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(54) Title: LENALIDOMIDE POLYMORPH

(57) Abstract: The present application relates to a crystalline polymorphic form of lenalidomide, processes for preparation thereof, and the use of the polymorphic form in the preparation of pharmaceutical compositions.



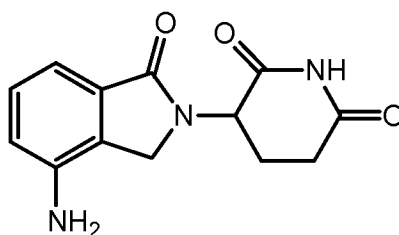
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LENALIDOMIDE POLYMORPH

INTRODUCTION

The present application relates to a crystalline polymorphic form of lenalidomide and processes for preparation thereof. The application also relates to uses of the polymorphic form in the preparation of pharmaceutical compositions.

The drug compound having the adopted name "lenalidomide" has a chemical name 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione, and is represented by structural formula I.



I

Lenalidomide, a thalidomide analogue, was initially intended for use as a treatment for multiple myeloma, for which thalidomide is an accepted therapeutic modality, but it has also shown efficacy in the hematological disorders known as the myelodysplastic syndromes (MDS). The exact mechanism of the immunomodulatory drugs (e.g. thalidomide, CC-4047/actimid, and lenalidomide) is not known. Apart from interfering with the immune system, they are also found to be active for angiogenesis. With myelodysplastic syndromes, the encouraging results of lenalidomide were also obtained in patients with deletion 5q cytogenetic abnormality (a chromosomal abnormality).

Lenalidomide is approved for treating patients with low or intermediate-1 risk MDS with 5q- with or without additional cytogenetic abnormalities.

The compound is the active ingredient in products sold by Celgene Corporation using the trademark REVLIMID, in the form of capsules containing 5 mg, 10 mg, 15 mg, and 25 mg of lenalidomide.

U.S. Patent No. 5,635,517 discloses substituted 1-oxo-2- (2, 6-dioxopiperidin-3-yl) isoindolines derivatives, pharmaceutical compositions containing these compounds and their use in the treatment of cancer.

International Application Publication No. WO 2005/023192, U.S. Patent No. 7,465,800 B2, and U.S. Patent Application Publication Nos. 2009/0062343 A1, 2009/0149499 A1, 2009/0149500 A1, 2009/0176832 A1, and 2009/0187023 A1 disclose crystalline lenalidomide hemihydrate, unsolvated crystalline lenalidomide, a solid form of lenalidomide comprising the unsolvated crystalline and amorphous lenalidomide, a crystalline lenalidomide dihydrate, a solid form of lenalidomide comprising dihydrate and amorphous lenalidomide, a solid form of lenalidomide comprising dihydrate and crystalline lenalidomide hemihydrate, a solid form of lenalidomide comprising crystalline lenalidomide hemihydrate and amorphous lenalidomide, a solid form of lenalidomide comprising crystalline Form F and amorphous lenalidomide and polymorphic forms designated as forms A, B, C, D, E, F, G, and H, pharmaceutical compositions comprising the various crystalline forms of lenalidomide, and mixtures of crystalline forms having greater than about 50% crystallinity. Further, processes for preparing the above said forms are also disclosed.

International Application Publication No. WO 2009/111948 A1 discloses lenalidomide strong acid salts such as salts with hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like, polymorphic forms of lenalidomide strong acid salts, and processes for the preparation thereof.

Despite the existence of various polymorphic forms of lenalidomide, there remains a need for new polymorphic forms, which are not only useful in the preparation of pharmaceutical compositions, but also have industrially feasible preparation processes.

SUMMARY

Aspects of the present invention relate to a polymorphic form of lenalidomide and processes for preparation thereof.

In one aspect, the present invention provides a crystalline polymorphic form of lenalidomide, which is designated herein as "Form I." Lenalidomide Form I may be characterized using one or more analytical methods.

In an embodiment, there is provided a crystalline polymorphic form of lenalidomide characterized by a powder X-ray diffraction (PXRD) pattern comprising one or more characteristic peaks located at 8.9, 25.9, and 27.5, ± 0.2 degrees 2-theta.

In an aspect, the present invention provides processes for the preparation of Form I of lenalidomide, embodiments comprising:

- a) providing a solution of lenalidomide in an organic solvent and
- b) precipitating a solid from the solution of step a) by combining with an anti-solvent.

In an aspect, there are provided processes for the preparation of crystalline Form I of lenalidomide, embodiments comprising:

- a) providing a solution of lenalidomide in a N,N-dimethylacetamide (DMAc) solvent; and
- b) precipitating a solid from the solution of step a) by combining with an anti-solvent.

In another aspect, the present invention provides pharmaceutical formulations comprising Form I of lenalidomide and at least one pharmaceutically acceptable excipient.

The crystalline Form I of lenalidomide produced according to the processes of the present invention is sufficiently stable to be useful for preparing pharmaceutical formulations.

The crystalline Form I of lenalidomide is useful for making pharmaceutical dosage forms for the treatment of diseases, including, but not limited to, multiple myeloma.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an illustrative example of a powder X-ray diffraction (PXRD) pattern of lenalidomide Form I, prepared according to Example 1.

Fig. 2 is an illustrative example of an infrared (IR) absorption spectrum of lenalidomide Form I, prepared according to Example 1.

Fig. 3 is an illustrative example of a differential scanning calorimetry (DSC) curve of lenalidomide Form I, prepared according to Example 1.

Figs. 4A and 4B are illustrative examples of optical microscope photographs of lenalidomide Form I, prepared according to Example 1.

DETAILED DESCRIPTION

As set forth herein, the present invention relates to crystalline polymorphic Form I of lenalidomide, and processes for preparation thereof.

A polymorphic form may be described by reference to patterns, spectra, or other graphical data as "substantially" shown or depicted in a figure, or by one or more data points. It will be appreciated that patterns, spectra, and other graphical data can have features that are shifted in their positions, relative intensities, or other values due to a number of factors known to those of skill in the art. For example, in the crystallographic and powder X-ray diffraction arts, shifts in peak positions or the relative intensities of one or more peaks of a pattern can occur because of, without limitation, the equipment used, the sample preparation protocol, preferred packing and orientations, the radiation source, operator error, method and length of data collection, and the like. However, those of ordinary skill in the art will be able to compare the figures herein with patterns, etc., that are generated for an unknown form of, in this case, lenalidomide, and confirm its identity with Form I disclosed herein. The same holds true for other techniques that may be reported herein.

In addition, where a reference is made to a drawing, it is permissible to, and this document includes and contemplates, the selection of any number of data points illustrated in the drawing that uniquely define a crystalline form, within any associated and recited margins of error, for purposes of identification.

All percentages and ratios used herein are by weight of the total composition and all measurements made are at about 25°C and about normal pressure, unless otherwise designated. All temperatures are in degrees Celsius unless specified otherwise. As used herein, "comprising" includes the elements recited, or their equivalent in structure or function, plus any other element or elements which are not recited. The terms "having" and "including" are also to be construed as open ended. As used herein, "consisting essentially of" means that the invention may include ingredients in addition to those recited in the claim, but only if the additional ingredients do not materially alter the basic and novel

characteristics of the claimed invention. All ranges recited herein include the endpoints, including those that recite a range “between” two values. Whether so indicated or not, all values recited herein are approximate as defined by the circumstances, including the degree of expected experimental error, technique error, and instrument error for a given technique used to measure a value.

The term “anti-solvent” refers to a liquid that, when combined with a solution of lenalidomide, reduces solubility of the lenalidomide in the solution, causing crystallization or precipitation in some instances spontaneously, and in other instances with additional steps, such as seeding, cooling, scratching, and/or concentrating.

In an embodiment, there is provided crystalline Form I of lenalidomide. Form I of lenalidomide may be characterized by any one or more analytical results, including powder X-ray diffraction (“PXRD”) patterns, differential scanning calorimetry (“DSC”) curves, and infrared (“IR”) absorption spectra.

PXRD data reported herein are obtained using copper K α radiation, and are generated using a Bruker AXS D8 Advance Powder X-ray Diffractometer.

DSC curves are obtained using a DSC Q1000 model instrument with a starting temperature of 40°C and with a 10°C/minute heating rate.

IR absorption spectra are obtained with the sample dispersed in potassium bromide and compressed into a pellet.

Crystalline Form I of lenalidomide of the present invention may be characterized by a PXRD pattern having peaks located substantially in accordance with Fig. 1.

Crystalline Form I of lenalidomide also may be characterized by a PXRD pattern comprising one or more characteristic peaks located at about 8.9, 25.9 and 27.5 ± 0.2 degrees 2-theta.

Peak locations in a particular example of a PXRD pattern of crystalline Form I of lenalidomide and their intensities are detailed in Table 1. The 2-theta angle locations of peaks listed below may have a deviation of about $\pm 0.2^\circ$.

Table 1

2-Theta (Degrees)	Intensity (%)
8.9	100
9.8	2

14.8	11
15.9	59
16.5	24
16.7	19
17.4	20
18	26
19.1	6
19.7	31
20	53
22.6	28
22.8	26
23.5	6
24.6	2
25.9	16
27.5	64
29.3	4
29.7	6
30.1	2
31.8	7
33.7	6
34.9	6
35.6	14
36	3
38.3	7
41.1	5

Lenalidomide Form I of the present invention may be characterized by a differential scanning calorimetry curve, having a peak in the range of about 267°C to about 271°C, or about $269 \pm 1^\circ\text{C}$, or by a DSC curve having a peak substantially at the location shown in Fig. 3.

Lenalidomide Form I of the present invention may be characterized by an infrared (IR) spectrum, comprising one or more characteristic peaks located at

about 1679, 1739, 2907, 3232, 3432, and 3584, $\pm 2 \text{ cm}^{-1}$, or by an IR absorption spectrum substantially in accordance with Fig. 2.

In an aspect, the present invention provides processes for the preparation of Form I of lenalidomide, embodiments comprising:

- a) providing a solution of lenalidomide in a organic solvent; and
- b) precipitating a solid from the solution of step a) by combining with an anti-solvent.

The individual steps are separately described hereinbelow.

Step a) involves providing a solution of lenalidomide in a organic solvent.

The organic solvent used in step a) may be N,N-dimethylacetamide (DMAc).

The solution of lenalidomide may be obtained by the dissolution of lenalidomide in the organic solvent, or it may be obtained from a previous processing step where lenalidomide is synthesized in solution. Any form of lenalidomide is acceptable for forming a solution, such as a crystalline or amorphous form, or mixtures thereof.

The solution may be prepared at any temperatures, such as from about 20°C to about 160°C, or at temperatures up to the boiling point of the solvent.

Optionally, the obtained solution may be cooled to lower temperatures, such as below about 20°C, or in the range of about 5°C to about 20°C.

The solution may be optionally treated with a clarifying agent, such as activated charcoal or sodium sulphate, and then filtered to remove the clarifying agent.

The solution may optionally be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent, such as CELITE. Depending upon the equipment used, as well as the concentration and temperature of the solution, the filtration apparatus may need to be heated or cooled to avoid undesired crystallization.

Step b) includes precipitating the solid from the solution of step a) by combining with an anti-solvent.

Precipitation of crystalline Form I from the solution of step a) may be carried out by adding an anti-solvent to a solution of lenalidomide, or *vice versa*.

Anti-solvents that may be used for the precipitation of crystalline Form I include: water; alcohols, including methanol, ethanol, isopropanol, and the like; nitriles including acetonitrile, propionitrile, and the like; esters, including ethyl acetate, n-propyl acetate, n-butyl acetate, and the like; ketones, including acetone, ethyl methyl ketone, methyl isobutyl ketone, and the like; halogenated hydrocarbons, including toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; and any mixtures thereof.

In a particular embodiment, the lenalidomide solution obtained in step a) is added to an anti-solvent. The precipitation may be obtained at any temperatures, such as below about 35°C, or in the range from about 5°C to about 20°C.

The obtained suspension may be stirred for about 15 minutes to about 2 hours, or longer, to enhance the extent of crystallization. Useful temperatures for maintaining a suspension may range from about 5°C to about 35°C.

The Form I of lenalidomide may be isolated from the suspension using general techniques known to persons skilled in the art for separating solids from liquids. For example, the Form I of lenalidomide may be isolated by using techniques such as, for example, filtration by gravity or by suction, centrifugation, decantation, and the like.

After isolation, the solid may optionally be washed with a suitable solvent such as: water; an alcohol like methanol; a ketone like acetone; a nitrile like acetonitrile; a halogenated hydrocarbon like dichloromethane; any mixtures thereof; etc.

Optionally, the obtained crystalline Form I of lenalidomide may be dried. The drying of solid material may be carried out under suitable conditions to afford the desired crystalline form of lenalidomide, substantially free of residual solvents. Drying may be carried out at reduced pressures, such as more than about 500 mm Hg, at temperatures such as about 35°C to about 70°C, or higher.

The drying may also be carried out in a controlled humidity environment having a relative humidity ("RH"), such as below about 75% RH or between about 30% and about 75% RH, at temperatures such as about 30-50°C. Exposure to an environment containing relative humidity can help to reduce the residual solvent content. The product obtained from a humidity drying may be further dried, using suitable techniques. The drying may be performed for any desired time periods

that achieve the desired purity, such as times about 1 to about 20 hours, or longer. Drying may also be carried out for shorter or longer periods of time, depending on the product specifications.

Drying may be suitably carried out in equipment such as a rotary dryer, tray dryer, vacuum oven, air oven, humidity dryer, fluidized bed dryer, spin flash dryer, flash dryer, or combinations thereof.

In an aspect, there are provided processes for the preparation of crystalline Form I of lenalidomide, embodiments comprising:

- a) providing a solution of lenalidomide in a N,N-dimethylacetamide (DMAc) solvent; and
- b) precipitating a solid from the solution of step a) by combining with an anti-solvent.

Precipitated solid can be isolated, using techniques previously described.

Form I of lenalidomide obtained by a process of the present invention may have a moisture content in the range of about 0.1% to about 4%, or in the range of about 1.5% to about 2.5%, as determined using a Karl Fisher technique.

Form I of lenalidomide of the present invention has particle morphology, shown in Figs. 4A and 4B, that can be used to distinguish it from other polymorphic forms of lenalidomide.

Crystalline Form I of lenalidomide of the present invention has a consistently obtained morphology. Such morphology and its consistency are unique and result in excellent powder properties such as flowability, bulk density and uniform particle size. This provides a significant advantage for preparing pharmaceutical formulations, in terms of active ingredient handling, formulation process development, and drug content uniformity of the finished formulations.

Form I of lenalidomide may be used as a starting material for conversion into other polymorphic forms, including an amorphous form as well as other crystalline polymorphs.

In a further embodiment, the present application provides pharmaceutical formulations comprising Form I of lenalidomide and at least one pharmaceutically acceptable excipient.

Certain specific aspects and embodiments of the present invention will be explained in more detail with reference to the following examples, which are

provided for purposes of illustration only and should not be construed as limiting the scope of the invention in any manner.

REFERENCE EXAMPLE A: Preparation of lenalidomide dimethylformamide solvate.

A methanesulfonic acid salt of lenalidomide (2 g), a mixture of N,N-dimethylformamide (DMF) and methanol (1:2 by volume, 18 mL), and triethylamine (0.8 mL) are charged into a round bottom flask and stirred for 2 hours at 25-35°C. The suspension is filtered and washed with the dimethylformamide and methanol mixture (4 mL). The solid is dried at 50°C for 4 hours, to afford 1.25 g of the title compound.

Purity: 99.96% by HPLC.

REFERENCE EXAMPLE B: Preparation of lenalidomide dimethylformamide solvate.

Lenalidomide (0.5 g) is mixed with dimethylformamide (10 mL) at room temperature and stirred for 10-15 minutes to dissolve. Toluene (80 mL) is added to the solution and stirred for 25 minutes. The formed solid is filtered and dried under vacuum at 25 to 35°C for 1 hour, to afford 0.42 g of the title compound.

EXAMPLE 1: Preparation of lenalidomide Form I.

Lenalidomide dimethylformamide solvate prepared by the method of a reference example (10 g) is dissolved in N,N-dimethylacetamide (44 mL) at room temperature. Sodium sulphate (2.5 g) is added and the mixture is stirred for 5 minutes. The mixture is filtered, the filtrate is cooled to 10-15°C, and the filtrate is added to 250 mL of water having a temperature in the range of about 10-15°C. The solid is filtered, washed with chilled water (50 mL), and then suction dried on the filter for 15 minutes. The obtained solid is dried at 40°C under vacuum for 3 hours.

Yield: 8 g of Form I of lenalidomide (approximately 80%).

The PXRD pattern, IR spectrum, and DSC curve are substantially in accordance with Figs. 1, 2, and 3, respectively.

Moisture content: 1.60% by Karl Fisher.

Purity: 99.9% by high performance liquid chromatography (HPLC).

EXAMPLE 2: Preparation of lenalidomide Form I.

Lenalidomide crystalline Form B (1 g) is dissolved in N,N-dimethylacetamide (4 mL) with stirring for 5 minutes at room temperature. The solution is filtered and the filtrate is cooled to 10-15°C. The filtrate is added to 50 ml of water having a temperature in the range of about 10-15°C. The solid is filtered, washed with chilled water (20 mL), and suction dried on the filter for 15 minutes. The solid is dried at 40°C under vacuum for 1 to 2 hours.

Yield: 0.5 g of Form I of lenalidomide (approximately 50%).

EXAMPLE 3: Preparation of lenalidomide Form I.

Lenalidomide (20 g) is dissolved in N,N-dimethylacetamide (120 mL) at room temperature. Sodium sulphate (5 g) is added and the mixture is stirred for 5 minutes. The mixture is filtered, the filtrate is cooled to 20°C, and the filtrate is added to 250 ml of water having a temperature in the range of about 5-10°C. The solid is filtered, washed with chilled water (100 mL), and then suction dried on the filter for 15 minutes. The solid is dried at 40°C under vacuum for 5 hours.

Yield: 16 g of Form I of lenalidomide (approximately 80%).

PXRD pattern is substantially in accordance with Fig. 1.

Moisture content: 2.35% by Karl Fisher.

CLAIMS:

1. Crystalline lenalidomide, having a powder X-ray diffraction pattern comprising one or more of peaks located at 8.9, 25.9, and 27.5 ± 0.2 degrees 2-theta.
2. Crystalline lenalidomide, having a powder X-ray diffraction pattern substantially in accordance with the pattern of Fig. 1.
3. Crystalline lenalidomide, having a differential scanning calorimetry curve substantially in accordance with the curve of Fig. 2.
4. Crystalline lenalidomide, having an infrared absorption spectrum substantially in accordance with the spectrum of Fig. 3.
5. Crystalline lenalidomide, having crystal morphology substantially as shown in either of Figs. 4A and 4B.
6. A process for preparing crystalline lenalidomide of any of claims 1-5, comprising:
 - a) providing a solution of lenalidomide in an organic solvent; and
 - b) precipitating a solid from the solution of step a) by combining with an anti-solvent.
7. The process according to claim 6, wherein an organic solvent is N,N-dimethylacetamide.
8. The process according to claim 6, wherein a solution of lenalidomide is prepared at temperatures about 25°C to about 160°C.
9. The process according to claim 6, wherein an anti-solvent is water, an alcohol, a nitrile, an ester, a ketone, a halogenated hydrocarbon, or any mixtures thereof.
10. The process according to claims 6, wherein an anti-solvent is water.

11. A process for preparing crystalline lenalidomide of any of claims 1-5, comprising:

- a) providing a solution of lenalidomide in a N,N-dimethylacetamide solvent;
- b) combining the solution with an anti-solvent; and
- c) isolating the crystalline lenalidomide.

12. The process according to claim 11, wherein an anti-solvent is water, an alcohol, a nitrile, an ester, a ketone, a halogenated hydrocarbon, or any mixtures thereof.

13. The process according to claim 11, wherein an anti-solvent is water.

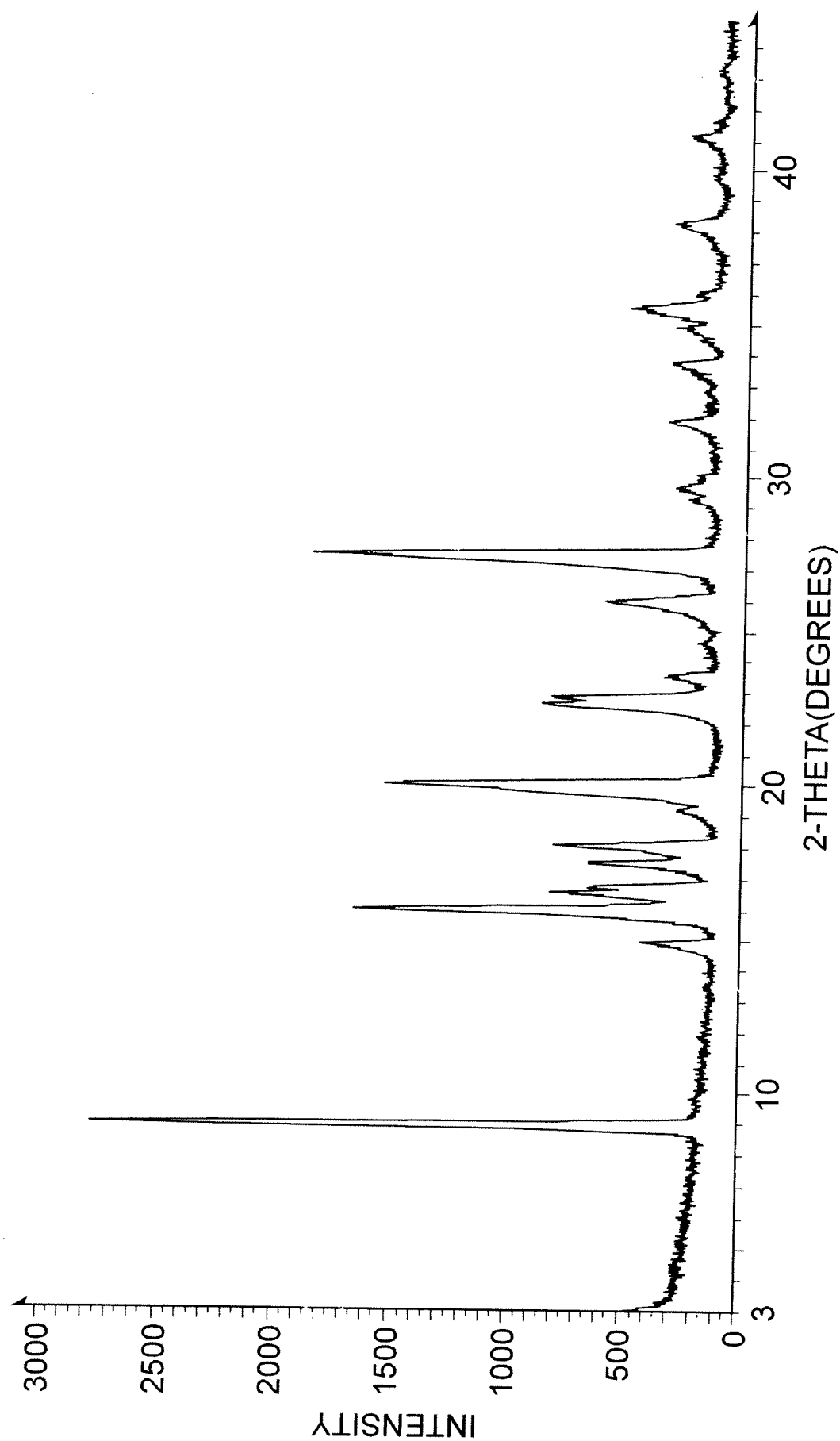


FIG. 1

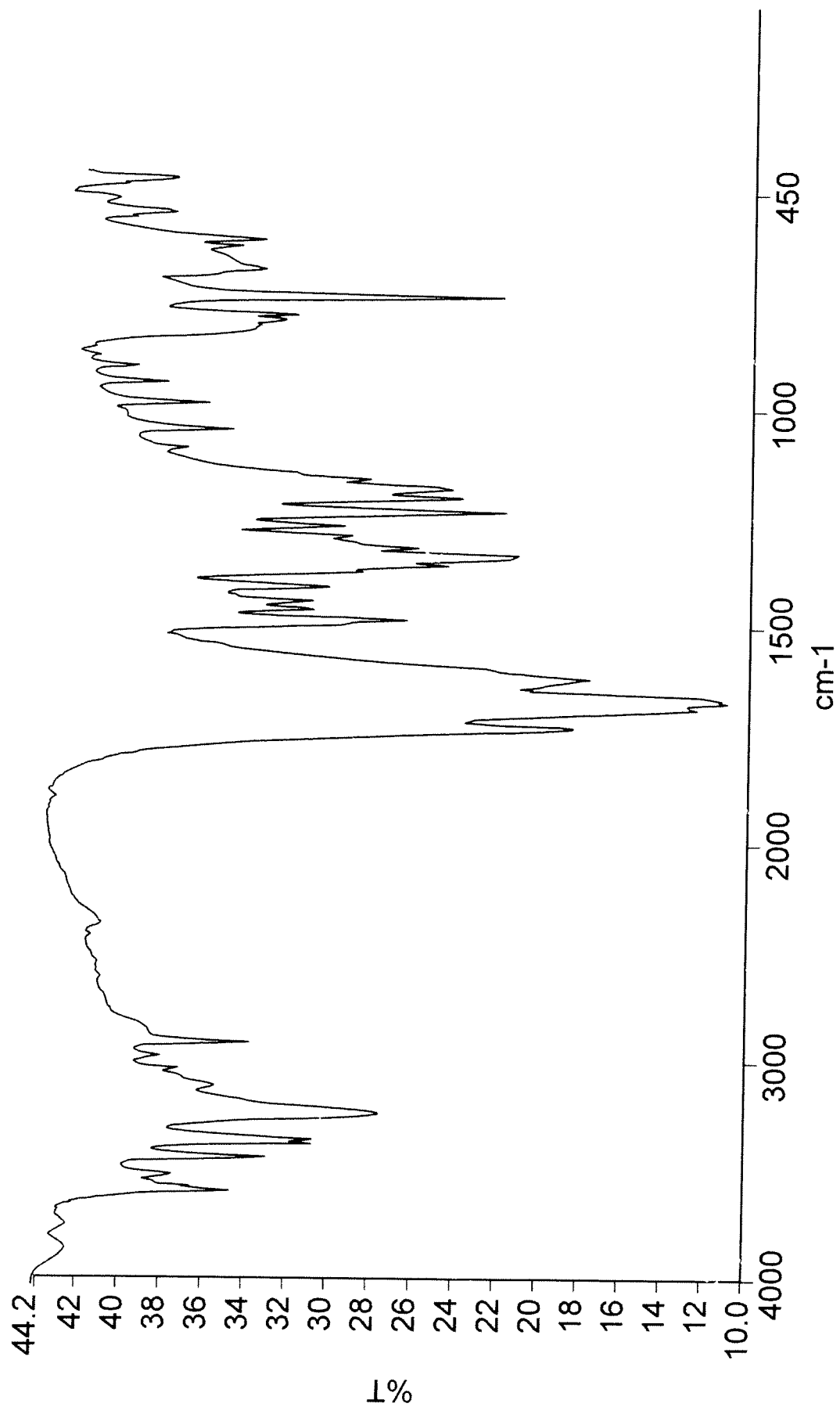


FIG. 2

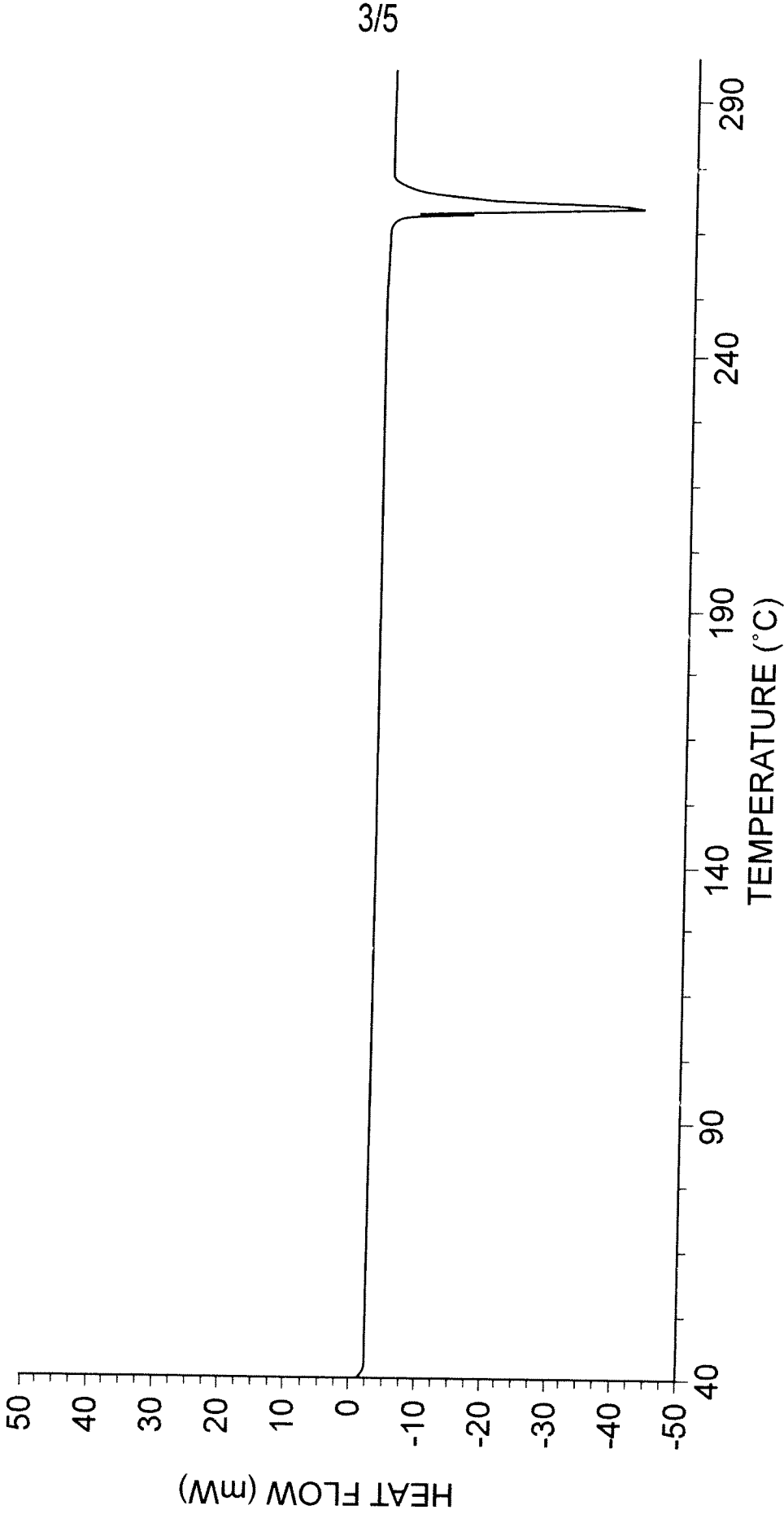


FIG. 3

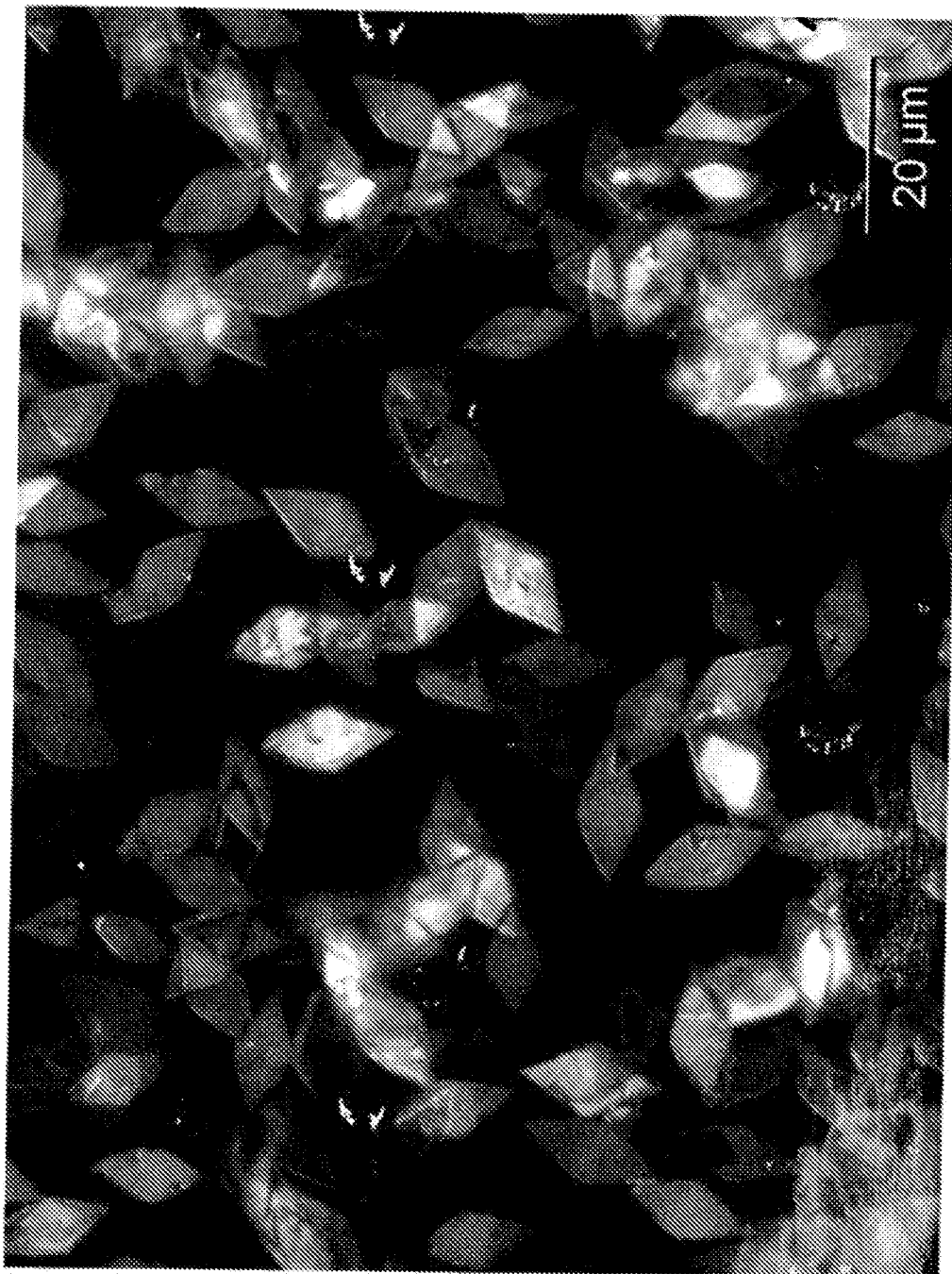


FIG. 4A

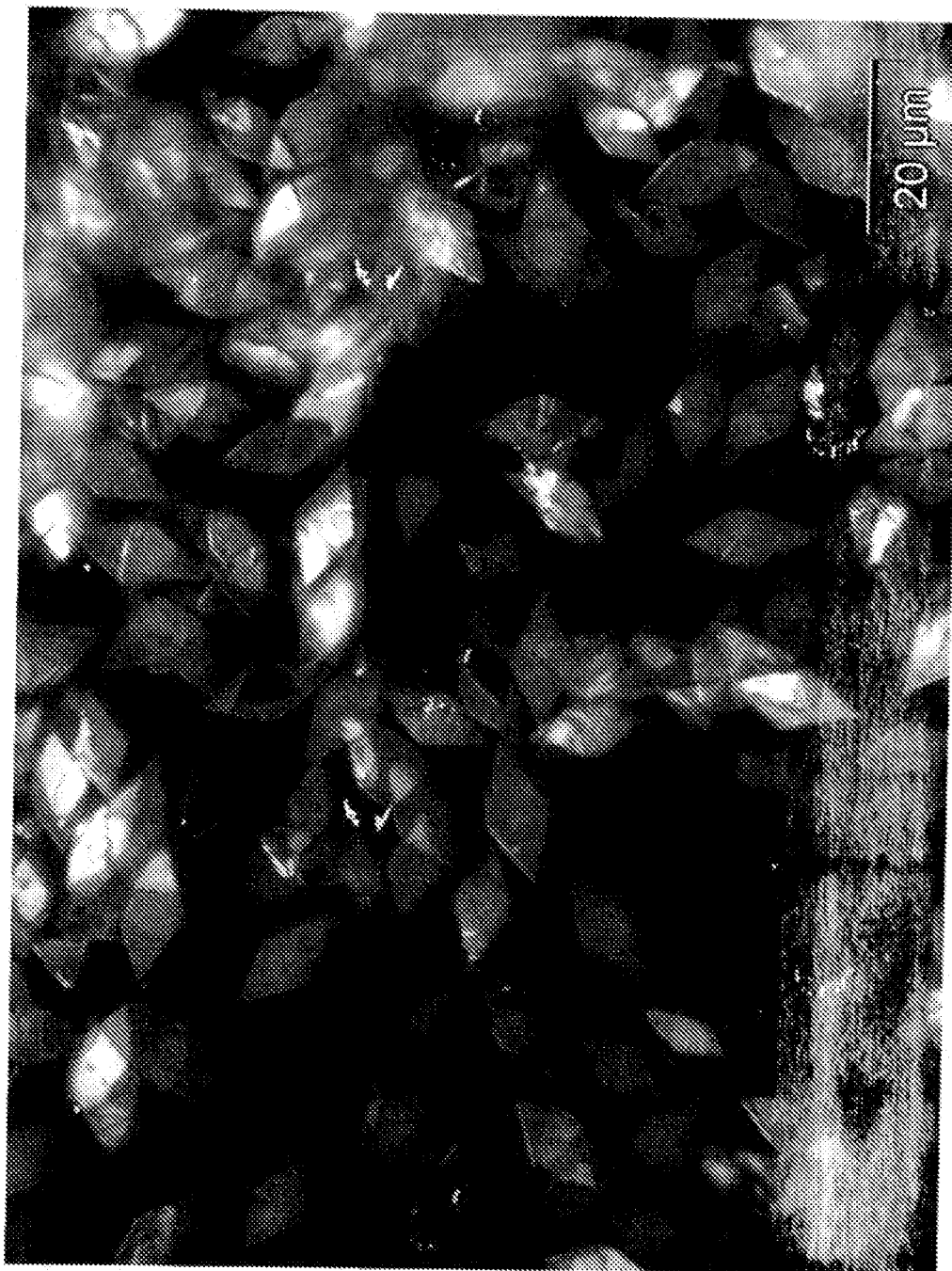


FIG. 4B