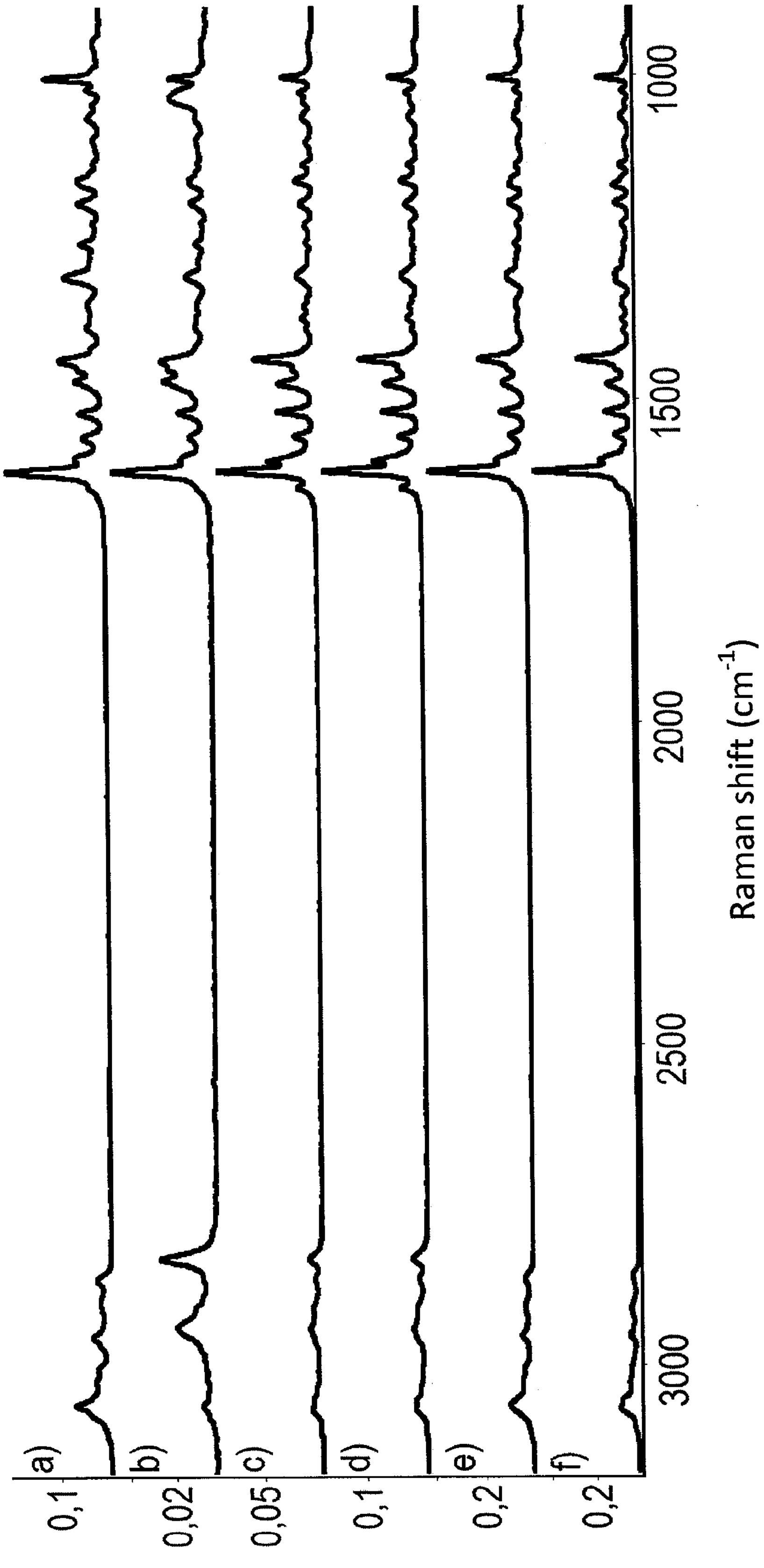

Figure 1.

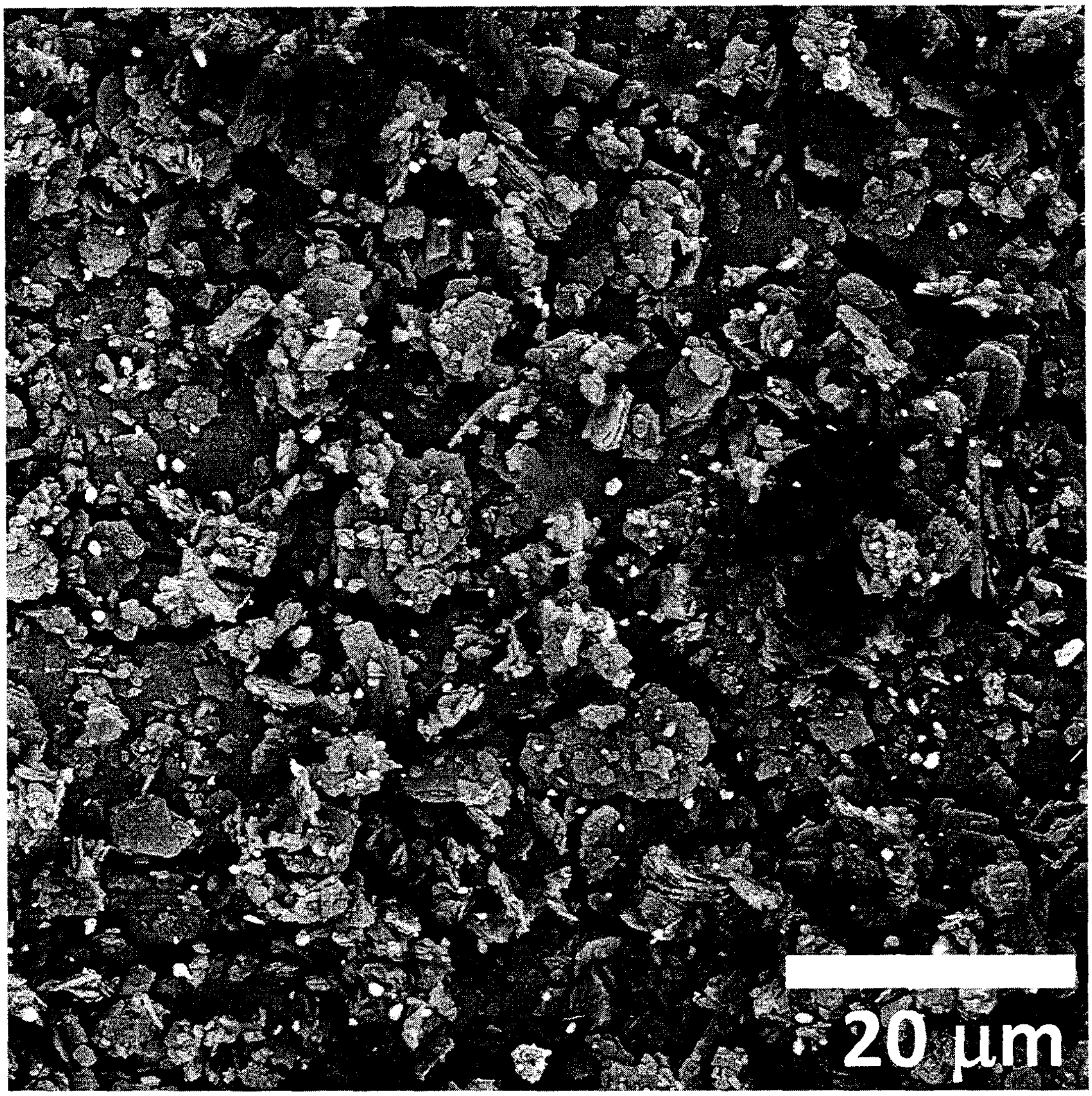

Figure 2.

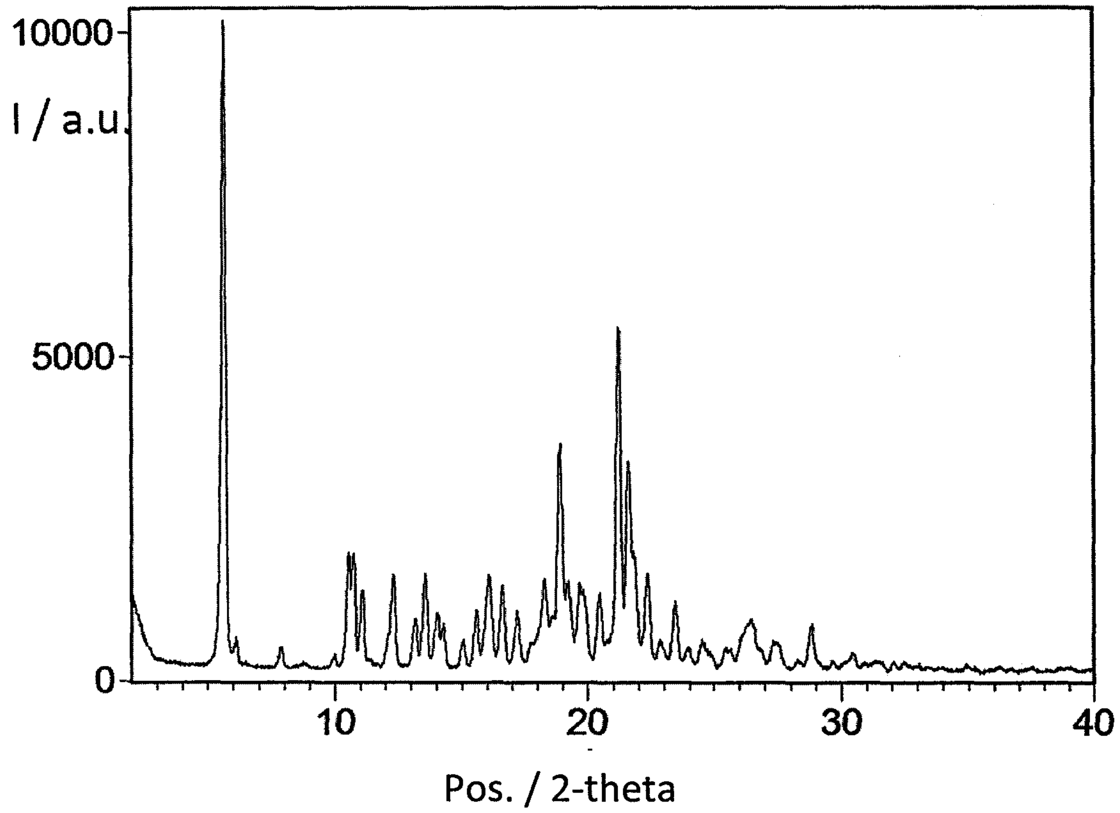

Figure 3.

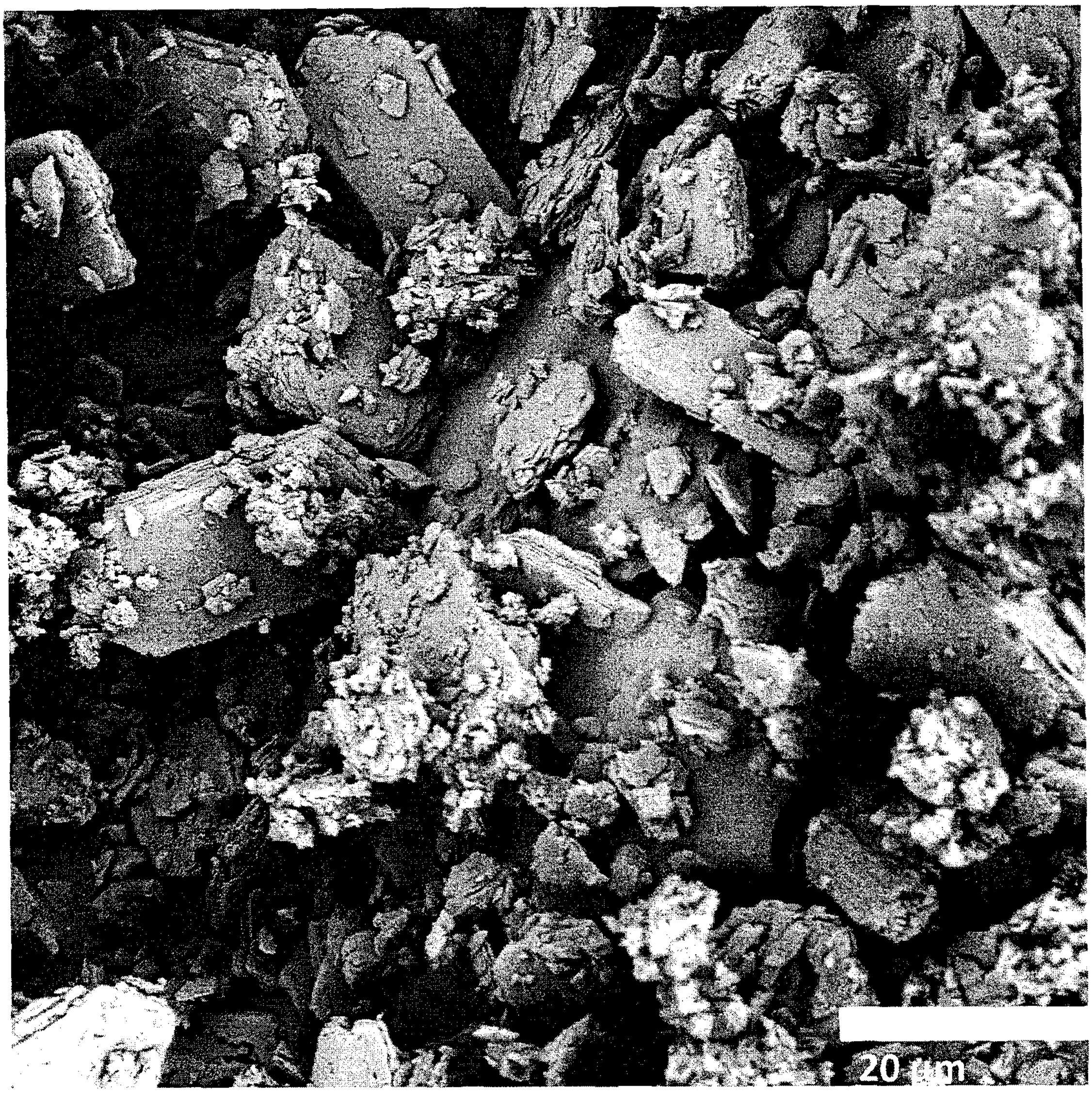

Figure 4.

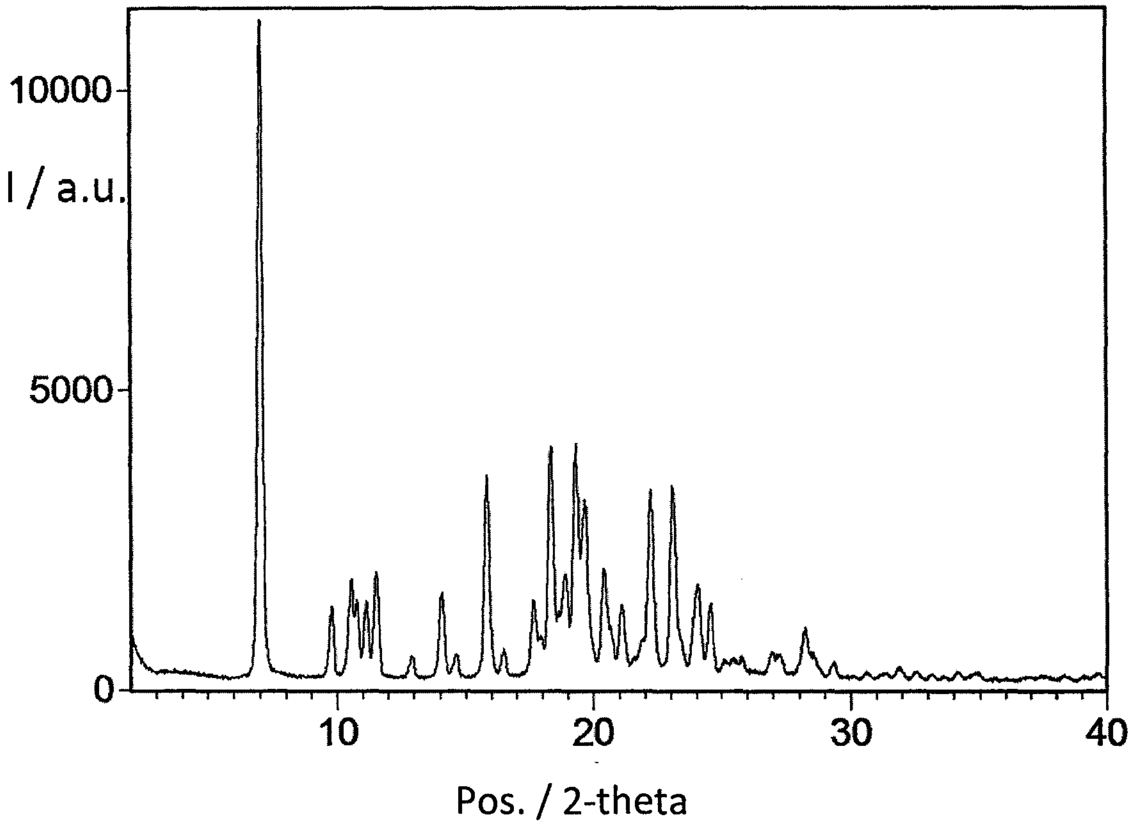

Figure 5.

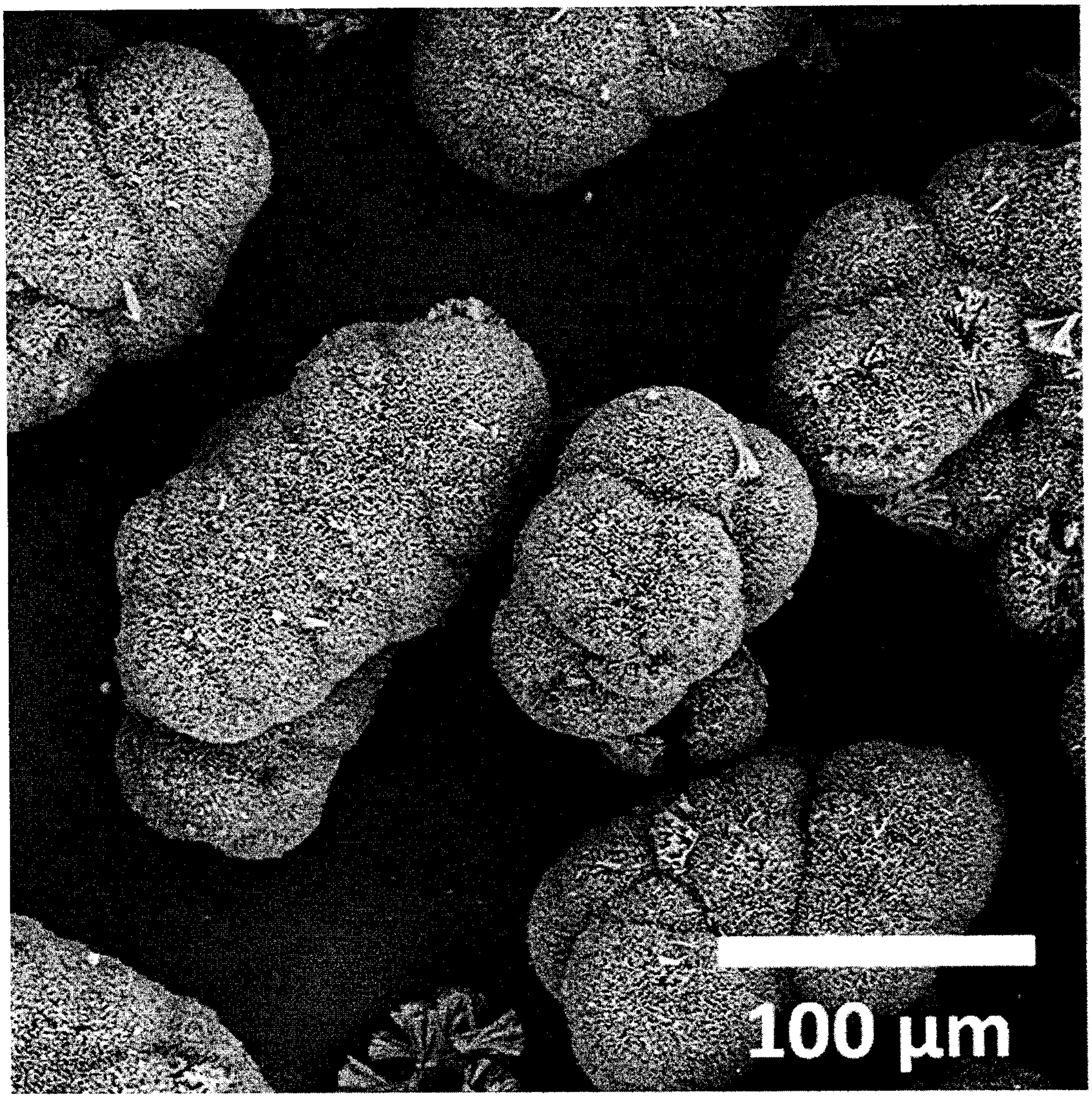

Figure 6.

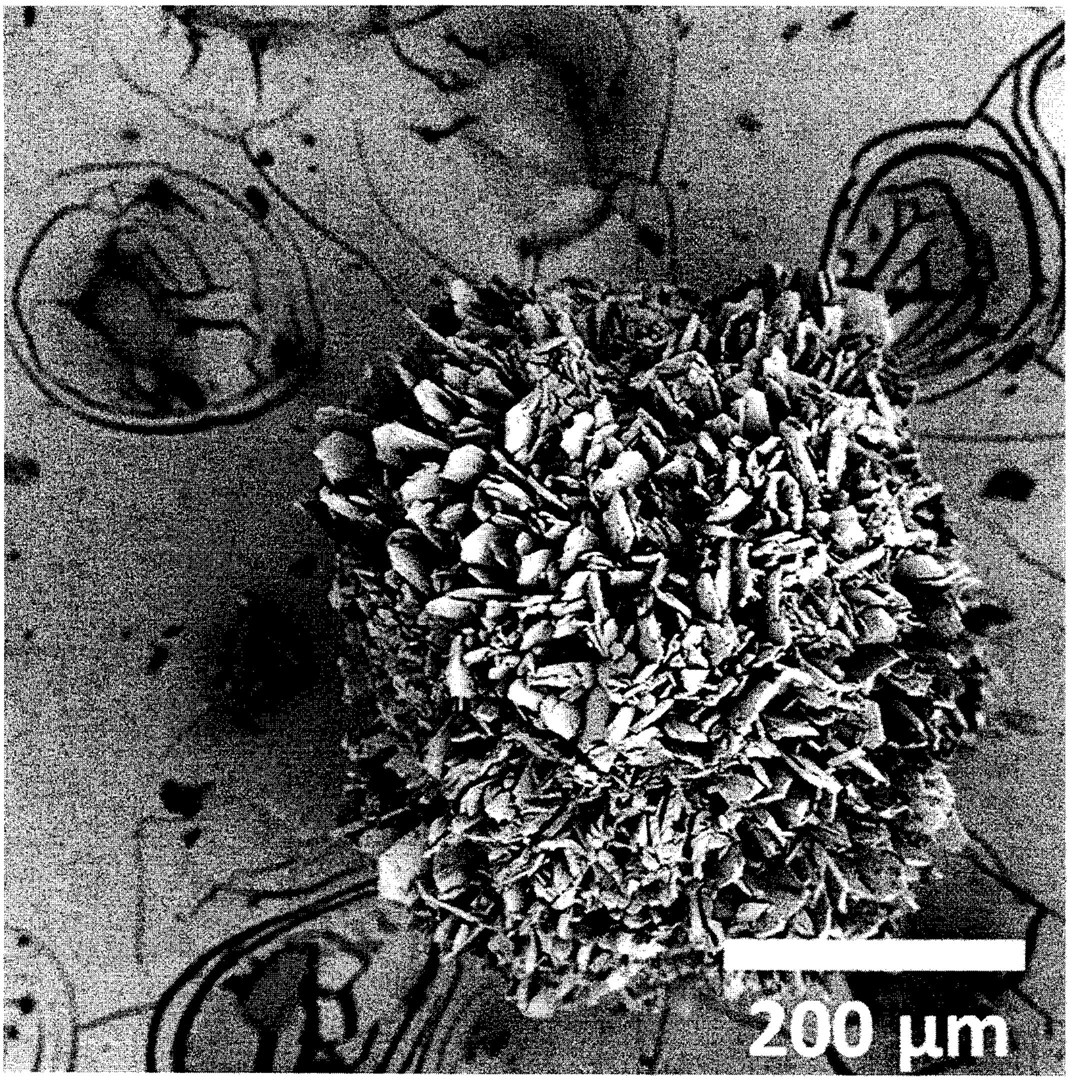

Figure 7.

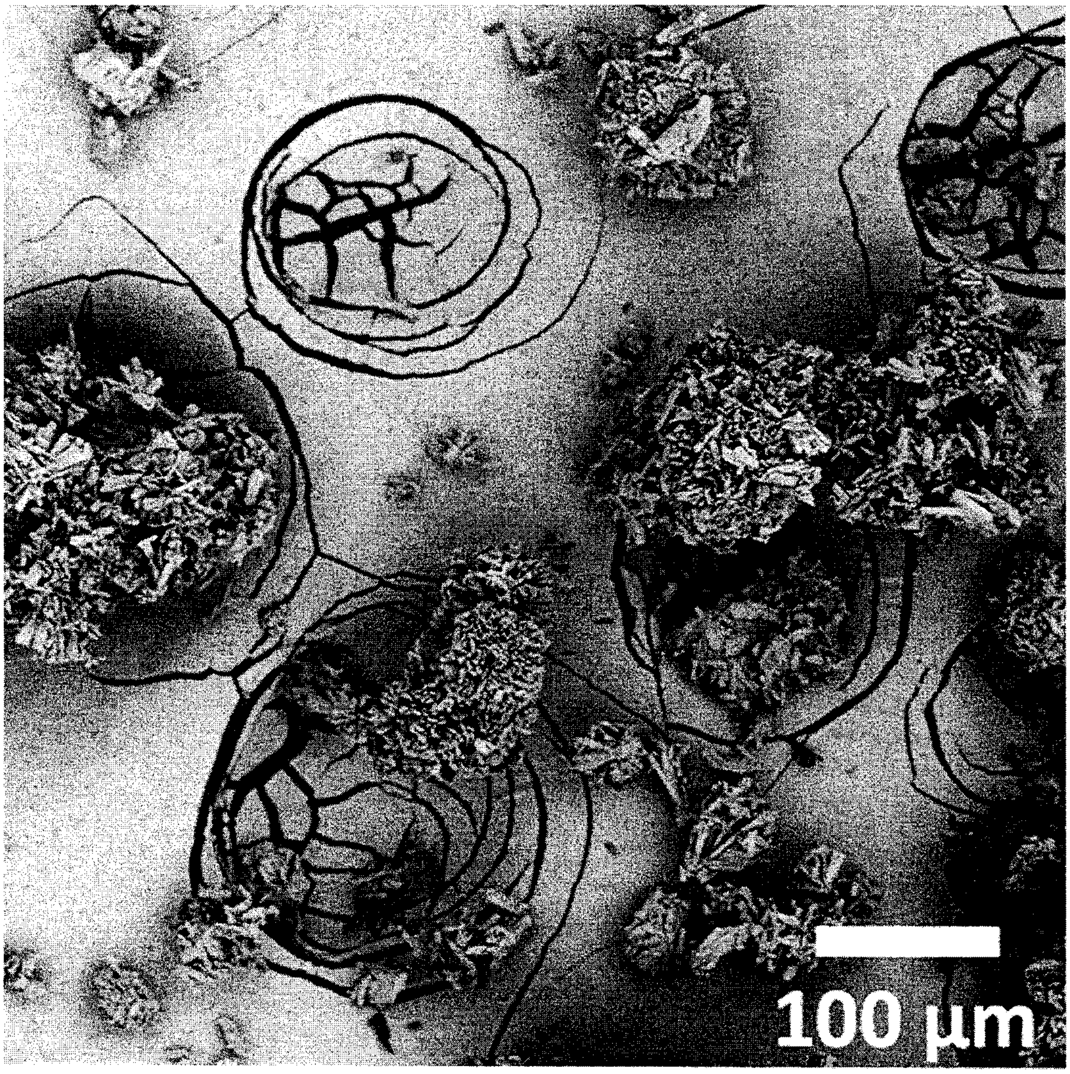

Figure 8.

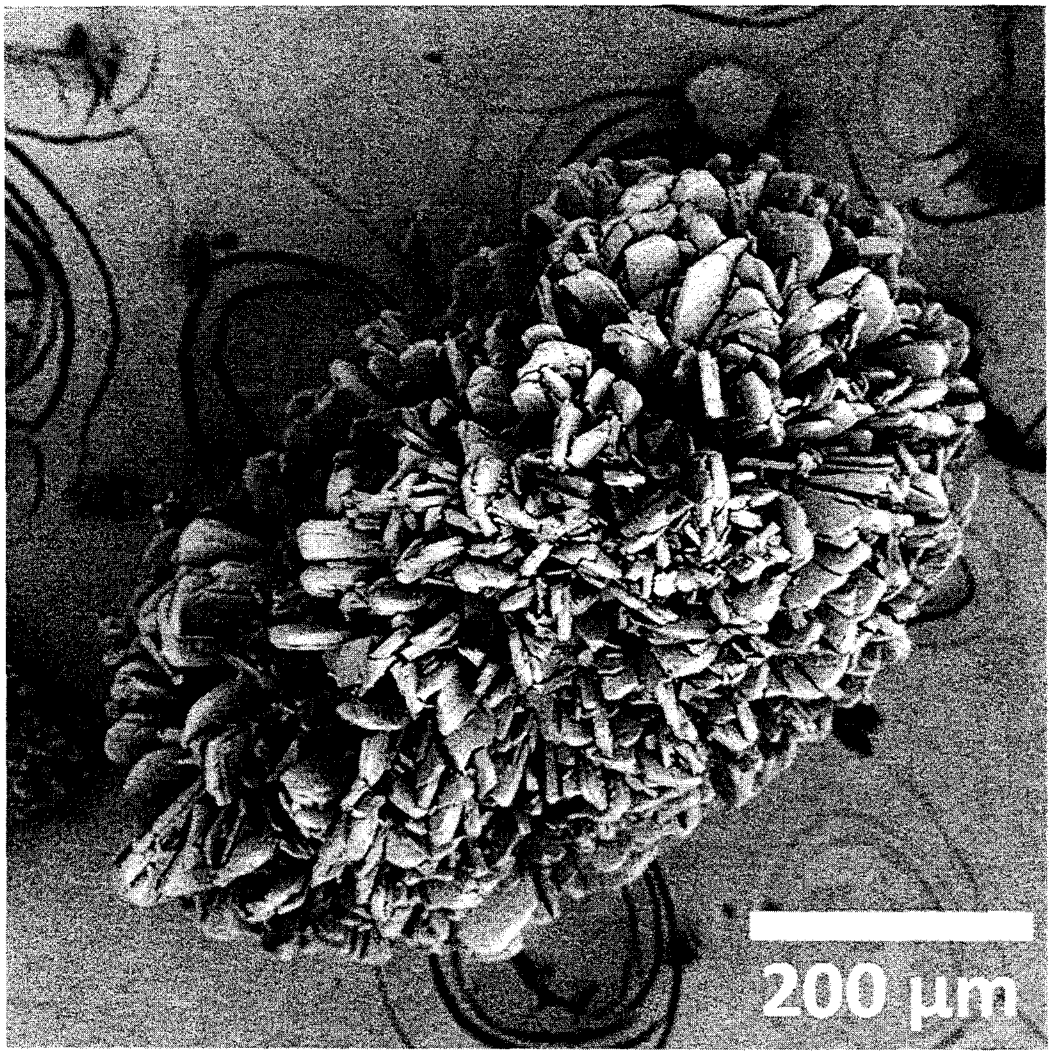

Figure 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2017/000019

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
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, CHEM ABS Data, WPI 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 2013/184572 A1 (PHARMACYCLICS INC [US]; PURRO NORBERT [US]) 12 December 2013 (2013-12-12) cited in the application paragraphs [00446], [00460] -----	1-10
A	WO 2008/039218 A2 (PHARMACYCLICS INC [US]; HONIGBERG LEE [US]; VERNER ERIK [US]; PAN ZHEN) 3 April 2008 (2008-04-03) cited in the application examples 1a, 1b -----	1-10
X,P	WO 2016/170545 A1 (MSN LABORATORIES PRIVATE LTD [IN]; THIRUMALAI RAJAN SRINIVASAN [IN]; E) 27 October 2016 (2016-10-27) examples 13, 24 -----	1-10

☐ 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 2 June 2017	Date of mailing of the international search report 12/06/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Schuemacher, Anne

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