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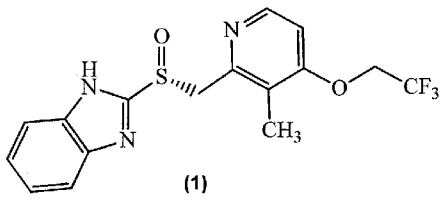
(54) Title: DEXLANSOPRAZOLE POLYMORPHIC FORMS



(1)

(57) Abstract: The application relates to polymorphic forms of dexlansoprazole that are useful in making pharmaceutically acceptable dosage forms, and processes for their preparation. The structure of dexlansoprazole (1) is shown below..

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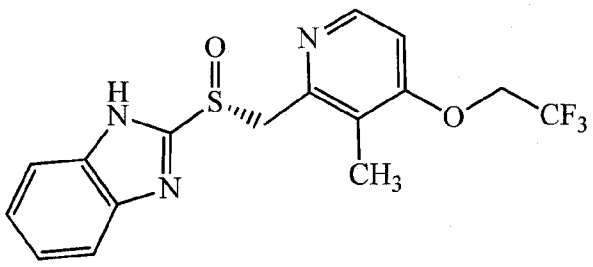
DEXLANSOPRAZOLE POLYMORPHIC FORMS

INTRODUCTION

Aspects of the present application relate to polymorphic forms of dexlansoprazole which are useful in making pharmaceutically acceptable dosage forms, and processes for their preparation.

The drug compound having the adopted name "dexlansoprazole" has a chemical name (+)-2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole, and can be represented by the structure of Formula I.



I

Dexlansoprazole is a proton pump inhibitor (PPI) indicated for: (a) healing of all grades of erosive esophagitis (EE); (b) maintaining healing of EE; and (c) treating heartburn associated with EE; and is contained in products sold as Dexilant™.

U.S. Patent No. 6,462,058 discloses crystalline (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (dexlansoprazole), characterized by an X-ray powder diffraction pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41, and 3.11 Angstroms. The patent also discloses crystalline dexlansoprazole 1.5-hydrate, characterized by an X-ray powder diffraction pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 4.49, 3.50, and 3.00 Angstroms.

International Application Publication No. WO 2009/088857 A1 discloses a hydrate dexlansoprazole crystal, a methanol solvate crystal, an ethanol solvate crystal, an ethanol hydrate crystal, and an isopropanol hydrate crystal, and processes for preparation thereof. International Application Publication No. WO 2009/113696 A1 discloses a crystalline dexlansoprazole, wherein the powder X-ray diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 10.06, 8.70, 6.57, 5.59, and 4.00 Angstrom.

The occurrence of different polymorphs is possible for some compounds. A single compound may give rise to a variety of solids having distinct physical properties, such as X-ray diffraction patterns, infrared absorption spectra, and NMR spectra. This variation in solid forms may be significant and may result in differences with respect to bioavailability, stability,

and other differences for formulated pharmaceutical products. Because polymorphic forms can vary in their physical properties, regulatory authorities require that efforts shall be made to identify all polymorphic forms, *e.g.*, crystalline, amorphous, solvated, *etc.*, of new drug substances.

The existence and possible numbers of polymorphic forms for a given compound cannot be predicted, and there are no "standard" procedures that can be used to prepare polymorphic forms of a substance. However, new forms of a pharmaceutically useful compound may provide an opportunity to improve the performance characteristics of pharmaceutical products. Further, discovery of additional polymorphic forms, including solvate polymorphs, may help in the identification of the polymorphic content of a batch of an active pharmaceutical ingredient. For example, in some cases, different forms of the same drug can exhibit very different solubility and different dissolution rates. The discovery of new polymorphic forms enlarges selection of materials with which formulation scientists can design a pharmaceutically acceptable dosage form of a drug with a targeted release profile or other desired characteristics. Therefore, there remains a need for preparing new and stable polymorphic forms of dexlansoprazole.

SUMMARY OF THE INVENTION

In an aspect, the present application provides a process for the preparation of crystalline Form A of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising propylene glycol; and

b) isolating the crystalline Form A of dexlansoprazole.

In an aspect, the application provides crystalline Form B of dexlansoprazole having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.7, 7.6, 17.1, 18.1, 20.2, and 22.4 ± 0.2 degrees 2-theta.

In an aspect, the present invention provides crystalline Form B of dexlansoprazole, characterized by a powder X-ray diffraction pattern having peak locations substantially as listed in Table 2.

In an aspect, the present invention provides crystalline Form B of dexlansoprazole characterized by a powder X-ray diffraction (PXRD) pattern with peaks located substantially as illustrated by Fig. 3.

In an aspect, the present application provides a process for the preparation of crystalline Form B of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising isobutyl alcohol; and

b) isolating the crystalline Form B of dexlansoprazole.

In an aspect, the application provides crystalline Form C of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.1, 8.8, 10.2, 11.7, 13.5, 15.5, 15.9, 18.4, 20.3, 22.3, 22.8, and 24.0 ± 0.2 degrees 2-theta.

In an aspect, the present application provides crystalline Form C of dexlansoprazole, characterized by a powder X-ray diffraction pattern having peak locations substantially as listed in Table 3.

In an aspect, the present application provides crystalline Form C of dexlansoprazole characterized by any one or more of: a powder X-ray diffraction (PXRD) pattern substantially as illustrated by Fig. 4; a differential scanning calorimetry (DSC) curve substantially as illustrated by Fig. 5; and a thermogravimetric analysis (TGA) curve substantially as illustrated by Fig. 6.

In an aspect, the present application provides a process for the preparation of crystalline Form C of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising isobutyl alcohol;

b) forming a solid; and

c) drying the solid to afford crystalline Form C of dexlansoprazole.

In an aspect, the application provides crystalline Form D of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.3, 6.1, 7.3, 10.0, 14.2, 16.0, 19.8, 21.7, 22.0, 22.8, and 25.0 ± 0.2 degrees 2-theta.

In an aspect, the present application provides crystalline Form D of dexlansoprazole, characterized by a powder X-ray diffraction pattern having peak locations substantially as listed in Table 4.

In an aspect, the present application provides crystalline Form D of dexlansoprazole, characterized by a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 7.

In an aspect, the present application provides a process for the preparation of crystalline Form D of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in isopropyl acetate; and

b) combining the solution with anti-solvent.

In an aspect, the application provides crystalline Form E of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at

about 8.5, 14.1, 14.9, 16.9, 17.4, 19.8, 20.6, 22.1, 23.2, 26.3, and 30.0 ± 0.2 degrees 2-theta.

In an aspect, the present application provides crystalline Form E of dexlansoprazole, with a powder X-ray diffraction pattern having peak locations substantially as listed in Table 5.

In an aspect, the present application provides crystalline Form E of dexlansoprazole, with a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 8.

In an aspect, the present application provides a process for the preparation of crystalline Form E of dexlansoprazole, comprising grinding dexlansoprazole in the presence of an organic solvent comprising dimethylsulfoxide.

In an aspect, the present application provides pharmaceutical formulations comprising crystalline polymorphic forms of dexlansoprazole, together with one or more pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is an illustration of a powder X-ray diffraction (PXRD) pattern of crystalline Form A of dexlansoprazole, prepared according to Example 2.

Fig. 2 is an illustration of a differential scanning calorimetry (DSC) curve of crystalline Form A of dexlansoprazole, prepared according to Example 2.

Fig. 3 is an illustration of a PXRD pattern of crystalline Form B of dexlansoprazole, prepared according to Example 3.

Fig. 4 is an illustration of a PXRD pattern of crystalline Form C of dexlansoprazole, prepared according to Example 4(B).

Fig. 5 is an illustration of a DSC curve of crystalline Form C of dexlansoprazole, prepared according to Example 4(B).

Fig. 6 is an illustration of a thermogravimetric analysis (TGA) curve of crystalline Form C of dexlansoprazole, prepared according to Example 4(B).

Fig. 7 is an illustration of a PXRD pattern of crystalline Form D of dexlansoprazole, prepared according to Example 5.

Fig. 8 is an illustration of a PXRD pattern of crystalline Form E of dexlansoprazole, prepared according to Example 6.

DETAILED DESCRIPTION

In an aspect, the application provides crystalline Form A of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.6, 7.6, 11.3, 17.0, and 22.6 ± 0.2 degrees 2-theta.

In an aspect, the application provides crystalline Form A of dexlansoprazole, characterized by a powder X-ray diffraction (PXRD) pattern having peaks located substantially as listed in Table 1.

Table 1

2θ (degrees) ± 0.2
5.6
7.6
9.8
11.3
13.3
13.5
14.6
15.3
17.0
18.3
18.9
19.7
20.3
21.3
22.6
23.0
23.6
25.4
25.9
26.6
27.7
28.5

In an aspect, the application provides crystalline Form A of dexlansoprazole characterized by a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 1.

In an aspect, the application provides crystalline Form A of dexlansoprazole characterized by a differential scanning calorimetry (DSC) thermogram substantially as illustrated by Fig 2.

In an aspect, the application provides crystalline Form A of dexlansoprazole characterized by either or both of: a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 1; and a differential scanning calorimetry (DSC) thermogram substantially as illustrated by Fig 2.

In an aspect, the present application provides a process for the preparation of crystalline Form A of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising propylene glycol; and

b) isolating the crystalline Form A of dexlansoprazole.

Step a) involves providing a solution of dexlansoprazole in a solvent comprising propylene glycol. Providing a solution includes:

i) direct use of a reaction mixture containing dexlansoprazole that is obtained in the course of its synthesis that comprises propylene glycol, or by adding propylene glycol to a reaction mixture; or

ii) dissolving dexlansoprazole in a solvent comprising propylene glycol, including mixtures of propylene glycol with other solvents.

Any physical forms of dexlansoprazole, such as crystalline, amorphous, or their mixtures may be utilized for providing the solution of dexlansoprazole in step a). Suitable solvents other than propylene glycol that may be used in step a) include, but are not limited to, ether solvents or mixtures thereof. The dissolution temperatures may range from about -20°C to about reflux temperature, or less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperatures depending on the solvent used for dissolution, as long as a clear solution of dexlansoprazole is obtained without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow), or any other suitable material to remove color and/or insoluble materials, and/or to improve clarity of the solution.

Optionally, the solution obtained above may be clarified using a suitable technique such as filtration, centrifugation, decantation, or any other suitable techniques, under pressure or under reduced pressure. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as Celite® or Hyflow. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step b) involves isolating crystalline Form A of dexlansoprazole. Isolation of crystalline Form A of dexlansoprazole in step b) may involve methods including removal of solvent, cooling, concentrating the mass, adding seed crystals to induce crystallization, adding an anti-solvent, extraction with a solvent, and the like. Stirring or other alternate methods such as shaking, agitation and the like may also be employed for the said isolation. Suitable temperatures for isolation may be less than about 60°C, less than about 40°C, less

than about 20°C, less than about 10°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures. The crystalline Form A of dexlansoprazole may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other techniques for the recovery of solids. The crystalline Form A of dexlansoprazole as isolated may carry some amount of occluded mother liquor and may have higher than desired levels of impurities. If desired, the crystals may be washed with a solvent or a mixture of solvents to wash out the impurities.

Optionally, the recovered solid may be dried. Drying may be carried out in a tray dryer, vacuum oven, air oven, fluidized bed dryer, cone vacuum dryer, rotary vacuum dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out at temperatures less than about 100°C, less than about 80°C, less than about 60°C, less than about 50°C, less than about 30°C, or any other suitable temperatures, at atmospheric pressure or under a reduced pressure, as long as the dexlansoprazole is not degraded in its quality.

In an aspect, the application provides crystalline Form B of dexlansoprazole having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.7, 7.6, 17.1, 18.1, 20.2, and 22.4 ± 0.2 degrees 2-theta.

In an aspect, the application provides crystalline Form B of dexlansoprazole, characterized by a powder X-ray diffraction (PXRD) pattern having peak locations substantially as listed in Table 2.

Table 2

2θ (degrees) ± 0.2
5.7
6.6
7.6
9.8
11.4
13.0
13.3
14.5
15.1
17.1
18.1
18.8
19.2
20.2
21.0
22.1
22.4
22.8
23.5
23.8
25.1

2θ (degrees) ± 0.2
25.4
26.2
27.6
28.2
28.6
30.4
31.1
32.4
33.6
39.3

In an aspect, the application provides crystalline Form B of dexlansoprazole characterized by a powder X-ray diffraction (PXRD) pattern with characteristic peaks located substantially as illustrated by Fig. 3.

In an aspect, the present application provides a process for the preparation of crystalline Form B of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising isobutyl alcohol; and

b) isolating the crystalline Form B of dexlansoprazole.

Providing a solution in step a) includes:

i) direct use of a reaction mixture containing dexlansoprazole that is obtained in the course of its synthesis that comprises isobutyl alcohol, or by adding isobutyl alcohol to a reaction mixture; or

ii) dissolving dexlansoprazole in a solvent comprising isobutyl alcohol, including mixtures of isobutyl alcohol with other solvents.

Any physical forms of dexlansoprazole, such as crystalline, amorphous or their mixtures may be utilized for providing the solution of dexlansoprazole in step a). The dissolution temperatures may range from about -20°C to about the reflux temperature, or less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperatures, depending on the solvent used for dissolution, as long as a clear solution of dexlansoprazole is obtained without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow) or any other suitable material to remove color, and/or insoluble materials, and/or to improve clarity of the solution.

Optionally, the solution obtained above may be filtered to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques under pressure or under reduced pressure.

The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as Celite® or Hyflow. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step b) involves isolating crystalline Form B of dexlansoprazole from the solution obtained in step a). Isolation of crystalline Form B of dexlansoprazole in step b) may involve methods including removal of solvent, cooling, concentrating the mass, adding an anti-solvent, extraction with a solvent, adding seed crystals to induce crystallization, and the like. Stirring or other alternate methods such as shaking, agitation, and the like, may also be employed for the isolation. Suitable temperatures for isolation may be less than about 60°C, less than about 40°C, less than about 20°C, less than about 10°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures.

Alternatively, isolation may be effected by combining a suitable anti-solvent with the solution obtained in step a). Anti-solvent as used herein refers to a liquid in which dexlansoprazole is less soluble or poorly soluble. Suitable anti-solvents that may be used include, but are not limited to: aliphatic or alicyclic hydrocarbon solvent; substituted hydrocarbon solvent such as nitromethane; aromatic hydrocarbon solvent; or any mixtures thereof. The crystalline Form B of dexlansoprazole may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other technique for the recovery of solids under pressure or under reduced pressure. The crystalline polymorphic forms of dexlansoprazole as isolated may carry some amount of occluded mother liquor and may have higher than desired levels of impurities. If desired, these crystals may be washed with a solvent or a mixture of solvents to wash out the impurities.

The recovered solid may optionally be dried. Drying may be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out at temperatures less than about 100°C, less than about 80°C, less than about 60°C, less than about 50°C, less than about 30°C, or any other suitable temperatures, at atmospheric pressure or under a reduced pressure, as long as the dexlansoprazole is not degraded in quality. The drying may be carried out for any desired times until the required product quality is achieved. The dried product may optionally be subjected to a size reduction procedure to produce desired particle sizes. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation, ball, roller and hammer milling, and jet milling.

In an aspect, the application provides crystalline Form C of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.1, 8.8, 10.2, 11.7, 13.5, 15.5, 15.9, 18.4, 20.3, 22.3, 22.8, and 24.0 ± 0.2 degrees 2-theta.

In an aspect, the application provides crystalline Form C of dexlansoprazole, characterized by a powder X-ray diffraction (PXRD) pattern having peak locations substantially as listed in Table 3.

Table 3

2θ (degrees) ± 0.2
5.1
8.8
9.2
10.2
11.0
11.7
13.5
15.5
15.9
16.7
17.6
17.8
18.4
18.9
19.2
19.9
20.3
20.9
21.3
21.6
22.3
22.8
23.4
24.0
24.2
24.8
25.5
26.0
26.6
27.8
28.8
29.8
30.6
30.7
36.0

In an aspect, the application provides crystalline Form C of dexlansoprazole prepared according to a process described in the present application is characterized by a powder X-ray diffraction (PXRD) pattern having peak locations substantially as illustrated by Fig. 4.

In an aspect, the application provides crystalline Form C of dexlansoprazole characterized by a powder X-ray diffraction (PXRD) pattern substantially as illustrated by Fig. 4.

In an aspect, the application provides crystalline Form C of dexlansoprazole characterized by a differential scanning calorimetry (DSC) curve substantially as illustrated by Fig. 5.

In an aspect, the application provides crystalline Form C of dexlansoprazole characterized by a thermogravimetric analysis (TGA) curve substantially as illustrated by Fig. 6.

In an aspect, the application provides crystalline Form C of dexlansoprazole characterized by any one or more of: a powder X-ray diffraction (PXRD) pattern substantially as illustrated by Fig. 4; a differential scanning calorimetry (DSC) curve substantially as illustrated by Fig. 5; and a thermogravimetric analysis (TGA) curve substantially as illustrated by Fig. 6.

In an aspect, the present application provides a process for the preparation of crystalline Form C of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising isobutyl alcohol;

b) forming a solid; and

c) drying the solid to afford crystalline Form C of dexlansoprazole.

Providing a solution in step a) includes:

i) direct use of a reaction mixture containing dexlansoprazole that is obtained in the course of its synthesis that comprises isobutyl alcohol, or by adding isobutyl alcohol to a reaction mixture; or

ii) dissolving dexlansoprazole in a solvent comprising isobutyl alcohol, including mixtures of isobutyl alcohol with other solvents.

Any physical form of dexlansoprazole, such as crystalline, amorphous or their mixtures may be utilized for providing the solution of dexlansoprazole in step a). The dissolution temperatures may range from about -20°C to about the reflux temperature, or less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperatures depending on the solvent used for dissolution, as long as a clear solution of dexlansoprazole is obtained

without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow) or any other suitable material to remove color and/or to improve clarity of the solution. Optionally, the solution obtained above may be clarified to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques, under pressure or under reduced pressure. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as Celite™ or Hyflow. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step b) involves isolating a solid. Isolation of a solid from the solution obtained in step a) may involve methods including removal of solvent, cooling, concentrating the mass, adding seed crystals to induce crystallization, adding an anti-solvent, extraction with a solvent, and the like. Stirring or other alternate methods such as shaking, agitation and the like may also be employed for the said isolation. Suitable temperatures for isolation may be less than about 60°C, less than about 40°C, less than about 20°C, less than about 10°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures. Alternatively, isolation may be effected by adding a suitable anti-solvent to the solution obtained in step a). Anti-solvent as used herein refers to a liquid, in which dexlansoprazole is less soluble or poorly soluble. Suitable anti-solvents that may be used include, but are not limited to: aliphatic or alicyclic hydrocarbon solvent; substituted hydrocarbon solvent such as nitromethane; aromatic hydrocarbon solvent; or mixtures thereof. The formed solid dexlansoprazole may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other technique for the recovery of solids. The formed solid of dexlansoprazole as isolated may carry some amount of occluded mother liquor and may have higher than desired levels of impurities. If desired, these crystals may be washed with a solvent or a mixture of solvents to wash out the impurities.

Step c) involves drying the solid to afford crystalline Form C of dexlansoprazole. The recovered solid in step b) may be subjected to drying. Drying may be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, cone-dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out at temperatures less than about 100°C, less than about 80°C, less than about 60°C, less than about 50°C, less than about 30°C, or any other suitable temperatures, at atmospheric pressure or under a reduced pressure, as long as the dexlansoprazole is not degraded in quality. The drying may be carried out for any desired times until the desired quality is

achieved. The dried product may optionally be subjected to size reduction, to get desired particle sizes. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation, ball, roller and hammer milling, and jet milling.

In embodiments, crystalline Form C of dexlansoprazole prepared according to a process described in the present application is substantially free of residual solvents. "Substantially free of residual solvents" as used herein refers to dexlansoprazole having residual solvent content meeting the ICH (International Conference on Harmonization) limits.

In an aspect, the application provides crystalline Form D of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.3, 6.1, 7.3, 10.0, 14.2, 16.0, 19.8, 21.7, 22.0, 22.8, and 25.0 ± 0.2 degrees 2-theta.

In an aspect, the application provides crystalline Form D of dexlansoprazole, characterized by a powder X-ray diffraction (PXRD) pattern having peak locations substantially as listed in Table 4.

Table 4

2θ (degrees) ± 0.2
4.9
5.3
6.1
7.3
8.7
10.0
10.6
11.4
13.4
14.2
15.0
15.5
16.0
17.5
17.8
19.8
20.4
20.9
21.7
22.0
22.4
22.8
23.4
24.4
25.0
25.3
26.2
26.7

2θ (degrees) ± 0.2
27.5
28.3
28.8
29.3
30.6
34.3
36.2

In an aspect, the application provides crystalline Form D of dexlansoprazole, characterized by a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 7.

In an aspect, the present application provides a process for the preparation of crystalline Form D of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in isopropyl acetate; and

b) combining the solution with anti-solvent.

Step (a) involves providing a solution of dexlansoprazole in isopropyl acetate.

Providing a solution in step a) includes:

i) direct use of a reaction mixture containing dexlansoprazole that is obtained in the course of its synthesis that comprises isopropyl acetate, or by adding isopropyl acetate to a reaction mixture; or

ii) dissolving dexlansoprazole in a solvent comprising isopropyl acetate.

Any physical form of dexlansoprazole, such as crystalline, amorphous or their mixtures may be utilized for providing the solution of dexlansoprazole in step a). The dissolution temperatures may range from about -20°C to about the reflux temperature, or less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperature depending on the solvent used for dissolution, as long as a clear solution of dexlansoprazole is obtained without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow) or any other suitable material to remove color and/or to improve clarity of the solution. Optionally, the solution obtained above may be clarified to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques, under pressure or under reduced pressure. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as Celite® or Hyflow. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step (b) involves combining the obtained solution of step (a) with anti-solvent. Combining the obtained solution of step (a) with anti-solvent may be effected by methods including adding a solution of dexlansoprazole in isopropyl acetate to the anti-solvent, or adding an anti-solvent to a solution of dexlansoprazole in isopropyl acetate. Anti-solvent as used herein refers to a liquid in which dexlansoprazole is less soluble or poorly soluble. Suitable anti-solvents that may be used include, but are not limited to: water; aliphatic or alicyclic hydrocarbon solvent; substituted hydrocarbon solvent such as nitromethane; aromatic hydrocarbon solvent; or any mixtures thereof. In embodiments, an anti-solvent used in step (b) may be previously cooled to 10 to -50°C, before combining with a solution of dexlansoprazole in isopropyl acetate. Suitable temperatures used in step (b) may be less than about 60°C, less than about 40°C, less than about 20°C, less than about 10°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures.

The crystalline Form D of dexlansoprazole may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other technique for the recovery of solids. The formed solid of dexlansoprazole as isolated may carry some amount of occluded mother liquor and may have higher than desired levels of impurities. If desired, these crystals may be washed with a solvent or a mixture of solvents to wash out the impurities. The recovered crystalline compound may optionally be dried. Drying may be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out at temperatures less than about 100°C, less than about 80°C, less than about 60°C, less than about 50°C, less than about 30°C, or any other suitable temperatures, at atmospheric pressure or under a reduced pressure, as long as the dexlansoprazole is not degraded in quality. The drying may be carried out for any desired times until the required quality is achieved. The dried product may optionally be subjected to size reduction to produce desired particle sizes. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation, ball, roller and hammer milling, and jet milling.

In an aspect, the application provides crystalline Form E of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 8.5, 14.1, 14.9, 16.9, 17.4, 19.8, 20.6, 22.1, 23.2, 26.3, and 30.0 ± 0.2 degrees 2-theta.

In an aspect, the application provides crystalline Form E of dexlansoprazole, with a powder X-ray diffraction (PXRD) pattern having peak locations substantially as listed in Table 5.

Table 5

2θ (degrees) ± 0.2
8.5
9.8
11.6
14.1
14.2
14.9
16.9
17.4
19.1
19.8
20.6
21.2
21.8
22.1
22.5
23.2
23.5
24.0
24.4
25.3
25.6
25.9
26.3
26.5
27.3
28.2
28.5
29.4
30.0
30.6
31.8
33.1
33.5
34.1
34.3
34.8
37.1
38.7
39.9
41.8

5

In an aspect, the application provides crystalline Form E of dexlansoprazole, with a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 8.

In an aspect, the application provides a process for the preparation of crystalline Form E of dexlansoprazole, comprising grinding dexlansoprazole in the presence of an organic solvent comprising dimethylsulfoxide.

In an aspect, the application provides polymorphic forms of dexlansoprazole, which are designated herein as "Form A," "Form B," "Form C," "Form D," and "Form E." These polymorphic forms may be characterized using one or more analytical methods.

For example, crystalline Form A of dexlansoprazole prepared according to a process described in the present application has a PXRD pattern with peaks located substantially as illustrated in Fig. 1.

For example, crystalline Form A of dexlansoprazole prepared according to a process described in the present application has an endothermic peak at about 76°C in a DSC curve. For example, crystalline Form A of dexlansoprazole prepared according to a process described in the present application has a DSC curve substantially as illustrated in Fig. 2.

Crystalline Form C of dexlansoprazole prepared according to a process described in the present application has an endothermic peak at about 151°C in a DSC curve. For example, crystalline Form C of dexlansoprazole prepared according to a process described in the present application has a DSC curve substantially as illustrated in Fig. 5.

In embodiments, crystalline Form C of dexlansoprazole prepared according to a process described in the present application has a TGA curve corresponding to a weight loss less than about 1.1% by weight, as illustrated in Fig. 6.

In an aspect, the application provides pharmaceutical formulations comprising one or more crystalline polymorphic forms of dexlansoprazole, together with one or more pharmaceutically acceptable excipients.

Dexlansoprazole together with one or more pharmaceutically acceptable excipients of the present application may be formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as, but not limited to, syrups, suspensions, dispersions, and emulsions; and injectable preparations such as, but not limited to, solutions, dispersions, and freeze dried compositions. Formulations may be in the forms of immediate release, delayed release, or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic

and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared using techniques such as direct blending, dry granulation, wet granulation, and extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated, and modified release coated. Compositions of the present application may further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that are useful in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, pregelatinized starches, and the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodium, colloidal silicon dioxide, and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate, and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins and resins; release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl methacrylates, waxes, and the like. Other pharmaceutically acceptable excipients that are of use include, but are not limited to, film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, and the like.

Crystalline forms are characterized by scattering techniques, *e.g.*, x-ray diffraction powder pattern, by spectroscopic methods, *e.g.*, infra-red, ^{13}C nuclear magnetic resonance spectroscopy, and by thermal techniques, *e.g.*, differential scanning calorimetry or differential thermal analysis. The compound of this application is best characterized by the X-ray powder diffraction pattern determined in accordance with procedures that are known in the art. For a discussion of these techniques see J. Haleblian, **J. Pharm. Sci.** 1975 64:1269-1288, and J. Haleblian and W. McCrone, **J. Pharm. Sci**. 1969 58:911-929. Crystal forms of the application can be further processed to modulate particle size. For example, the crystal forms of the application can be milled to reduce average crystal size and/or to prepare a sample suitable for manipulation and formulation.

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 be 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.* generated for an unknown form of, in this case, dexlansoprazole, and confirms its identity as one of the forms disclosed and claimed herein. The same holds true for other techniques which 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 from the drawing that uniquely define that crystalline form, within any associated and recited margin 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 atmospheric pressure, unless otherwise designated. All temperatures are in degrees Celsius unless specified otherwise. As used herein, "comprising" means the elements recited, or their equivalents 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.

Generally, a diffraction angle (2θ) in powder X-ray diffractometry may have an error in the range of ±.0.2°. Therefore, the aforementioned diffraction angle values should be understood as including values in the range of about ±.0.2°. Accordingly, the present application includes not only crystals whose peak diffraction angles in powder X-ray diffractometry completely coincide with each other, but also crystals whose peak diffraction angles coincide with each other with an error of about ±.0.2°. Therefore, in the present specification, the phrase "having a diffraction peak at a diffraction angle (2θ ±.0.2°) of 7.9°" means "having a diffraction peak at a diffraction angle (2θ) of 7.7° to 8.1°. Although the intensities of peaks in the x-ray powder diffraction patterns of different batches of a

compound may vary slightly, the peaks and the peak locations are characteristic for a specific polymorphic form. Alternatively, the term "about" means within an acceptable standard error of the mean, when considered by one of ordinary skill in the art. The relative intensities of the XRD peaks can vary depending on the sample preparation technique, crystal size distribution, various filters used, the sample mounting procedure, and the particular instrument employed. Moreover, instrument variation and other factors can affect the 2-theta values. Therefore, the term "substantially" in the context of XRD is meant to encompass that peak assignments can vary by plus or minus about 0.2.degree. Moreover, new peaks may be observed or existing peaks may disappear, depending on the type of the machine or the settings (for example, whether a Ni filter is used or not.

DEFINITIONS

The following definitions are used in connection with the present application unless the context indicates otherwise. The term "anti-solvent" refers to a liquid that, when combined with a solution of dexlansoprazole, reduces solubility of the dexlansoprazole 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. Celite® is flux-calcined diatomaceous earth. Celite® is a registered trademark of World Minerals Inc. Hyflow is flux-calcined diatomaceous earth treated with sodium carbonate. Hyflo Super Cel™ is a registered trademark of the Manville Corp. Polymorphs are different solids sharing the same molecular formula, yet having distinct physical properties when compared to other polymorphs of the same formula.

An "aliphatic or alicyclic hydrocarbon solvent" refers to a liquid, non-aromatic, hydrocarbon, which may be linear, branched, or cyclic. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of a hydrocarbon solvent include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isoheptane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, C_5-C_8aliphatic hydrocarbons, ligroin, petroleum ethers, or mixtures thereof.

"Aromatic hydrocarbon solvent" refers to a liquid, unsaturated, cyclic, hydrocarbon containing one or more rings which has at least one 6-carbon ring containing three double bonds. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of an aromatic hydrocarbon solvent include, but are not limited to, benzene toluene, ethylbenzene, m-xylene, o-xylene, p-xylene, indane, naphthalene, tetralin, trimethylbenzene,

chlorobenzene, fluorobenzene, trifluorotoluene, anisole, C_6-C_{10}aromatic hydrocarbons, or mixtures thereof.

An "ether solvent" is an organic solvent containing an oxygen atom –O- bonded to two other carbon atoms. "Ether solvents" include but are not limited to diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C_{2-6}ethers, or the like.

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 be 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.* generated for an unknown form of, in this case, dexlansoprazole, and confirms its identity as one of the forms disclosed and claimed herein. The same holds true for other techniques which 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 from the drawing that uniquely define that crystalline form, within any associated and recited margin 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 atmospheric pressure, unless otherwise designated. All temperatures are in degrees Celsius unless specified otherwise. As used herein, "comprising" means the elements recited, or their equivalents 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 application 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.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Reasonable variations of the described procedures are intended to be within the scope of the present invention. While particular aspects of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

EXAMPLES

All PXRD data reported herein are obtained using a Bruker AXS D8 Advance Powder X-ray Diffractometer or a PANalytical X-ray Diffractometer, using copper Kα radiation. Differential scanning calorimetric analyses reported herein are carried out using a DSC Q1000 model from TA Instruments with a ramp of 10°C/minute from 20°C up to 200°C. Thermogravimetric analyses are performed using a model TGA Q500 from TA Instruments. The thermograms are recorded from 20 to 200°C under a nitrogen gas purge at a flow of 40 mL/minute for the balance and 60 mL/minute for the sample, with a heating rate of 10°C/minute.

EXAMPLE 1: Preparation of crystalline Form A of dexlansoprazole. Dexlansoprazole (3.0 g) and propylene glycol (15 mL) are charged into a beaker. The mixture is sonicated at room temperature for 20 minutes to dissolve dexlansoprazole completely. The solution is filtered. The filtrate is kept in a refrigerator below -10°C for 21 hours. The obtained solid is filtered under reduced pressure and dried under reduced pressure at 25 to 35°C to afford 1.9 g of the title compound.

EXAMPLE 2: Preparation of crystalline Form A of dexlansoprazole. Dexlansoprazole (10.0 g) is dissolved in a mixture of methyl tertiary-butyl ether (180 mL) and propylene glycol (20 mL), at 40-50°C. The solution is filtered under reduced pressure. The obtained filtrate is cooled to 0-5°C and stirred for 15-20 minutes. The obtained solid is collected by filtration under reduced pressure, washed with chilled methyl tertiary-butyl ether (40 mL), and dried under reduced pressure at 25-35°C to afford 8.5 g of the title compound. PXRD pattern is in accordance with Fig. 1; DSC curve is in accordance with Fig. 2.

EXAMPLE 3: Preparation of crystalline Form B of dexlansoprazole. Dexlansoprazole (5.0 g) is dissolved in isobutyl alcohol (40 mL) at 25-35°C and stirred for 5-10 minutes. The solution is filtered. n-Hexane (200 mL) is added to the filtrate. The mixture is cooled to 0-5°C and stirred for 45-50 minutes. The obtained solid is collected by filtration

under reduced pressure, washed with n-hexane (25 mL), and dried at room temperature under reduced pressure for 16 hours to afford 1.87 g of the title compound. PXRD pattern is in accordance with Fig. 3.

EXAMPLE 4: Preparation of crystalline Form C of dexlansoprazole. A) Dexlansoprazole (20.0 g) and isobutyl alcohol (160 mL) are charged into a round bottom flask at 29°C and stirred for 25-30 minutes to dissolve dexlansoprazole completely. The solution is filtered. n-Hexane (800 mL) is added to the filtrate. The mixture is cooled to 0-5°C and stirred for 30-45 minutes. The obtained solid is collected by filtration under reduced pressure and washed with n-hexane (100 mL) to afford 21.0 g of the wet title compound.

B) Dexlansoprazole (3.0 g) prepared in Example 4A) is placed in a Petri dish and subjected to vacuum tray drying at 40°C for 65-70 hours, to afford 2.8 g of the title compound. Purity by HPLC: 98.67%; DSC endotherm: 151°C; TGA weight loss: 1.1% w/w; moisture content by KF: 0.77% w/w. PXRD pattern is in accordance with Fig. 4; DSC curve is in accordance with Fig. 5; TGA curve is in accordance with Fig. 6.

EXAMPLE 5: Preparation of crystalline Form D of dexlansoprazole. Dexlansoprazole (10.0 g) and isopropyl acetate (50 mL) are charged into a round bottom flask and stirred at room temperature to form a solution. The solution of dexlansoprazole in isopropyl acetate is added to chilled n-heptane (500 mL; 0-5°C) and stirred for 5-10 minutes. The obtained solid is collected by filtration under reduced pressure and suction dried for 10 minutes to afford 9.55 g of the title compound. PXRD pattern is in accordance with Fig. 7.

EXAMPLE 6: Preparation of crystalline Form E of dexlansoprazole. Dexlansoprazole (4.0 g) is placed in a mortar and dimethylsulfoxide (1.5 mL) is added. The mixture is subjected to grinding at 25-35°C for 10-15 minutes, to afford 3.9 g of the title compound. PXRD pattern is in accordance with Fig. 8.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the application described and claimed herein.

While particular embodiments of the present application have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the application. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

CLAIMS:

1. A process for the preparation of crystalline Form A of dexlansoprazole, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising propylene glycol; and

b) isolating the crystalline Form A of dexlansoprazole.

2. Crystalline Form B of dexlansoprazole having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.7, 7.6, 17.1, 18.1, 20.2, and 22.4 ± 0.2 degrees 2-theta.

3. The crystalline Form B of dexlansoprazole of claim 2, with a powder X-ray diffraction pattern having peak locations substantially as listed in Table 2.

4. The crystalline Form B of dexlansoprazole of claim 2, with a powder X-ray diffraction (PXRD) pattern with peaks located substantially as illustrated by Fig. 3.

5. A process for the preparation of crystalline Form B of dexlansoprazole of claim 2, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising isobutyl alcohol; and

b) isolating the crystalline Form B of dexlansoprazole.

6. The crystalline Form C of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.1, 8.8, 10.2, 11.7, 13.5, 15.5, 15.9, 18.4, 20.3, 22.3, 22.8, and 24.0 ± 0.2 degrees 2-theta.

7. The crystalline Form C of dexlansoprazole of claim 6, with a powder X-ray diffraction pattern having peak locations substantially as listed in Table 3.

8. The crystalline Form C of dexlansoprazole of claim 6, with any one or more of: a powder X-ray diffraction (PXRD) pattern substantially as illustrated by Fig. 4; a differential scanning calorimetry (DSC) curve substantially as illustrated by Fig. 5; and a thermogravimetric analysis (TGA) curve substantially as illustrated by Fig. 6.

9. A process for the preparation of crystalline Form C of dexlansoprazole of claim 6, comprising:

a) providing a solution of dexlansoprazole in a solvent comprising isobutyl alcohol;

b) forming a solid; and

c) drying the solid to afford crystalline Form C of dexlansoprazole.

10. The crystalline Form D of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 5.3, 6.1, 7.3, 10.0, 14.2, 16.0, 19.8, 21.7, 22.0, 22.8, and 25.0 ± 0.2 degrees 2-theta.

11. The crystalline Form D of dexlansoprazole of claim 10, with a powder X-ray diffraction pattern having peak locations substantially as listed in Table 4.

12. The crystalline Form D of dexlansoprazole of claim 10, with a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 7.

13. A process for the preparation of crystalline Form D of dexlansoprazole of claim 10, comprising:

a) providing a solution of dexlansoprazole in isopropyl acetate; and

b) combining the solution with anti-solvent.

14. The crystalline Form E of dexlansoprazole, having a powder X-ray diffraction (PXRD) pattern with two or more characteristic peaks located at about 8.5, 14.1, 14.9, 16.9, 17.4, 19.8, 20.6, 22.1, 23.2, 26.3, and 30.0 ± 0.2 degrees 2-theta.

15. The crystalline Form E of dexlansoprazole of claim 14, with a powder X-ray diffraction pattern having peak locations substantially as listed in Table 5.

16. The crystalline Form E of dexlansoprazole of claim 14, with a powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated by Fig. 8.

17. A process for the preparation of crystalline Form E of dexlansoprazole of claim 14, comprising grinding dexlansoprazole in the presence of an organic solvent comprising dimethylsulfoxide.

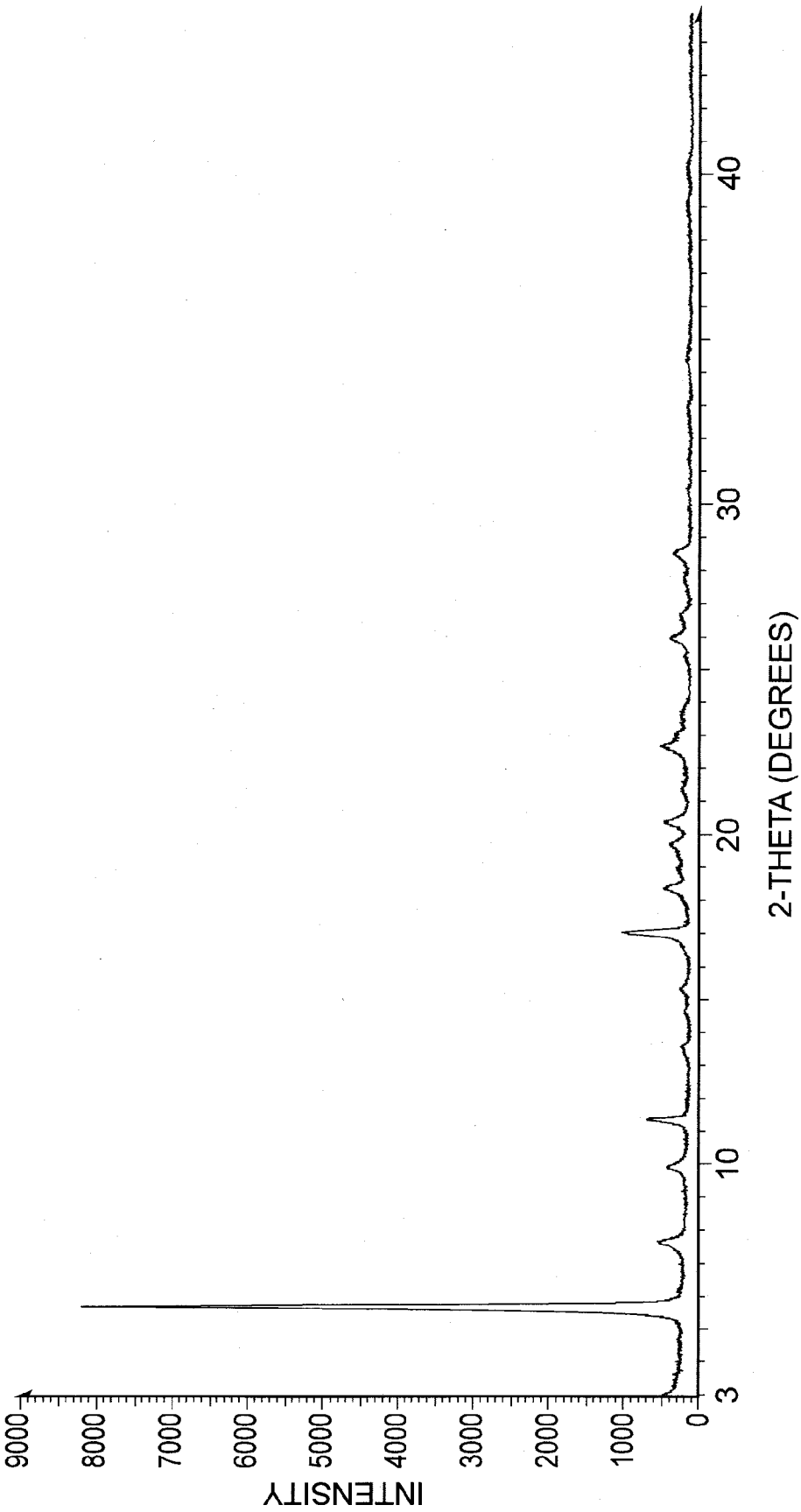

INTENSITY
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-THETA (DEGREES)

FIG. 1

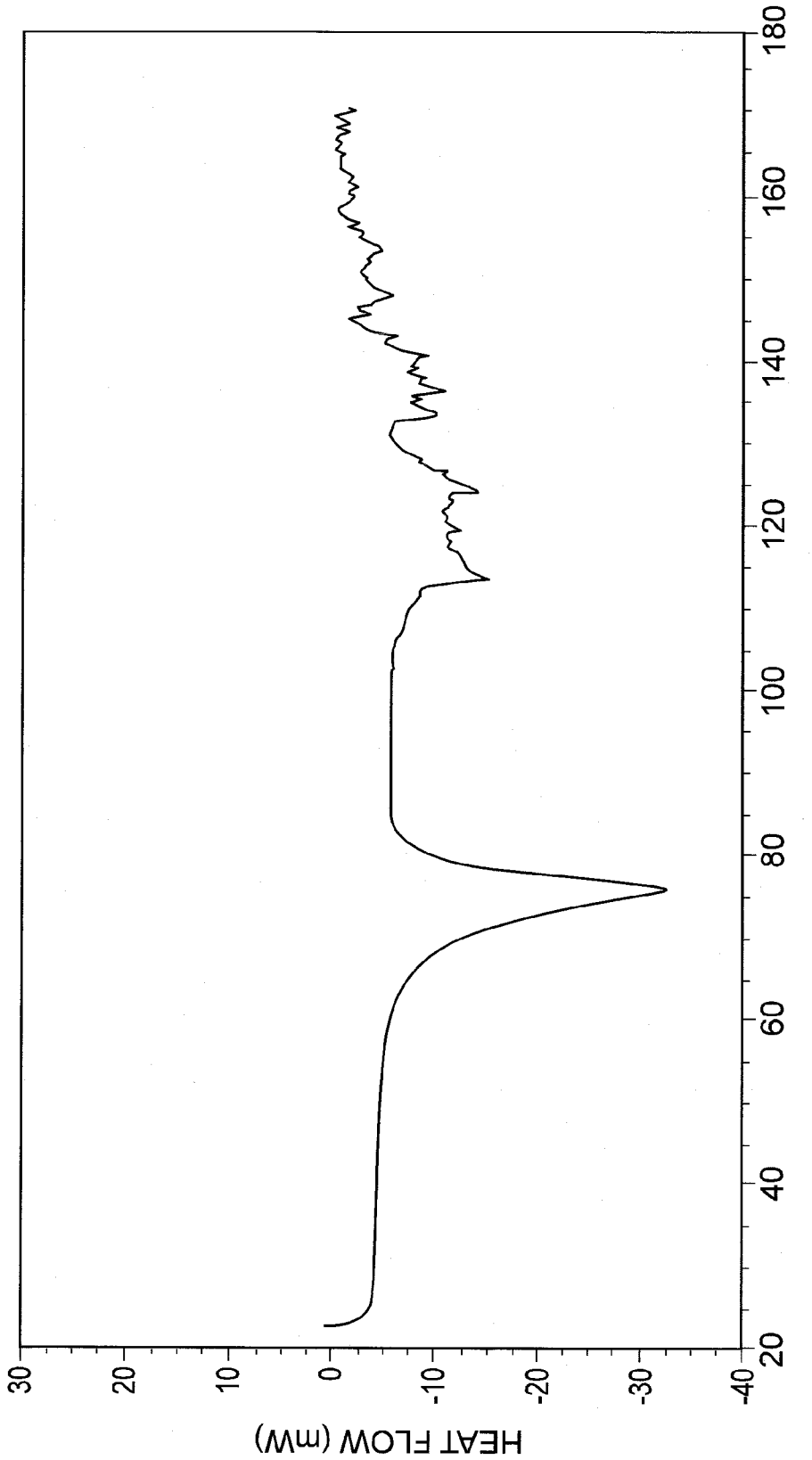

HEAT FLOW (mW)
30
20
10
0
-10
-20
-30
-40
20
40
60
80
100
120
140
160
180
TEMPERATURE (C°)

FIG. 2

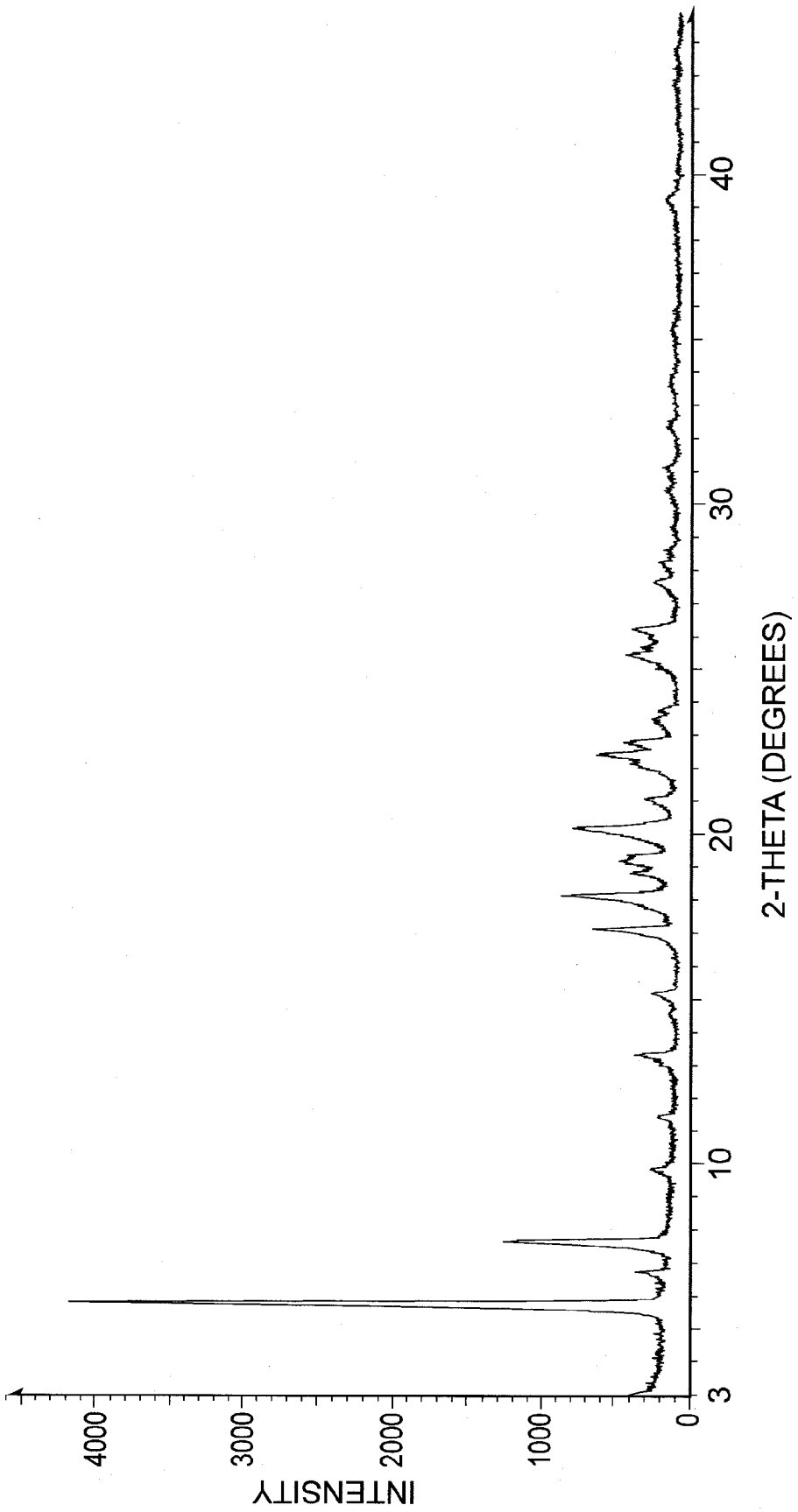


FIG. 3

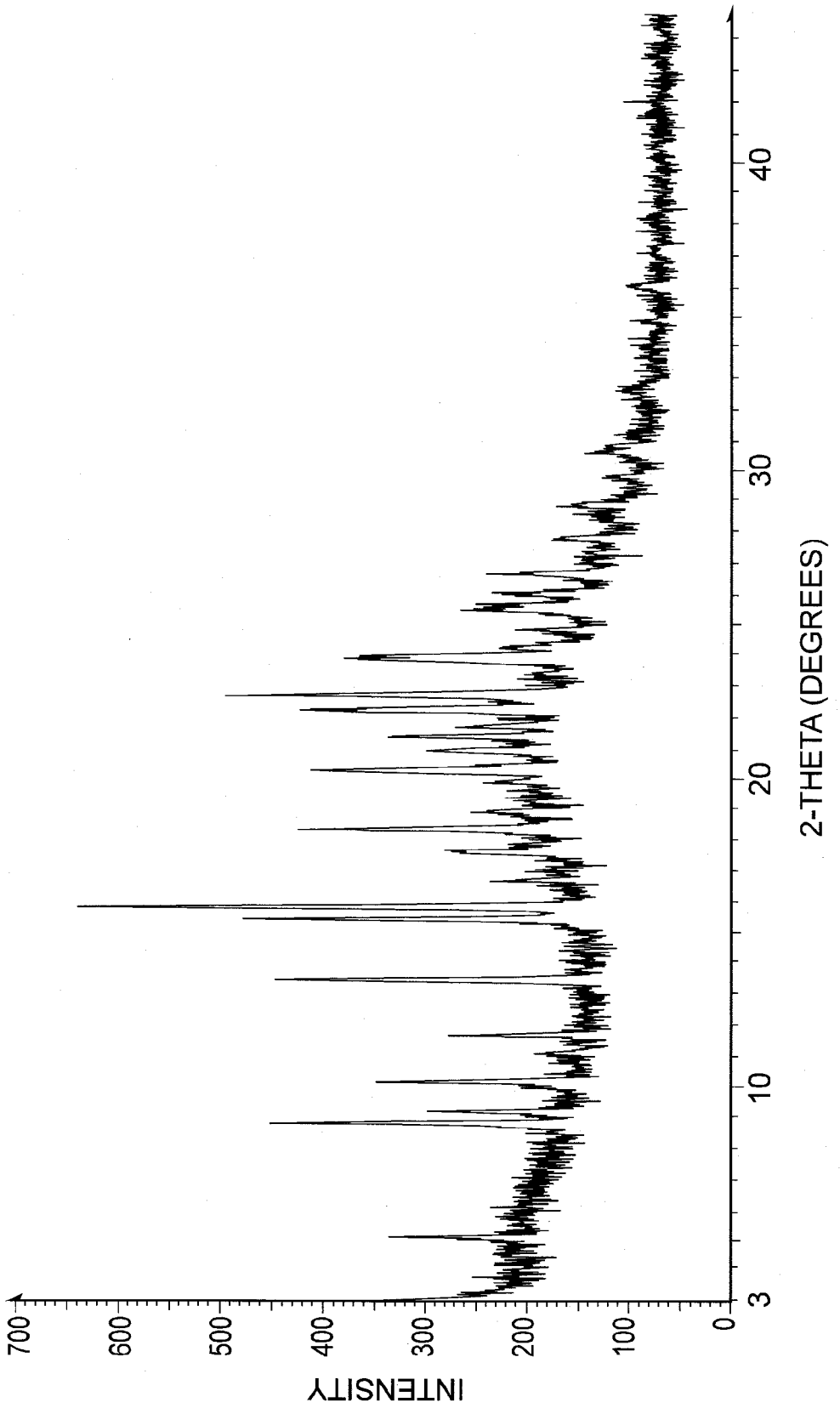

INTENSITY
700
600
500
400
300
200
100
0
3
10
20
30
40
2-THETA (DEGREES)

FIG. 4

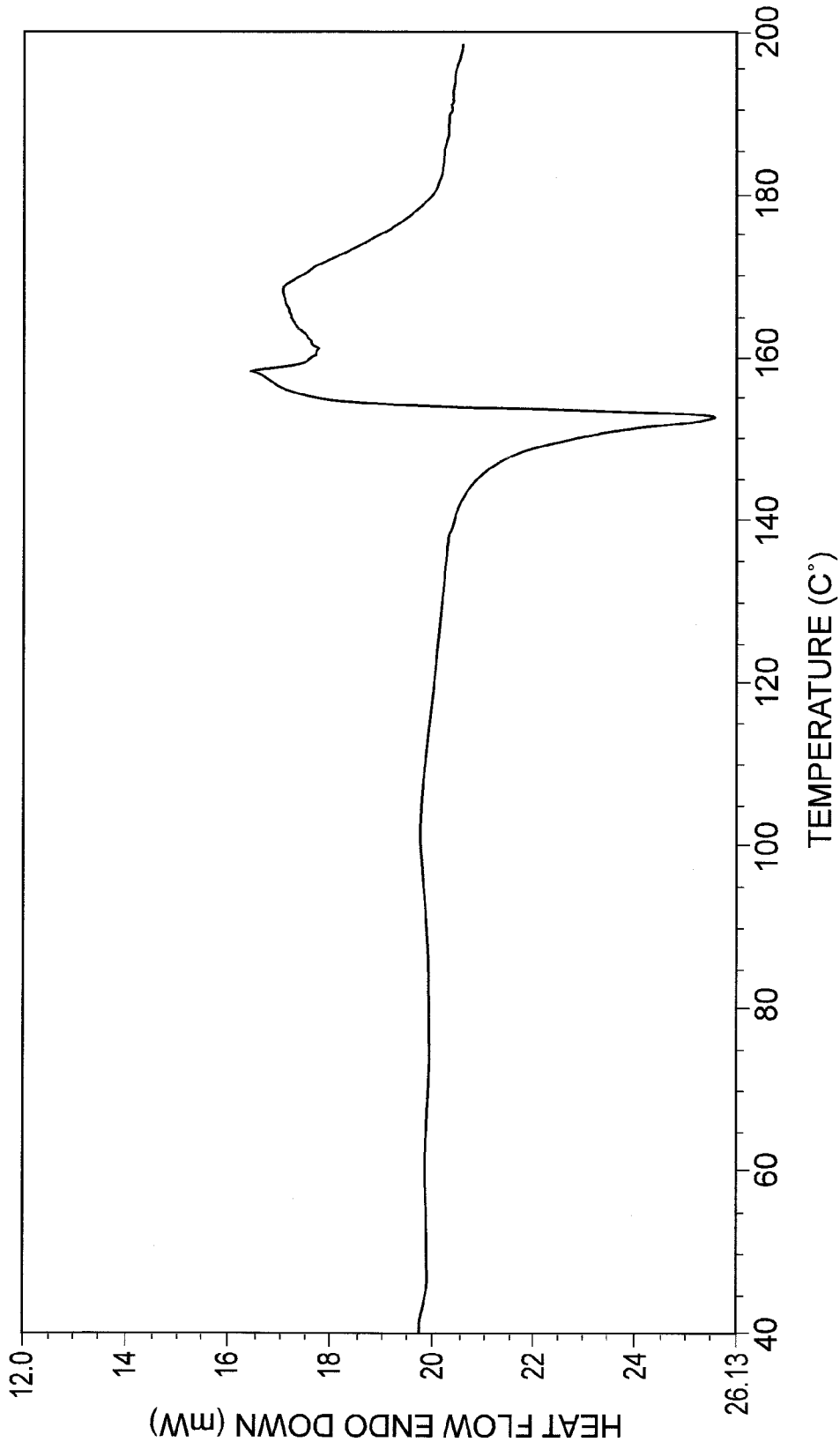

HEAT FLOW ENDO DOWN (mW)
12.0
14
16
18
20
22
24
26.13
40
60
80
100
120
140
160
180
200
TEMPERATURE (C°)

FIG. 5

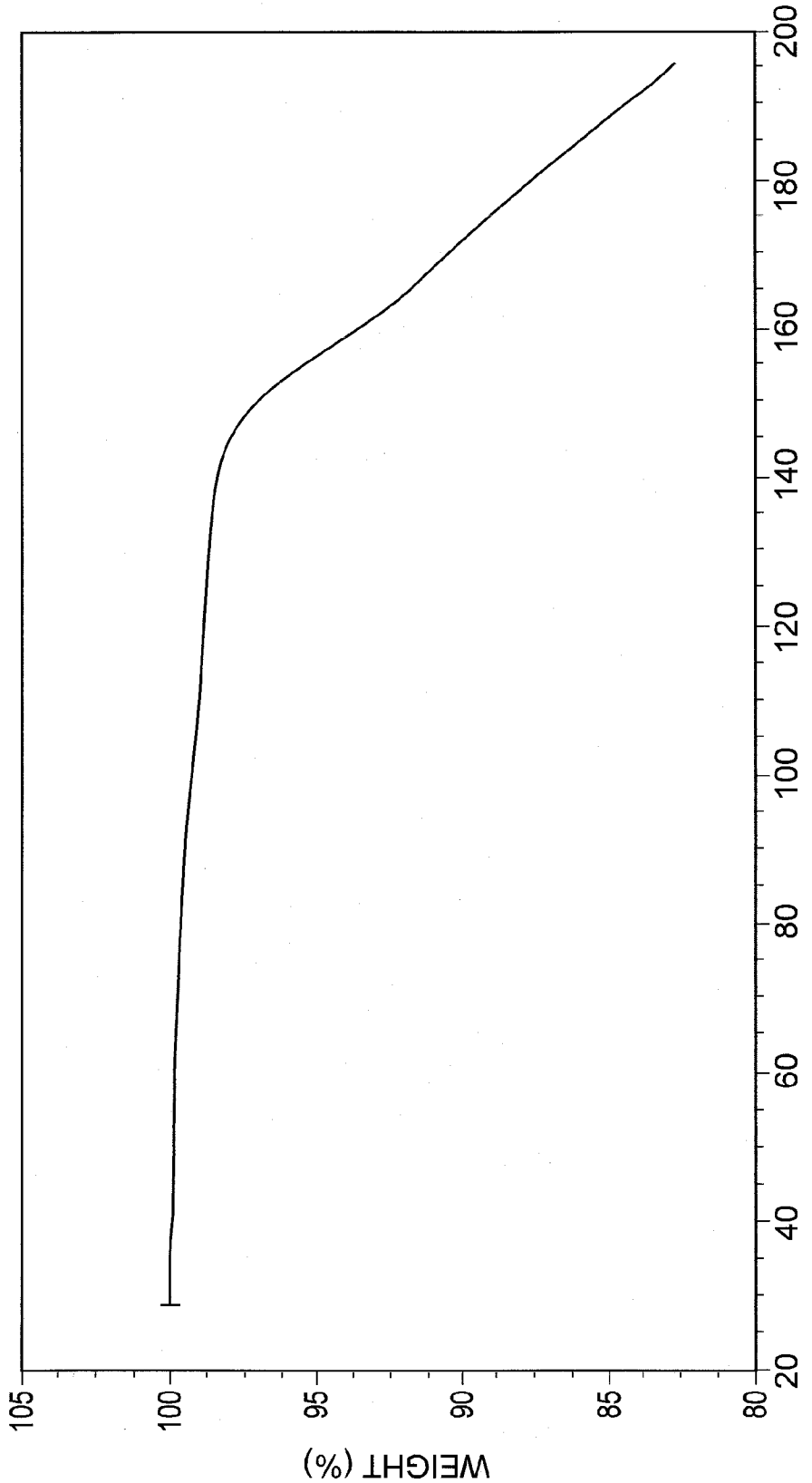

WEIGHT (%)
105
100
95
90
85
80
TEMPERATURE (C°)
20
40
60
80
100
120
140
160
180
200

FIG. 6

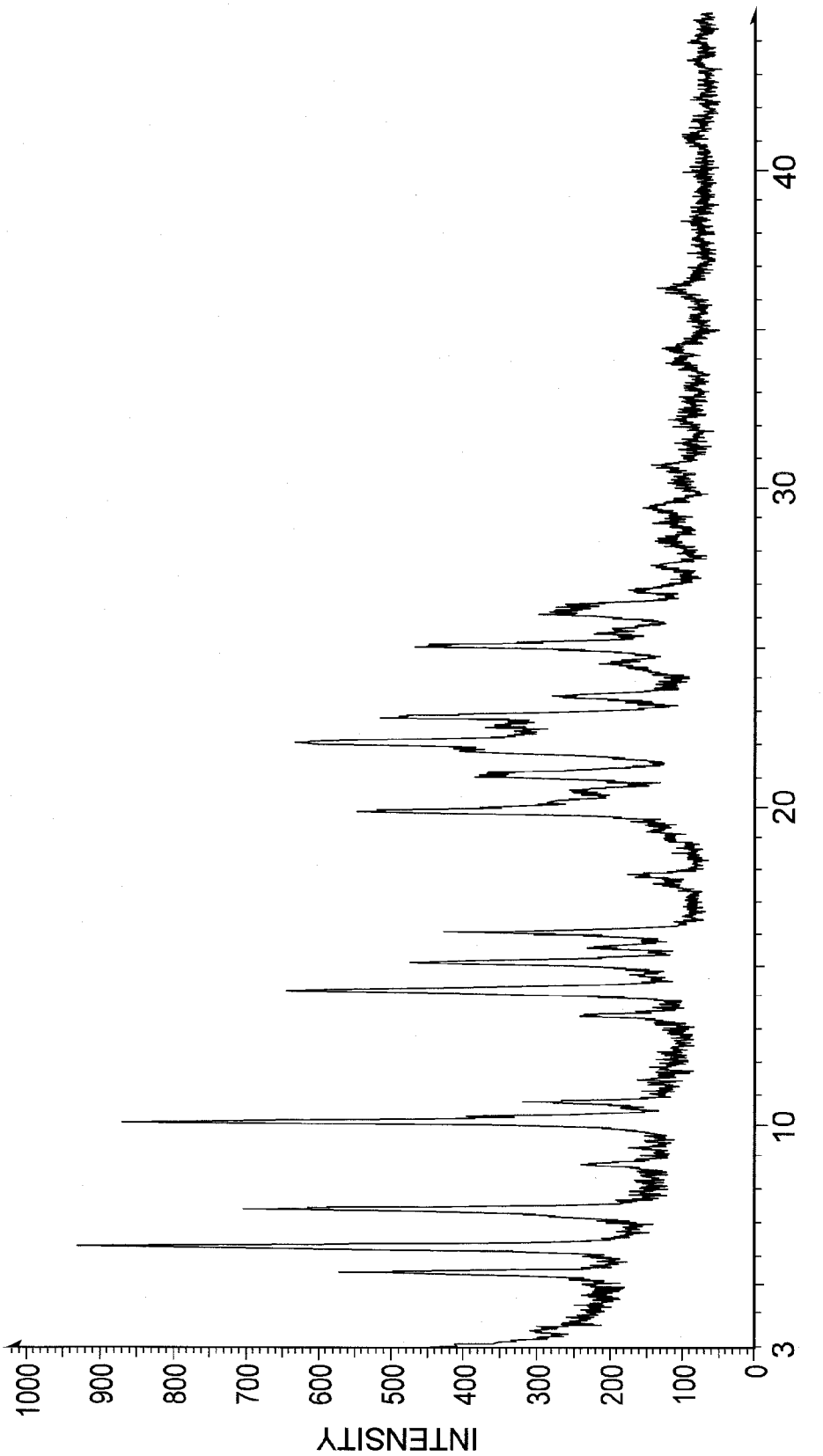

INTENSITY
1000
900
800
700
600
500
400
300
200
100
0
3
10
20
30
40
2-THETA (DEGREES)

FIG. 7

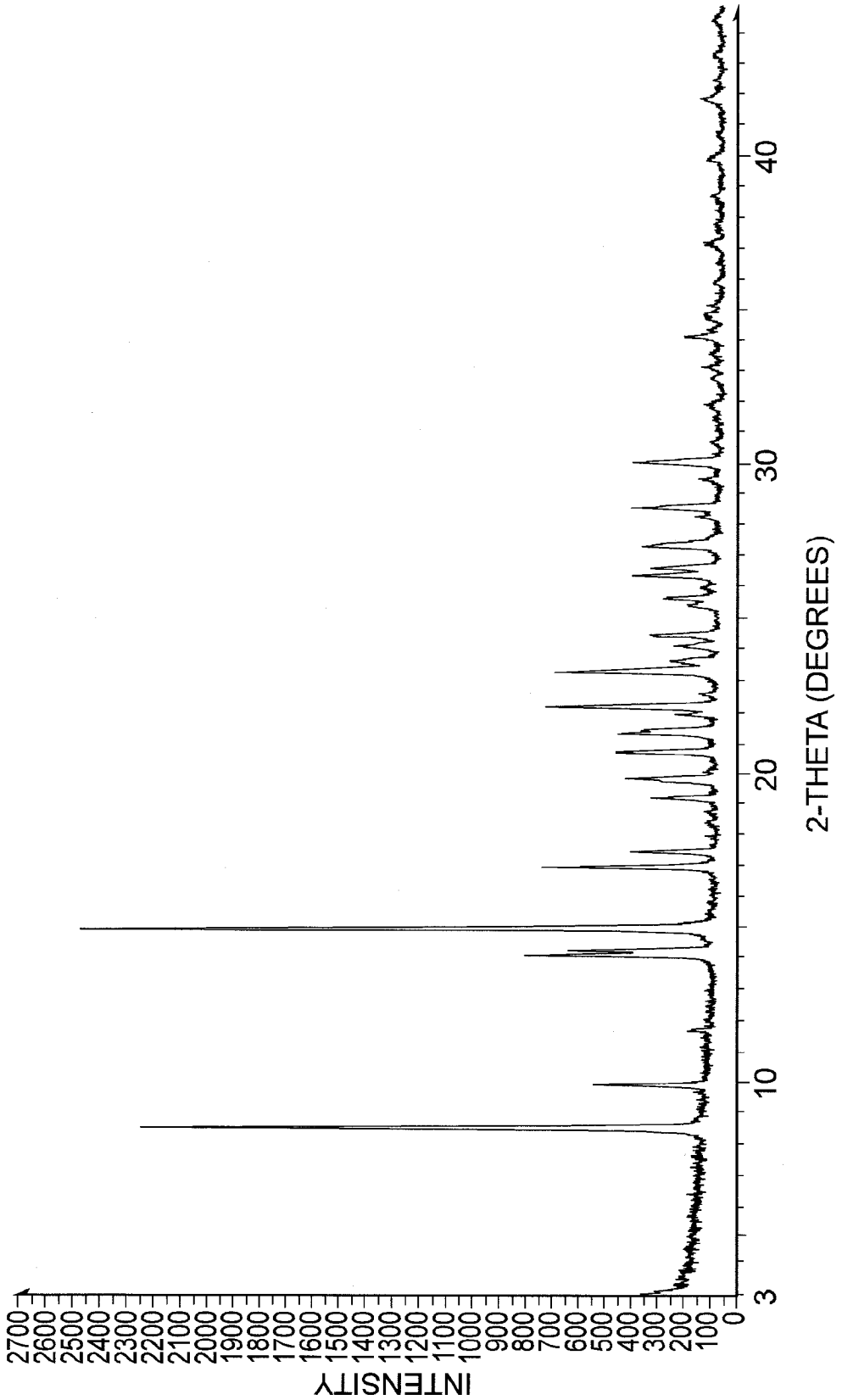

INTENSITY
2700
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
3
10
20
30
40
2-THETA (DEGREES)

FIG. 8