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(54) **Title**: CRYSTALLINE FORMS OF DABIGATRAN ETEXILATE AND PROCESS FOR THEIR PREPARATION

(57) **Abstract**: The present invention relates to crystalline Form 1, Form 2, Form 3, and Form 4 of dabigatran etexilate, and processes for their preparation. The present invention further relates to processes for the preparation of a dabigatran etexilate methanesulfonate salt using crystalline Form 1, Form 2, Form 3, and Form 4 of dabigatran etexilate.

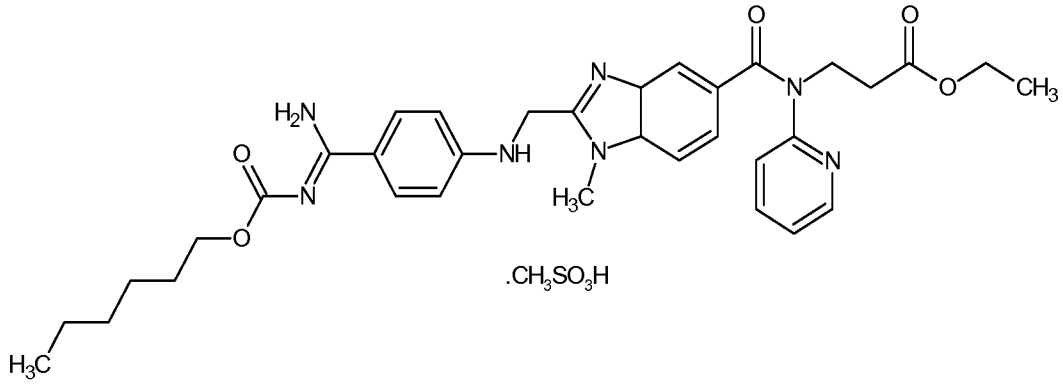
CRYSTALLINE FORMS OF DABIGATRAN ETEXILATE AND PROCESS FOR THEIR PREPARATION

Field of the Invention

The present invention relates to crystalline Form 1, Form 2, Form 3, and Form 4 of dabigatran etexilate and processes for their preparation. The present invention further relates to processes for the preparation of a dabigatran etexilate methanesulfonate salt using crystalline Form 1, Form 2, Form 3, and Form 4 of dabigatran etexilate.

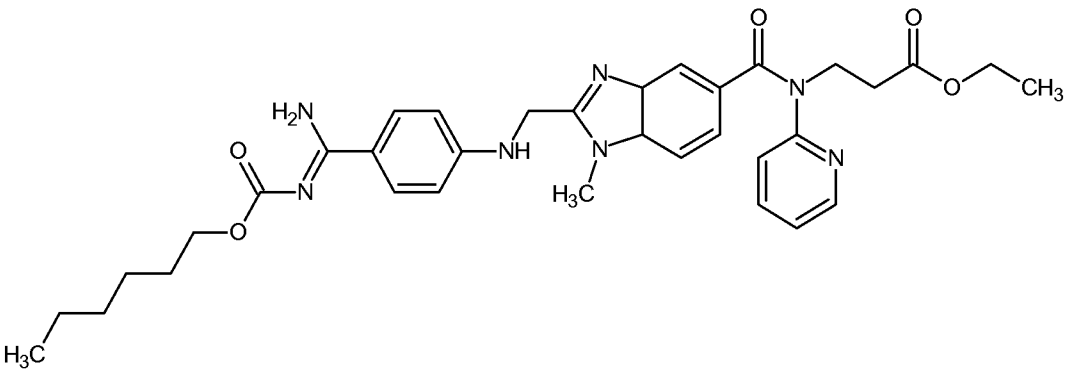
Background of the Invention

The drug substance used in the commercial drug product formulation of PRADAXA® is the methanesulfonate salt of dabigatran etexilate, which is chemically described as β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate salt of Formula I.



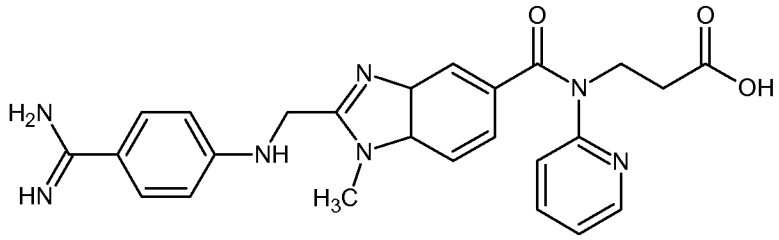
FORMULA I

Dabigatran etexilate of Formula II



FORMULA II

is a prodrug of dabigatran of Formula III



FORMULA III

which is a direct thrombin inhibitor. Dabigatran etexilate is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It may be used alone or in combination with other therapeutic agents.

Processes for the preparation of dabigatran etexilate and its methanesulfonate salt are described in U.S. Patent No. 6,087,380; U.S. Patent Application Nos. 2006/0183779, 2006/0276513, and PCT Publication Nos. WO 2012/027543, WO 2008/059029, WO 2011/110478.

Summary of the Invention

The present invention relates to crystalline Form 1, Form 2, Form 3, and Form 4 of dabigatran etexilate and processes for their preparation. The present invention further relates to processes for the preparation of dabigatran etexilate methanesulfonate salt using crystalline Form 1, Form 2, Form 3, and Form 4 of dabigatran etexilate.

Brief Description of the Drawings

Figure 1 depicts the X-ray powder diffraction (XRPD) pattern of crystalline Form 1 of dabigatran etexilate obtained according to Example 1.

Figure 1A provides the table of values for the XRPD pattern depicted in Figure 1.

Figure 2 depicts the XRPD pattern of crystalline Form 2 of dabigatran etexilate obtained according to Example 2.

Figure 2A provides the table of values for the XRPD pattern depicted in Figure 2.

Figure 3 depicts the XRPD pattern of crystalline Form 3 of dabigatran etexilate obtained according to Example 3.

Figure 3A provides the table of values for the XRPD pattern depicted in Figure 3.

Figure 4 depicts the XRPD pattern of crystalline Form 4 of dabigatran etexilate obtained according to Example 4.

Figure 4A provides the table of values for the XRPD pattern depicted in Figure 4.

Figure 5 depicts the Differential Scanning Calorimetry (DSC) thermogram of crystalline Form 1 of dabigatran etexilate obtained according to Example 1.

Figure 6 depicts the DSC thermogram of crystalline Form 2 of dabigatran etexilate obtained according to Example 2.

Figure 7 depicts the DSC thermogram of crystalline Form 3 of dabigatran etexilate obtained according to Example 3.

Detailed Description of the Invention

A first aspect of the present invention provides crystalline Form 1 of dabigatran etexilate.

The crystalline Form 1 of dabigatran etexilate has substantially the same XRPD (X-ray powder diffraction) pattern as depicted in Figure 1. The crystalline Form 1 of dabigatran etexilate is characterized by an XRPD pattern having interplanar spacing (d) values substantially at 5.74, 4.42, 4.00, 3.68, 3.63, and 3.48 Å. The crystalline Form 1 of dabigatran etexilate is further characterized by an XRPD pattern having interplanar spacing (d) values at about 20.03, 18.28, 10.62, 10.06, 8.53, 7.68, 6.69, 6.44, 6.04, 5.74, 5.34, 5.23, 4.94, 4.42, 4.28, 4.13, 4.00, 3.92, 3.82, 3.68, 3.63, 3.48, 3.35, 3.25, 3.16, 3.11, 3.03, 2.87, 2.78, 2.72, 2.65, 2.59, 2.46, and 2.32 Å.

The crystalline Form 1 of dabigatran etexilate may further be characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as that depicted in Figure 5. The crystalline Form 1 of dabigatran etexilate has characteristic DSC endothermic peaks at about 51.42°C, 73.42°C, 99.62°C, 108.41°C, 121.91°C, and 131.52°C.

A second aspect of the present invention provides crystalline Form 2 of dabigatran etexilate.

The crystalline Form 2 of dabigatran etexilate has substantially the same XRPD pattern as depicted in Figure 2. The crystalline Form 2 of dabigatran etexilate is characterized by an XRPD pattern having interplanar spacing (d) values at about 14.95,

7.48, 4.96, 4.49, 4.27, 4.16, 3.57, and 3.40 Å. The crystalline Form 2 of dabigatran etexilate is further characterized by an XRPD pattern having interplanar spacing (d) values at about 14.95, 13.43, 10.69, 8.04, 7.48, 7.28, 6.74, 6.45, 5.92, 5.75, 4.96, 4.49, 4.40, 4.27, 4.16, 3.84, 3.67, 3.57, 3.40, 3.32, 3.16, 2.73, and 2.49 Å.

The crystalline Form 2 of dabigatran etexilate may further be characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as that depicted in Figure 6. The crystalline Form 2 of dabigatran etexilate has a characteristic DSC endothermic peak at about 77.61°C.

A third aspect of the present invention provides crystalline Form 3 of dabigatran etexilate.

The crystalline Form 3 of dabigatran etexilate has substantially the same XRPD pattern as depicted in Figure 3. The crystalline Form 3 of dabigatran etexilate is characterized by an XRPD pattern having interplanar spacing (d) values at about 6.57, 5.71, 4.00, 3.93, 3.62, and 3.47 Å. The crystalline Form 3 of dabigatran etexilate is further characterized by an XRPD pattern having interplanar spacing (d) values at about 27.77, 19.61, 18.13, 10.59, 10.01, 9.07, 8.51, 7.64, 6.57, 6.43, 6.04, 5.71, 5.32, 5.13, 4.92, 4.47, 4.41, 4.27, 4.12, 4.00, 3.93, 3.82, 3.62, 3.47, 3.33, 3.25, 3.17, 3.10, 3.01, 2.97, 2.86, 2.77, 2.72, 2.58, 2.46, and 2.31 Å.

The crystalline Form 3 of dabigatran etexilate may further be characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as depicted in Figure 7. The crystalline Form 3 of dabigatran etexilate has characteristic DSC endothermic peaks at about 53.67°C, 75.66°C, 106.58°C, 122.12°C, and 131.22°C.

A fourth aspect of the present invention provides crystalline Form 4 of dabigatran etexilate.

The crystalline Form 4 of dabigatran etexilate has substantially the same XRPD pattern as depicted in Figure 4. The crystalline Form 4 of dabigatran etexilate is characterized by an XRPD pattern having interplanar spacing (d) values at about 10.00, 5.71, 5.33, 4.41, 3.68, and 3.62 Å. The crystalline Form 4 of dabigatran etexilate is further characterized by an XRPD pattern having interplanar spacing (d) values at about 18.05, 10.45, 10.00, 8.53, 7.61, 6.70, 6.50, 6.34, 6.03, 5.71, 5.33, 5.09, 4.88, 4.41, 4.27, 4.13, 4.01, 3.91, 3.81, 3.68, 3.62, 3.54, 3.48, 3.34, 3.25, 3.17, 3.12, 3.02, 2.85, 2.78, 2.72, 2.66, 2.58, 2.46, and 2.32 Å.

A fifth aspect of the present invention provides a process for the preparation of crystalline Form 1 of dabigatran etexilate wherein the process comprises:

a) treating dabigatran etexilate with hexanol; and

b) isolating Form 1 of dabigatran etexilate from the mixture thereof.

Dabigatran etexilate existing in any solid or non-solid form known in the prior art may be used as the starting material. Dabigatran etexilate may be prepared, for example, according to the methods disclosed in U.S. Patent No. 6,087,380. Dabigatran etexilate is treated with hexanol. The treatment with hexanol may be carried out at a temperature of about 10°C to about 100°C, for example, about 20°C to about 80°C. The treatment with hexanol may be carried out for about 2 hours to about 7 hours, for example, about 4 hours to about 5 hours. The hexanol may be used alone or in combination with an organic solvent. The treatment with hexanol is optionally preceded or followed by treatment with an organic solvent. The organic solvent may be selected from the group comprising of alcohols, esters, nitriles, or mixtures thereof. The alcohol may be, for example, ethanol, methanol, 2-propanol, or butanol. The ester may be, for example, methyl acetate, ethyl acetate, or butyl acetate. The nitrile may be, for example, acetonitrile. The reaction mixture is stirred for about 1 hour to about 5 hours, for example, about 2 hours to about 3 hours. The crystalline Form 1 of dabigatran etexilate may be isolated from the reaction mixture by filtration, cooling, evaporation, decantation, distillation, vacuum drying, or combinations thereof.

A sixth aspect of the present invention provides a process for the preparation of crystalline Form 2 of dabigatran etexilate, wherein the process comprises:

a) treating dabigatran etexilate with t-butanol; and

b) isolating Form 2 of dabigatran etexilate from the mixture thereof.

Dabigatran etexilate existing in any solid or non-solid form known in the prior art may be used as the starting material. Dabigatran etexilate may be prepared, for example, according to the methods disclosed in U.S. Patent No. 6,087,380. Dabigatran etexilate is treated with t-butanol at a temperature of about 10°C to about 100°C, for example, about 20°C to about 80°C. The treatment with t-butanol may be carried out for about 2 hours to about 7 hours, for example about 4 hours to about 5 hours. The t-butanol may be used alone, or in combination with an organic solvent. The treatment with t-butanol is

optionally preceded or followed by treatment with an organic solvent. The organic solvent may be selected from the group comprising of alcohols, esters, nitriles, or mixtures thereof. The alcohol may be, for example, ethanol, methanol, 2-propanol, or butanol. The ester may be, for example, methyl acetate, ethyl acetate, or butyl acetate. The nitrile may be, for example, acetonitrile. The reaction mixture is stirred for about 1 hour to about 5 hours, for example, about 2 hours to about 3 hours. The crystalline Form 2 of dabigatran etexilate may be isolated from the reaction mixture by filtration, cooling, evaporation, decantation, distillation, vacuum drying, or combinations thereof.

A seventh aspect of the present invention provides a process for the preparation of crystalline Form 3 of dabigatran etexilate wherein the process comprises:

a) treating dabigatran etexilate with toluene; and

b) isolating Form 3 of dabigatran etexilate from the mixture thereof.

Dabigatran etexilate existing in any solid or non-solid form known in the prior art may be used as the starting material. Dabigatran etexilate may be prepared, for example, according to the methods disclosed in U.S. Patent No. 6,087,380. Dabigatran etexilate is treated with toluene at a temperature of about 10°C to about 100°C, for example, about 20°C to about 80°C, for about 2 hours to about 7 hours, for example, about 4 hours to about 5 hours. The toluene may be used alone, or in combination with an organic solvent. The treatment with toluene is optionally preceded or followed by treatment with an organic solvent. The organic solvent may be selected from the group comprising of alcohols, esters, nitriles, or mixtures thereof. The alcohol may be, for example, ethanol, methanol, 2-propanol, or butanol. The ester may be, for example, methyl acetate, ethyl acetate, or butyl acetate. The nitrile may be, for example, acetonitrile. The reaction mixture is stirred for about 1 hour to about 5 hours, for example, about 2 hours to about 3 hours. The crystalline Form 3 of dabigatran etexilate may be isolated from the reaction mixture by filtration, cooling, evaporation, decantation, distillation, vacuum drying, or combinations thereof.

An eighth aspect of the present invention provides a process for the preparation of crystalline Form 4 of dabigatran etexilate wherein the process comprises:

a) treating dabigatran etexilate with methyl acetate; and

b) isolating Form 4 of dabigatran etexilate from the mixture thereof.

Dabigatran etexilate existing in any solid or non-solid form known in the prior art may be used as the starting material. Dabigatran etexilate may be prepared, for example, according to the methods disclosed in U.S. Patent No. 6,087,380. Dabigatran etexilate is treated with methyl acetate. The treatment with methyl acetate may be carried out at a temperature of about 10°C to about 100°C, for example, about 20°C to about 80°C. The treatment with methyl acetate may be carried out for about 2 hours to about 7 hours, for example, about 4 hours to about 5 hours. The methyl acetate may be used alone or in combination with an organic solvent. The treatment with methyl acetate is optionally preceded or followed by treatment with an organic solvent. The organic solvent may be selected from the group comprising of alcohols, esters, nitriles, or mixtures thereof. The alcohol may be, for example, ethanol, methanol, 2-propanol, or butanol. The ester may be, for example, ethyl acetate, or butyl acetate. The nitrile may be, for example, acetonitrile. The reaction mixture is stirred for about 1 hour to about 5 hours, for example, about 2 hours to about 3 hours. The crystalline Form 4 of dabigatran etexilate may be isolated from the reaction mixture by filtration, cooling, evaporation, decantation, distillation, vacuum drying, or combinations thereof.

A ninth aspect of the present invention provides a process for the preparation of dabigatran etexilate methanesulfonate salt wherein the process comprises:

a) treating crystalline Form 1, Form 2, Form 3, or Form 4 of dabigatran etexilate with methane sulfonic acid; and

b) isolating dabigatran etexilate methanesulfonate salt from the mixture thereof.

A tenth aspect of the present invention provides a pharmaceutical composition comprising crystalline Form 1, Form 2, Form 3, or Form 4 of dabigatran etexilate, or any combination of said forms, and a pharmaceutically acceptable excipient.

An eleventh aspect of the present invention provides a method of treating or preventing blood clots in a patient suffering from or susceptible to the formation of blood clots, comprising administering a pharmaceutical composition comprising crystalline Form 1, Form 2, Form 3, or Form 4 of dabigatran etexilate, or any combination of said forms.

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

EXAMPLES

Example 1: Preparation of Crystalline Form 1 of Dabigatran Etexilate

Dabigatran etexilate (2 g) was added to hexanol (25 mL) at 25°C to 30°C. The temperature of the reaction mixture was increased to 70°C to 75°C, and the mixture was stirred for 5 minutes to 10 minutes. The reaction mixture was cooled to 20°C to 25°C and stirred for 2 hours to 3 hours. The solid obtained was filtered under vacuum, and washed with hexanol (10 mL). The solid obtained was suck dried, and further dried under vacuum at 50°C to 55°C for 15 hours to give the title compound having an XRPD pattern as shown in Figure 1.

Yield: 60%

Example 2: Preparation of Crystalline Form 2 of Dabigatran Etexilate

Dabigatran etexilate (2 g) was added to t-butanol (25 mL) at 25°C to 30°C. The temperature of the reaction mixture was increased to 70°C to 75°C, and it was stirred for 5 minutes to 10 minutes. The reaction mixture was cooled to 20°C to 25°C and stirred for 2 hours to 3 hours. The solid obtained was filtered under vacuum and washed with t-butanol (10 mL). The solid obtained was suck dried, and further dried under vacuum at 50°C to 55°C for 15 hours to give the title compound having an XRPD pattern as shown in Figure 2.

Yield: 67.5%

Example 3: Preparation of Crystalline Form 3 of Dabigatran Etexilate

Dabigatran etexilate (2 g) was added to toluene (25 mL) at 25°C to 30°C. The temperature of the reaction mixture was increased to 70°C to 75°C, and it was stirred for 5 minutes to 10 minutes. The reaction mixture was cooled to 20°C to 25°C and stirred for 2 hours to 3 hours. The solid obtained was filtered under vacuum and washed with toluene (10 mL). The solid obtained was suck dried, and further dried under vacuum at 50°C to 55°C for 15 hours to give the title compound having an XRPD pattern as shown in Figure 3.

Yield: 85%

Example 4: Preparation of Crystalline Form 4 of Dabigatran Etexilate

Dabigatran etexilate (2 g) was added to methyl acetate (25 mL) at 25°C to 30°C. The temperature of the reaction mixture was increased to 70°C to 75°C, and it was stirred for 5 minutes to 10 minutes. The reaction mixture was cooled to 20°C to 25°C, and stirred for 2 hours to 3 hours. The solid obtained was filtered under vacuum and washed with methyl acetate (10 mL). The solid obtained was suck dried, and further dried under vacuum at 50°C to 55°C for 15 hours to give the title compound having XRPD as shown in Figure 4.

Yield: 70%

We claim:

1. Crystalline Form 1 of dabigatran etexilate having substantially the same XRPD (X-ray powder diffraction) pattern as depicted in Figure 1.

2. Crystalline Form 1 of dabigatran etexilate characterized by an XRPD pattern having interplanar spacing (d) values at about 5.74, 4.42, 4.00, 3.68, 3.63, and 3.48 Å.

3. The crystalline Form 1 of dabigatran etexilate according to claim 2, further characterized by an XRPD pattern having interplanar spacing (d) values at about 20.03, 18.28, 10.62, 10.06, 8.53, 7.68, 6.69, 6.44, 6.04, 5.74, 5.34, 5.23, 4.94, 4.42, 4.28, 4.13, 4.00, 3.92, 3.82, 3.68, 3.63, 3.48, 3.35, 3.25, 3.16, 3.11, 3.03, 2.87, 2.78, 2.72, 2.65, 2.59, 2.46, and 2.32 Å.

4. Crystalline Form 1 of dabigatran etexilate having substantially the same differential scanning calorimetry (DSC) thermogram as depicted in Figure 5.

5. The crystalline Form 1 of dabigatran etexilate according to claim 4, further characterized by DSC endothermic peaks at about 51.42°C, 73.42°C, 99.62°C, 108.41°C, 121.91°C, and 131.52°C.

6. Crystalline Form 2 of dabigatran etexilate substantially having the same XRPD pattern as depicted in Figure 2.

7. Crystalline Form 2 of dabigatran etexilate characterized by an XRPD pattern having interplanar spacing (d) values at about 14.95, 7.48, 4.96, 4.49, 4.27, 4.16, 3.57, and 3.40 Å.

8. The crystalline Form 2 of dabigatran etexilate according to claim 7, further characterized by an XRPD pattern having interplanar spacing (d) values at about 14.95, 13.43, 10.69, 8.04, 7.48, 7.28, 6.74, 6.45, 5.92, 5.75, 4.96, 4.49, 4.40, 4.27, 4.16, 3.84, 3.67, 3.57, 3.40, 3.32, 3.16, 2.73, and 2.49 Å.

9. Crystalline Form 2 of dabigatran etexilate having substantially the same differential scanning calorimetry (DSC) thermogram as depicted in Figure 6.

10. The crystalline Form 2 of dabigatran etexilate according to claim 9, further characterized by a DSC endothermic peak at about 77.61°C.

11. Crystalline Form 3 of dabigatran etexilate having substantially the same XRPD pattern as depicted in Figure 3.

12. Crystalline Form 3 of dabigatran etexilate characterized by an XRPD pattern having interplanar spacing (d) values at about 6.57, 5.71, 4.00, 3.93, 3.62, and 3.47 Å.

13. The crystalline Form 3 of dabigatran etexilate according to claim 12, further characterized by an XRPD pattern having interplanar spacing (d) values at about 27.77, 19.61, 18.13, 10.59, 10.01, 9.07, 8.51, 7.64, 6.57, 6.43, 6.04, 5.71, 5.32, 5.13, 4.92, 4.47, 4.41, 4.27, 4.12, 4.00, 3.93, 3.82, 3.62, 3.47, 3.33, 3.25, 3.17, 3.10, 3.01, 2.97, 2.86, 2.77, 2.72, 2.58, 2.46, and 2.31 Å.

14. Crystalline Form 3 of dabigatran etexilate having substantially the same differential scanning calorimetry (DSC) thermogram as depicted in Figure 7.

15. The crystalline Form 3 of dabigatran etexilate according to claim 14, further characterized by DSC endothermic peaks at about 53.67°C, 75.66°C, 106.58°C, 122.12°C, and 131.22°C.

16. Crystalline Form 4 of dabigatran etexilate having substantially the same XRPD pattern as depicted in Figure 4.

17. Crystalline Form 4 of dabigatran etexilate characterized by an XRPD pattern having interplanar spacing (d) values at about 10.00, 5.71, 5.33, 4.41, 3.68, and 3.62 Å.

18. The crystalline Form 4 of dabigatran etexilate according to claim 17, further characterized by an XRPD pattern having interplanar spacing (d) values at about 18.05, 10.45, 10.00, 8.53, 7.61, 6.70, 6.50, 6.34, 6.03, 5.71, 5.33, 5.09, 4.88, 4.41, 4.27, 4.13, 4.01, 3.91, 3.81, 3.68, 3.62, 3.54, 3.48, 3.34, 3.25, 3.17, 3.12, 3.02, 2.85, 2.78, 2.72, 2.66, 2.58, 2.46, and 2.32 Å.

19. A process for the preparation of crystalline Form 1 of dabigatran etexilate wherein the process comprises:

a) treating dabigatran etexilate with hexanol; and

b) isolating Form 1 of dabigatran etexilate from the mixture thereof.

20. A process for the preparation of crystalline Form 2 of dabigatran etexilate, wherein the process comprises:

a) treating dabigatran etexilate with t-butanol; and

b) isolating Form 2 of dabigatran etexilate from the mixture thereof.

21. A process for the preparation of crystalline Form 3 of dabigatran etexilate wherein the process comprises:

a) treating dabigatran etexilate with toluene; and

b) isolating Form 3 of dabigatran etexilate from the mixture thereof.

22. A process for the preparation of crystalline Form 4 of dabigatran etexilate wherein the process comprises:

a) treating dabigatran etexilate with methyl acetate; and

b) isolating Form 4 of dabigatran etexilate from the mixture thereof.

23. A process for the preparation of dabigatran etexilate methanesulfonate salt wherein the process comprises:

a) treating crystalline Form 1, Form 2, Form 3, or Form 4 of dabigatran etexilate with methane sulfonic acid; and

b) isolating dabigatran etexilate methanesulfonate salt from the mixture thereof.

24. A pharmaceutical composition comprising crystalline Form 1, Form 2, Form 3, or Form 4 of dabigatran etexilate, or combinations thereof, and a pharmaceutically acceptable excipient.

25. A method of treating or preventing blood clots in a patient suffering from or susceptible to the formation of blood clots, comprising administering a pharmaceutical composition comprising crystalline Form 1, Form 2, Form 3, or Form 4 of dabigatran etexilate, or combinations thereof.

Figure 1: X-ray powder diffraction pattern (XRPD) of crystalline Form 1 of dabigatran etexilate obtained according to Example 1.

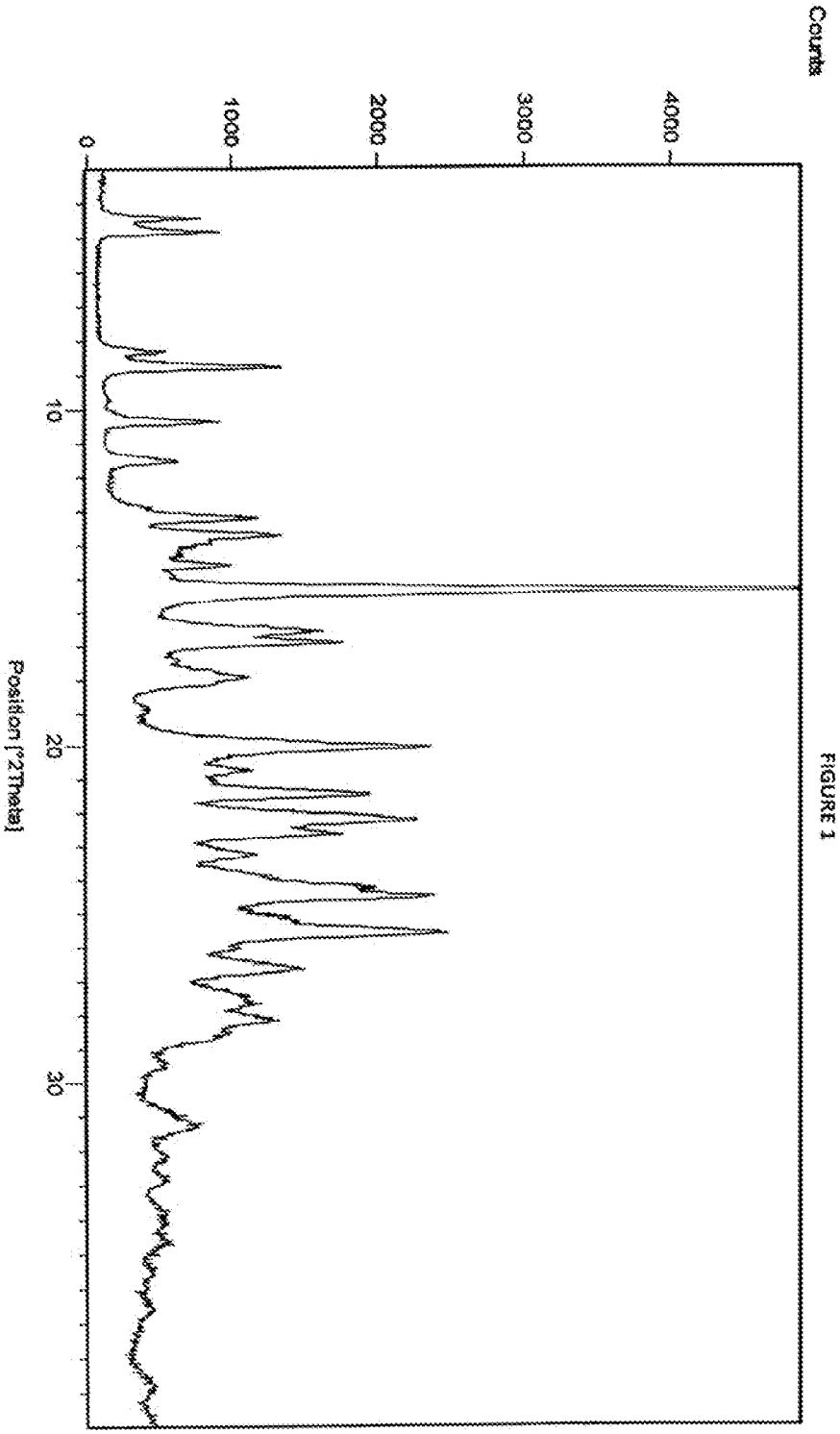


Figure 1A: Table of values for the XRPD pattern depicted in Figure 1.

Pos. [°2TH.]	d-spacing [Å]	Rel. Int. [%]
4.41	20.03	13.76
4.83	18.28	17.25
8.33	10.62	9.02
8.79	10.06	26.92
10.37	8.53	17.15
11.53	7.68	11.90
13.23	6.69	23.85
13.74	6.44	26.87
14.66	6.04	18.12
15.44	5.74	100.00
16.59	5.34	32.31
16.94	5.23	34.73
17.95	4.94	22.08
20.09	4.42	46.60
20.73	4.28	21.83
21.52	4.13	34.98
22.24	4.00	46.96
22.66	3.92	33.98
23.26	3.82	22.51
24.19	3.68	38.96
24.53	3.63	48.81
25.62	3.48	50.06
26.62	3.35	29.70
27.48	3.25	21.91
28.20	3.16	25.18
28.68	3.11	17.41
29.48	3.03	9.47
31.18	2.87	13.97
32.16	2.78	9.84
32.97	2.72	9.13
33.84	2.65	9.59
34.66	2.59	10.27
36.57	2.46	7.60
38.81	2.32	7.74

Figure 2: X-ray powder diffraction pattern (XRPD) of crystalline Form 2 of dabigatran etexilate obtained according to Example 2.

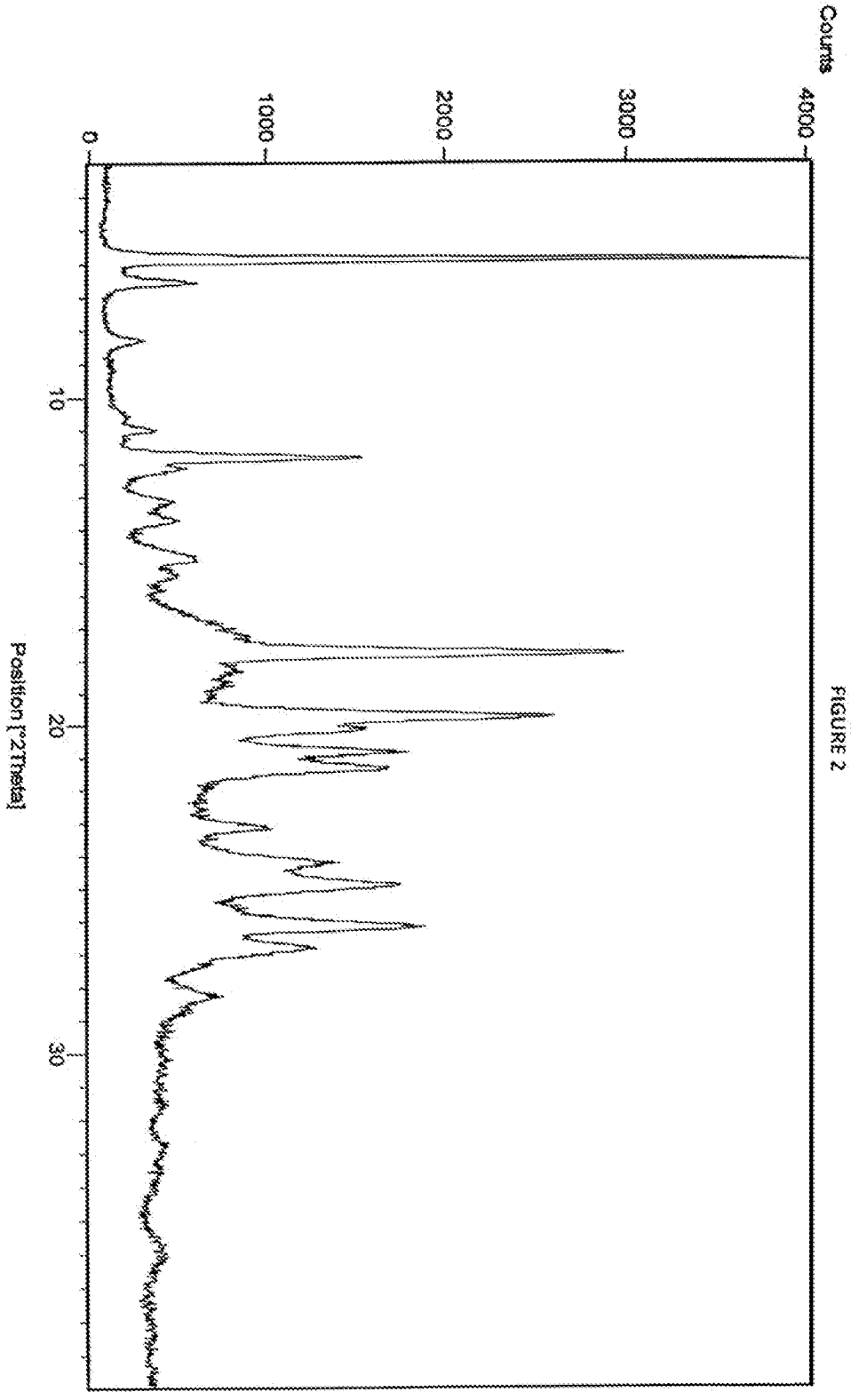


FIGURE 2

Figure 2A: Table of values for the XRPD pattern depicted in Figure 2.

Pos. [°2TH.]	d-spacing [Å]	Rel. Int. [%]
5.91	14.95	100.00
6.58	13.43	13.82
8.27	10.69	5.36
11.00	8.04	6.43
11.83	7.48	37.85
12.15	7.28	10.15
13.12	6.74	7.85
13.74	6.45	8.54
14.95	5.92	10.97
15.40	5.75	7.73
17.88	4.96	66.07
19.76	4.49	61.56
20.16	4.40	34.56
20.82	4.27	40.01
21.36	4.16	37.60
23.16	3.84	19.20
24.23	3.67	28.20
24.90	3.57	39.08
26.22	3.40	37.92
26.82	3.32	25.26
28.21	3.16	8.70
32.83	2.73	1.99
36.00	2.49	2.58

Figure 3: X-ray powder diffraction pattern (XRPD) of crystalline Form 3 of dabigatran etexilate obtained according to Example 3.

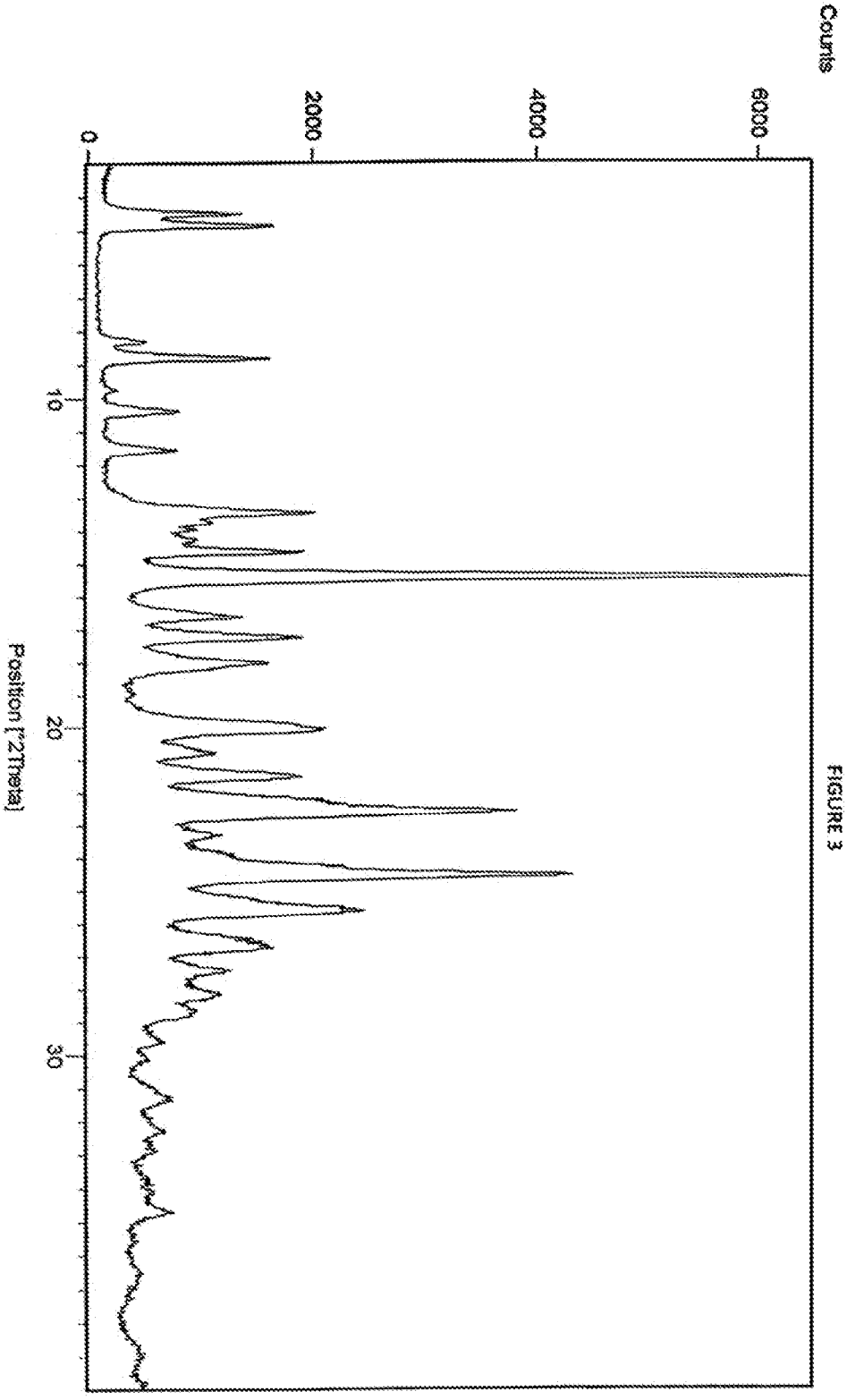


Figure 3A: Table of values for the XRPD pattern depicted in Figure 3.

Pos. [°2TH.]	d-spacing [Å]	Rel. Int. [%]
3.18	27.77	1.59
4.50	19.61	20.72
4.87	18.13	26.17
8.35	10.59	6.40
8.83	10.01	24.49
9.76	9.07	2.80
10.40	8.51	11.83
11.58	7.64	11.44
13.49	6.57	31.50
13.76	6.43	16.64
14.67	6.04	29.53
15.51	5.71	100.00
16.65	5.32	19.86
17.28	5.13	28.84
18.03	4.92	24.94
19.85	4.47	27.69
20.14	4.41	31.59
20.80	4.27	16.65
21.59	4.12	25.54
22.19	4.00	31.36
22.62	3.93	58.92
23.29	3.82	17.48
24.59	3.62	68.84
25.69	3.47	35.83
26.76	3.33	24.18
27.43	3.25	18.85
28.12	3.17	18.01
28.75	3.10	13.79
29.61	3.01	9.56
30.11	2.97	7.11
31.31	2.86	10.40
32.27	2.77	9.44
32.90	2.72	8.12
34.73	2.58	10.24
36.49	2.46	6.14
39.02	2.31	6.08

Figure 4: X-ray powder diffraction pattern (XRPD) of crystalline Form 4 of dabigatran etexilate obtained according to Example 4.

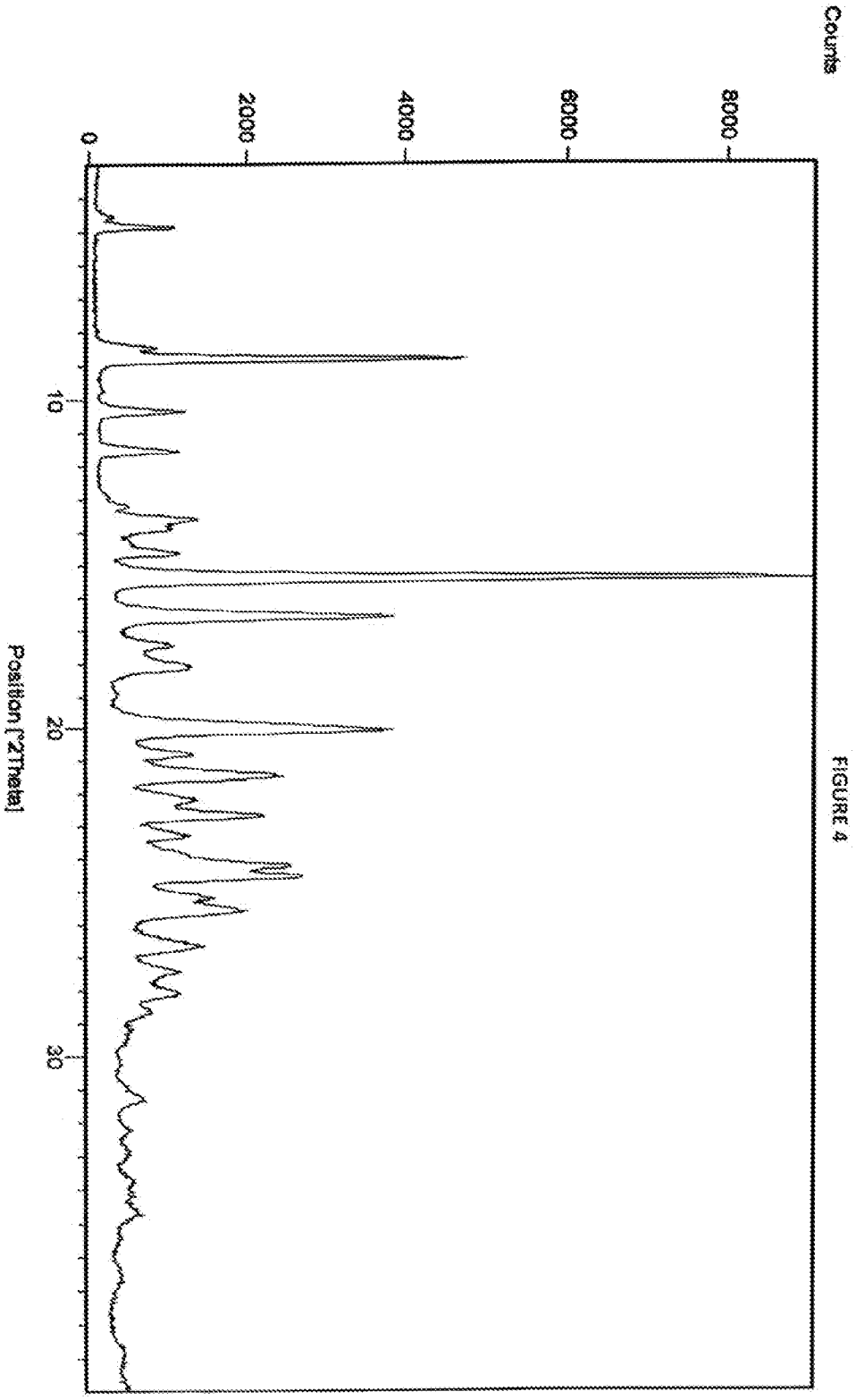


Figure 4A: Table of values for the XRPD pattern depicted in Figure 4.

Pos. [°2TH.]	d-spacing [Å]	Rel. Int. [%]
4.90	18.05	11.62
8.46	10.45	9.38
8.84	10.00	52.24
10.37	8.53	14.14
11.63	7.61	11.69
13.21	6.70	5.53
13.61	6.50	16.23
13.97	6.34	11.28
14.69	6.03	12.79
15.50	5.71	100.00
16.63	5.33	45.82
17.42	5.09	12.45
18.19	4.88	15.22
20.12	4.41	42.86
20.80	4.27	15.38
21.53	4.13	26.81
22.17	4.01	16.25
22.73	3.91	24.26
23.32	3.81	14.93
24.20	3.68	32.41
24.61	3.62	3045
25.17	3.54	18.91
25.61	3.48	23.78
26.68	3.34	17.09
27.42	3.25	13.87
28.11	3.17	13.38
28.64	3.12	9.16
29.54	3.02	5.25
31.35	2.85	7.55
32.23	2.78	5.73
32.91	2.72	5.69
33.74	2.66	6.28
34.70	2.58	7.16
36.59	2.46	4.32
38.84	2.32	4.83

Figure 5: Differential Scanning Calorimetry (DSC) thermogram of crystalline Form 1 of dabigatran etexilate obtained according to Example 1.

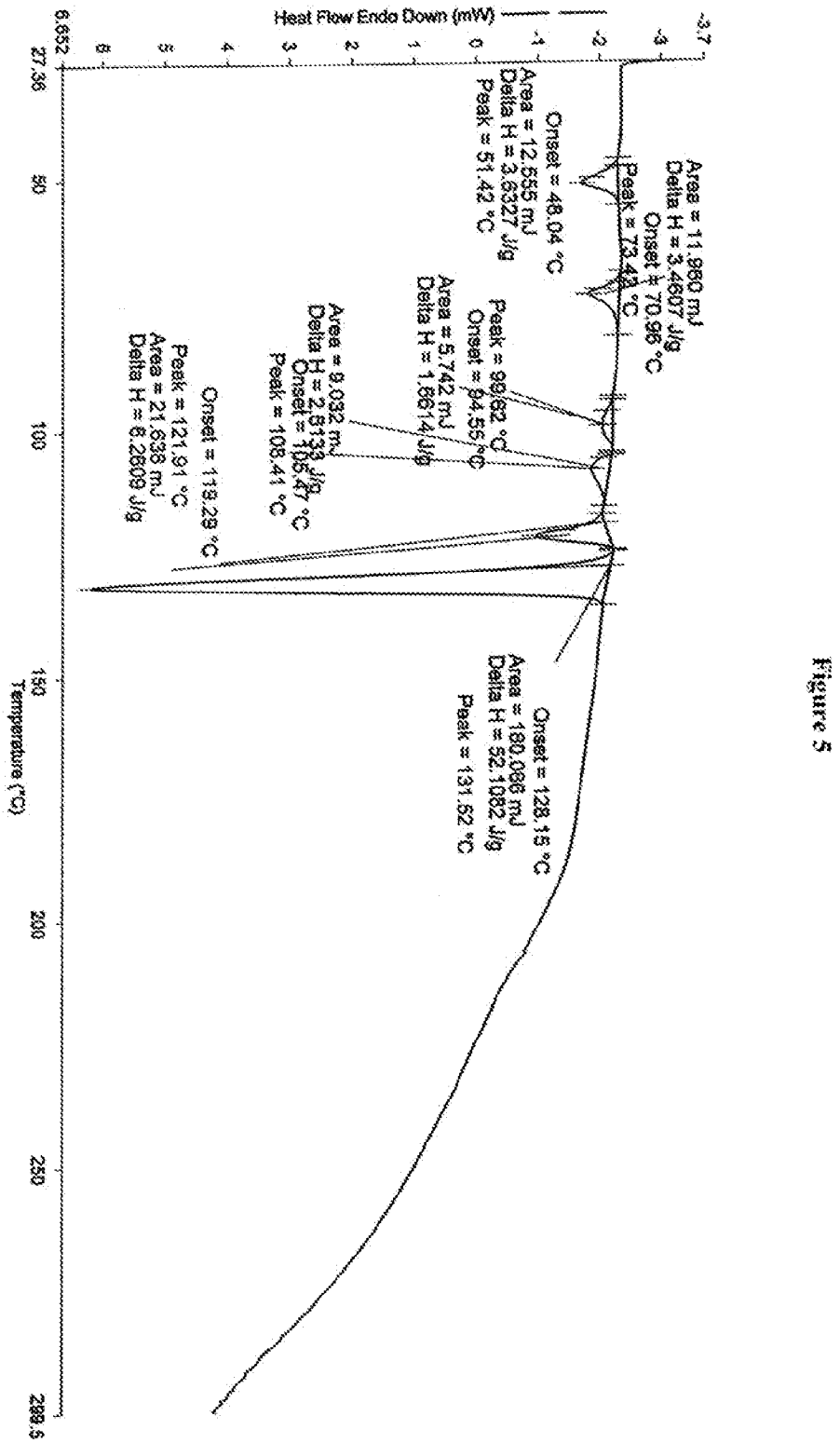


Figure 5

Figure 6: Differential Scanning Calorimetry (DSC) thermogram of crystalline Form 2 of dabigatran etexilate obtained according to Example 2.

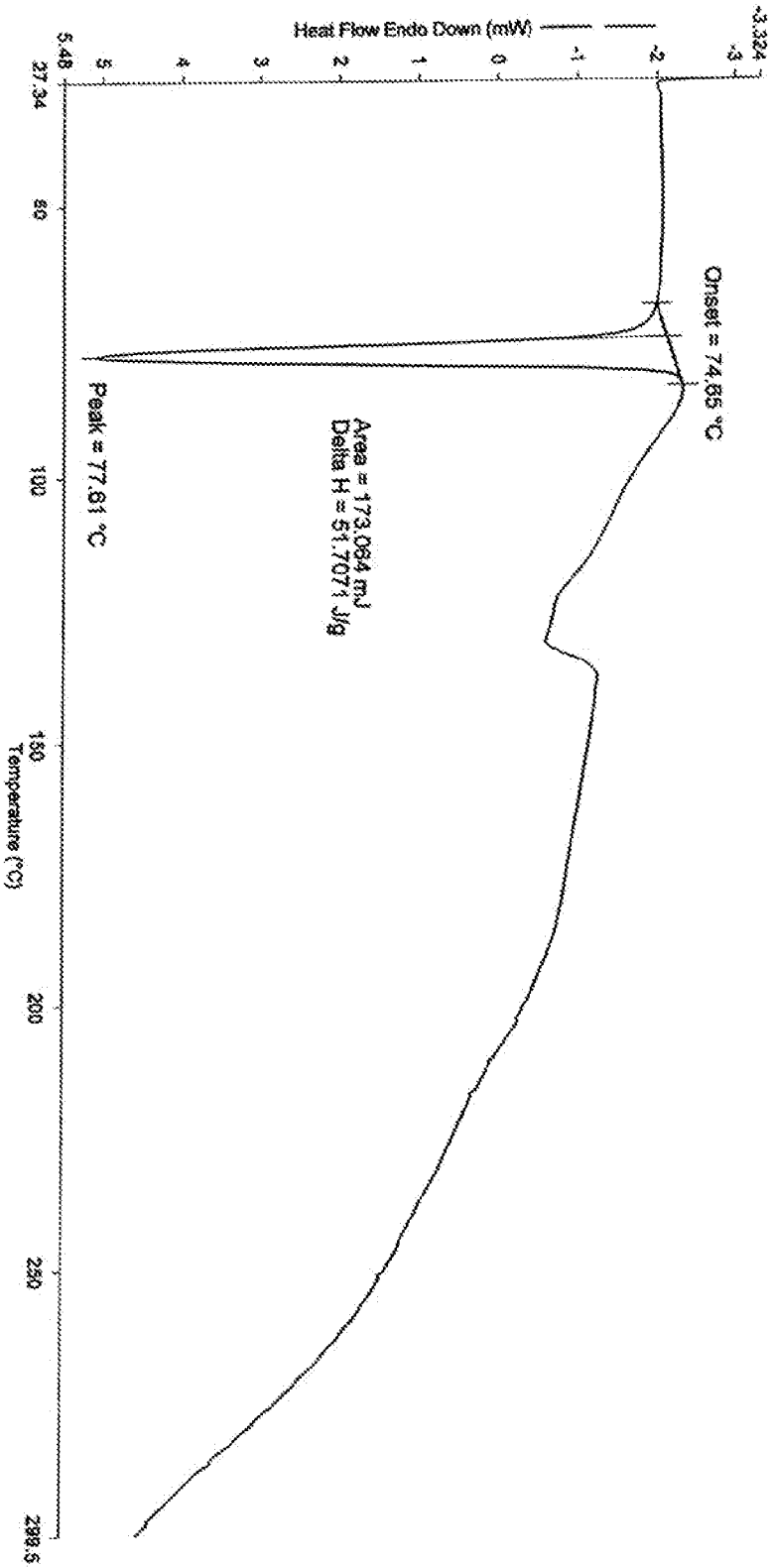


Figure 6

Figure 7: Differential Scanning Calorimetry (DSC) thermogram of crystalline Form 3 of dabigatran etexilate obtained according to Example 3.

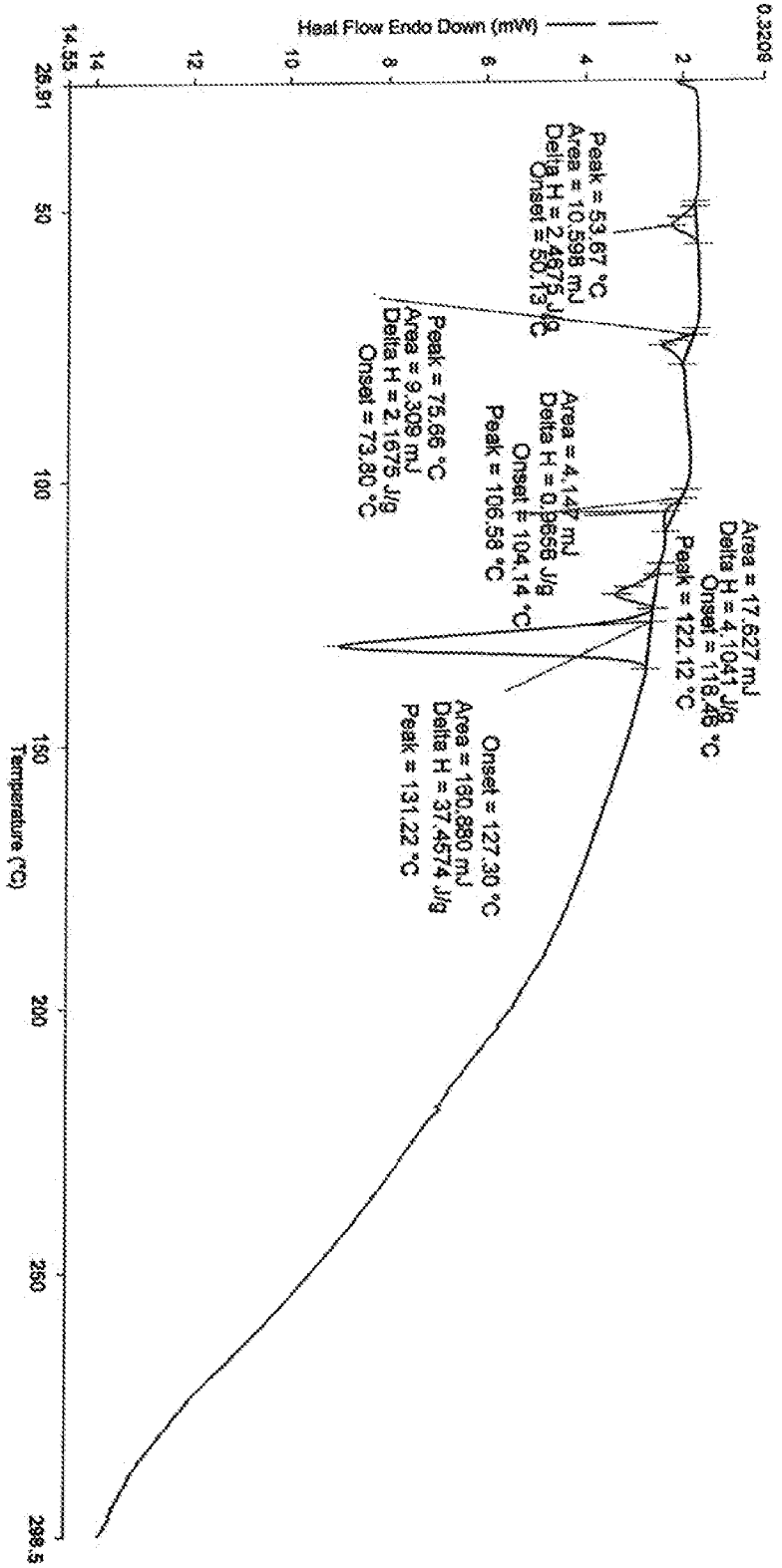


Figure 7