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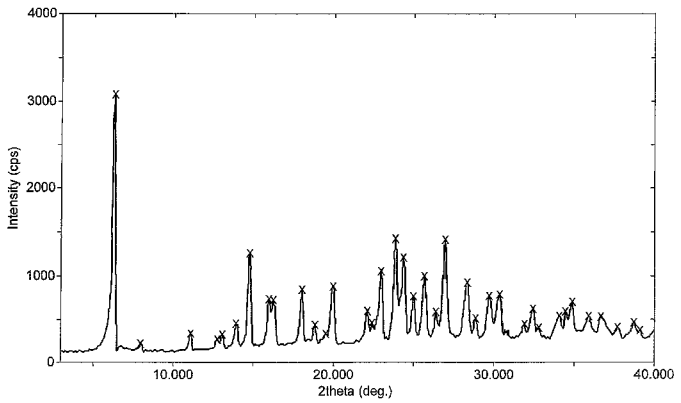

FIG. 1

(57) Abstract: The present invention provides a polymorph of esomeprazole potassium termed "Form C", which is in the form of an ethanol solvate. There is also provided processes for preparing Form C of esomeprazole potassium and pharmaceutical compositions comprising it.

ESOMEPRAZOLE POTASSIUM POLYMORPH AND ITS PREPARATION

Field of the Invention

The present invention relates to a crystalline form of 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium (esomeprazole potassium), a process for its preparation and pharmaceutical compositions thereof.

Background and Prior Art

Omeprazole, chemically known as 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, is a proton pump inhibitor and exists as a racemic mixture containing equal amounts of both (R) and (S)-enantiomers. As compared to a racemic mixture, (S)-enantiomer of omeprazole has shown to possess improved efficacy and hence is mostly used in pharmaceutical compositions.

US 5,948,789 and US 5,693,818 disclose processes for resolving enantiomers of omeprazole from their racemic mixture.

WO2005/023797 discloses a preparation of salts of the (R)- and (S)-enantiomers of omeprazole.

Certain salts of (S)-enantiomer of omeprazole and their preparation are disclosed in EP0897386, EP1885711, EP1801110, WO2005082888 and WO2007142580.

EP2000468 discloses esomeprazole salts and processes for their preparation. EP2000468 discloses seven crystalline polymorphs of the potassium salt of esomeprazole, processes for their preparation (examples 14 to 20) and their respective XRPD patterns (figures 13 to 19).

EP1919897 discloses a method of preparing optically pure esomeprazole, and its salt, from omeprazole by applying an optical resolution process. Example 19 refers to a preparation of the monohydrate of the potassium salt of esomeprazole.

WO98/54171 discloses a synthesis of the magnesium salt of esomeprazole trihydrate, wherein the potassium salt of esomeprazole is used as an intermediate. The intermediate esomeprazole potassium, which is a methanol solvate, is hereinafter designated as Form A.

WO2000/044744 discloses Form B characterized as being a hydrate of esomeprazole potassium, the process for its preparation and pharmaceutical compositions thereof.

WO2007/148213 discloses Form X of esomeprazole potassium which is crystallised using a dichloromethane solvent.

WO2008/102145 discloses the preparation of esomeprazole magnesium dihydrate. The magnesium dihydrate form may be prepared from the potassium salt of esomeprazole.

Summary of the Invention

According to a first aspect of the present invention, there is provided a new crystalline form of esomeprazole potassium which is hereinafter designated as "Form C".

Crystalline Form C of esomeprazole potassium is an ethanol solvate. The amount of ethanol in the polymorph may range from about 5% to about 25% by weight of the esomeprazole potassium, typically from about 10% to about 20% by weight of the esomeprazole potassium. In an embodiment, the amount of ethanol in the polymorph may be about 15% by weight of the esomeprazole potassium.

The Form C ethanol solvate may be characterised by having an X-ray powder diffraction (XRPD) pattern comprising peaks at 13.1 and 14.0 °2θ ± 0.2 °2θ. The XRPD pattern may

further comprise peaks at 6.3, 14.8, 16.0 and 16.3 °2θ ± 0.2 °2θ. The XRPD pattern may comprise yet further peaks at 8.0 and 12.7 °2θ ± 0.2 °2θ. The XRPD pattern may comprise still further peaks at 18.0, 18.8, 23.0, 23.9 and 25.7 °2θ ± 0.2 °2θ. Thus, in an embodiment, the XRPD pattern may comprise peaks at 6.3, 8.0, 12.7, 13.1, 14.0, 14.8, 16.0, 16.3, 18.0, 18.8, 23.0, 23.9 and 25.7 °2θ ± 0.2 °2θ. The XRPD pattern may comprise still yet further peaks at 20.0, 24.4, 25.0, 27.0, 28.3, 29.7, 30.3 and 34.8 2θ ± 0.2 °2θ. The XRPD pattern may yet further comprise peaks at 11.1, 19.5, 22.1, 22.4, 26.4, 28.8, 30.8, 31.9, 32.4, 32.7, 34.0, 34.4, 35.9, 36.6, 37.7, 38.7 and 39.1 °2θ ± 0.2 °2θ.

Therefore, in an embodiment, crystalline Form C of esomeprazole potassium ethanol solvate is characterised by having an X-ray powder diffraction (XRPD) pattern comprising peaks at the °2θ positions (± °2θ) as shown in Table 1.

Peak listing (°2θ ± °2θ)
6.3
8.0
11.1
12.7
13.1
14.0
14.8
16.0
16.3
18.0
18.8
19.5
20.0
22.1
22.4
23.0
23.9
24.4
25.0
25.7
26.4
27.0

28.3
28.8
29.7
30.3
30.8
31.9
32.4
32.7
34.0
34.4
34.8
35.9
36.6
37.7
38.7
39.1

The d-values corresponding to the peaks listed above, as measured by the Rigaku diffractometer detailed below, and as shown in Figure 1, are shown in Table 2 below.

In an embodiment, crystalline Form C of esomeprazole potassium ethanol solvate is characterised by having an X-ray powder diffraction (XRPD) pattern as shown in Figure 1.

In another embodiment, crystalline Form C of esomeprazole potassium ethanol solvate is characterised by having an infrared spectrum with characteristic IR spectra peaks at about 3397 cm^{-1}, 2937 cm^{-1}, 1611 cm^{-1}, 1563 cm^{-1}, 1476 cm^{-1}, 1439 cm^{-1}, 1378 cm^{-1}, 1358 cm^{-1}, 1296 cm^{-1}, 1267 cm^{-1}, 1224 cm^{-1}, 1198 cm^{-1}, 1151 cm^{-1}, 1074 cm^{-1}, 1033 cm^{-1}, 1000 cm^{-1}, 949 cm^{-1}, 872 cm^{-1}, 836 cm^{-1}, 817 cm^{-1}, 801 cm^{-1}.

In an embodiment, crystalline Form C of esomeprazole potassium ethanol solvate is characterised by having an IR spectrum as shown in Figure 2.

In a further embodiment, crystalline Form C of esomeprazole potassium ethanol solvate is characterized by having a DSC thermogram exhibiting a significant exothermic peak at

112.71^{0}C and endothermic peak at 206.99^{0}C. The DSC of crystalline esomeprazole potassium Form C is shown in Figure 3.

In an embodiment, crystalline Form C of esomeprazole potassium ethanol solvate has a purity of greater than or equal to about 95%, preferably greater than or equal to about 99%, more preferably greater than or equal to about 99.8%.

According to another aspect of the present invention, there is provided a process for preparing crystalline Form C of esomeprazole potassium ethanol solvate. The process comprises treating esomeprazole with a potassium source to obtain the esomeprazole potassium salt, dissolving the salt in a first solvent, adding ethanol to the reaction mass and isolating the crystalline Form C. In an embodiment, the process comprises concentrating the solution of the salt in the first solvent to obtain a residue, adding the ethanol to the residue, and isolating the crystalline Form C. Advantageously, the process highly reproducible

The potassium source may be selected from methanolic potassium hydroxide, ethanolic potassium hydroxide or methanolic potassium methoxide.

The first solvent used for dissolving esomeprazole potassium may be a polar aprotic solvent which may be selected from dichloromethane, tetrahydrofuran, acetonitrile, acetone, methyl isobutyl ketone and methyl ethyl ketone. Preferably the first solvent used in the process is acetone. The solution of esomeprazole potassium in the first solvent may be concentrated under vacuum to yield a residue.

The residue obtained on concentration may be stirred at a temperature ranging from about 20^{0}C to about 25^{0}C in the ethanol. The solution thus obtained is typically cooled to a temperature ranging from about 0^{0}C to about 10^{0}C, preferably from about 0^{0}C to about 5^{0}C. The resulting solid may be dried under vacuum at a temperature ranging from about 35^{0}C to about 50^{0}C, preferably at a temperature ranging from about 40^{0}C to about 45^{0}C to obtain Form C esomeprazole potassium.

The esomeprazole free base starting material may be prepared in accordance with the procedures described in WO2008/102145.

According to another aspect of the present invention, there is provided crystalline Form C of esomeprazole potassium prepared according to the process described above.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising esomeprazole potassium Form C as described above together with one or more pharmaceutically acceptable excipients.

According to another aspect of the present invention, there is provided esomeprazole potassium Form C described above for use in medicine, particularly for use as a gastric acid secretion suppressant.

According to another aspect of the present invention, there is provided esomeprazole potassium Form C described above for use in suppressing gastric acid secretion.

According to another aspect of the present invention, there is provided a method of suppressing gastric acid secretion, the method comprising administering a therapeutically effective amount of esomeprazole potassium Form C described above to a patient in need thereof.

Brief Description of the Drawings

Figure 1 shows the powder X-ray diffractogram (XRPD) pattern of crystalline Form C of esomeprazole potassium ethanol solvate.

Figure 2 shows the FT-IR (KBr) spectrum of crystalline Form C of esomeprazole potassium ethanol solvate.

Figure 3 shows the Differential Scanning Calorimetry (DSC) thermogram of crystalline Form C of esomeprazole potassium ethanol solvate.

Detailed Description of the Invention

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

The present invention relates to a new stable polymorphic form of esomeprazole potassium which is hereinafter designated as Form C.

The present invention provides a process for preparing stable esomeprazole potassium Form C, having good flow characteristics, in high yield and purity.

The crystalline nature of polymorph Form C of esomeprazole potassium has been analysed, characterized and differentiated by X-ray diffractogram, infrared spectrum and differential scanning calorimetry thermogram techniques.

The X-ray powder diffraction pattern of crystalline polymorph Form C of esomeprazole potassium was measured on a Rigaku Dmax 2200 advanced X-ray powder diffractometer with a copper-K-α radiation source. The details of the diffractometer are as follows.

Instrument - RIGAKU MINIFLEX

1. Source :	Cu K-α
2. Scan axis :	theta/2theta
3. Voltage :	30Kv
4. Current :	15mA
5. Measurement method :	Continuous
6. Scanning range :	3° to 40° 2θ
7. Counting unit :	Cps

8. Divergence slit : Variable
9. Receiving slit : 0.3mm
10. Detector type : Scintillation counter
11.Wavelength : 1.5405Å
12. Goniometer speed : 2° 2θ/min

In an embodiment, the present invention provides crystalline Form C of esomeprazole potassium ethanol solvate characterized by having an XRPD pattern with d-values as listed in Table 2. In an embodiment, the present invention provides crystalline Form C of esomeprazole potassium ethanol solvate characterized by having an XRPD pattern with peaks at the °2θ positions (± 0.2 °2θ) as listed in Table 2.

Table 2: XRPD values of Form C

Peak listing (°2θ)	Diffraction angles (d value)	Relative Intensity
6.3	14.0	100
8.0	11.1	7
11.1	8.0	11
12.7	6.9	9
13.1	6.8	11
14.0	6.3	15
14.8	6.0	41
16.0	5.5	24
16.3	5.4	24
18.0	4.9	27
18.8	4.7	14
19.5	4.5	11
20.0	4.4	28
22.1	4.0	19
22.4	4.0	14
23.0	3.9	33
23.9	3.7	46
24.4	3.6	39
25.0	3.6	24
25.7	3.5	31

26.4	3.4	18
27.0	3.3	45
28.3	3.2	29
28.8	3.1	16
29.7	3.0	24
30.3	2.9	25
30.8	2.9	10
31.9	2.8	13
32.4	2.8	19
32.7	2.7	12
34.0	2.6	16
34.4	2.6	18
34.8	2.6	21
35.9	2.5	16
36.6	2.5	16
37.7	2.4	12
38.7	2.3	13
39.1	2.3	10

The present invention also provides crystalline Form C of esomeprazole potassium ethanol solvate characterized by having a FT-IR (KBr disk) spectrum having characteristic peaks at 3397 cm^{-1}, 2937 cm^{-1}, 1611 cm^{-1}, 1563 cm^{-1}, 1476 cm^{-1}, 1439 cm^{-1}, 1378 cm^{-1}, 1358 cm^{-1}, 1296 cm^{-1}, 1267 cm^{-1}, 1224 cm^{-1}, 1198 cm^{-1}, 1151 cm^{-1}, 1074 cm^{-1}, 1033 cm^{-1}, 1000 cm^{-1}, 949 cm^{-1}, 872 cm^{-1}, 836 cm^{-1}, 817 cm^{-1}, 801 cm^{-1}, for example as depicted in Figure 2.

In another aspect, the present invention provides crystalline Form C of esomeprazole potassium ethanol solvate characterized by having a differential scanning calorimetry thermogram exhibiting a significant exothermic peak at 112.71^{0}C and endothermic peak at 206.99^{0}C. The DSC of Form C of esomeprazole potassium of the present invention is depicted in Figure 3.

In another aspect, the present invention provides a process for preparing crystalline esomeprazole potassium which comprises:

(a) preparing the potassium salt of esomeprazole by treating esomeprazole with a potassium source;

(b) dissolving esomeprazole potassium in first solvent and concentrating to obtain a residue;

(c) stirring the residue in a second solvent;

(d) cooling and isolating crystalline esomeprazole potassium.

The crystalline forms prepared according to the above process also form another aspect of the present invention.

The potassium source used for preparing the esomeprazole potassium salt may be selected from methanolic potassium hydroxide, ethanolic potassium hydroxide or methanolic potassium methoxide.

The first solvent used for dissolving esomeprazole potassium may be a polar aprotic solvent which may be selected from dichloromethane, tetrahydrofuran, acetonitrile, acetone, methyl isobutyl ketone and methyl ethyl ketone. Preferably the first solvent used in the process is acetone. The solution of esomeprazole potassium is concentrated under vacuum to yield the residue.

The residue obtained on concentration may be stirred at a temperature ranging from about 20^0C to about 25^0C in a second solvent which may be selected from ethanol, isopropyl alcohol and n-butanol, most preferably ethanol (in which case Form C of esomeprazole potassium is formed). The solution thus obtained is cooled to 0-10^0C, preferably at 0-5^0C. The resulting solid is dried under vacuum at 35 - 50^0C preferably at 40 - 45^0C to obtain crystalline esomeprazole potassium. When ethanol is the second solvent, an ethanol solvate is formed.

The esomeprazole free base starting material may be prepared in accordance with the procedures disclosed in WO2008/102145.

The Form C esomeprazole potassium ethanol solvate of the present invention is readily isolated, shows reproducibility, is safe to handle during manufacturing and shows stability on isolation and drying.

The process of the present invention is simple, economical and highly reproducible and provides Form C esomeprazole potassium ethanol solvate in relatively high purity of greater than or equal to about 95%, preferably greater than or equal to about 99%, more preferably greater than or equal to 99.8%.

The following examples will further illustrate the preparation of potassium salt of esomeprazole Form C, but are not intended to limit the scope of the invention as defined hereinabove or as claimed.

Examples

Example 1 -

In a reactor, toluene (250 ml) followed by D-(-)-diethyl tartrate (9.5 g) and titanium (IV) isopropoxide (6.5 g) are added and contents stirred for 15 minutes. Based on the moisture content of reaction mass, upto 0.4% water was added and contents stirred for 30 minutes at 25-30°C to form a chiral titanium complex. Further, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (50 g) was added to the complex and the contents heated to 70°C over a period of 1 hour and maintained at 70 - 75°C for 30 minutes. The reaction mass was then cooled to 10 - 15°C and cumene hydroperoxide (57 g) was slowly added at 10 - 15°C over a period of 3 hours.

After completion of reaction, methanolic potassium hydroxide solution (10 g of potassium hydroxide dissolved in 100 ml of methanol) was added at 10 - 15°C, reaction mass was stirred at 25 - 30°C for 2 hours and contents chilled to 10°C. The precipitated product was filtered under nitrogen atmosphere and washed with toluene (75 ml). The solid was

dissolved in acetone (1000 ml). The solvent was displaced off with methanol (82 ml) to obtain pure potassium salt of esomeprazole (33.3 g, 63% yield and 99.0% purity).

25 g of pure esomeprazole potassium was dissolved in 250 ml acetone, concentrated at 55 - 60°C and solvent was distilled off under vacuum. To this 25 ml of ethanol was added and solution was stirred at 25 - 30°C for 1 hour. The solution was cooled to 0 - 5°C, filtered and then dried under vacuum at 40 - 45°C to obtain esomeprazole potassium Form C (19.5 g).

Yield = 78 %
Purity = 99.8 %
Residual ethanol content – 10 - 20% (determined by gas chromatography)
Water content – Not more than 3.0%
Tap and Bulk density – 0.40 g/mL

Example 2 -

A solution of 20 g of esomeprazole potassium in acetone (200 ml) was concentrated at 55 - 60°C and solvent was distilled off under vacuum below 50^0C. Ethanol (20 ml) was added and contents stirred at 25 - 30°C for 1 hour. The solution was cooled to 0 - 5°C, filtered and then dried under vacuum at 40 - 45°C to obtain esomeprazole potassium Form C (15.2 g).

Yield = 76 %
Purity = 99.7 %
Residual ethanol content – 10 - 20% (determined by gas chromatography)
Water content – Not more than 3.0%
Tap and Bulk density – 0.38 g/mL

Example 3 -

Toluene (125 ml) was charged followed by D-(-)-diethyl tartrate (4.75 g), titanium (IV) isopropoxide (3.25 g) and stirred for 15 minutes. To this water was charged up to 0.4% based on the moisture content of reaction mass. The reaction mass was stirred for 30 minutes at 25 - 30°C to form a chiral titanium complex. Further, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (25 g) was charged to the complex and the contents were heated to 70°C over a period of 1 hour and maintained at 70 - 75°C for 30 minutes. The reaction mass was then cooled to 10 - 15°C, cumene hydroperoxide (28.5 g) was slowly added at 10 - 15°C over a period of 3 hours.

After reaction completion methanolic potassium hydroxide solution (5 g of potassium hydroxide dissolved in 50 ml of methanol) was added to the reaction mass at 10 - 15°C, the contents were stirred at 25 - 30°C for 2 hours and chilled to 10°C. The precipitated product was filtered under nitrogen atmosphere, washed with toluene (40 ml). The precipitated esomeprazole potassium was dissolved in 125 ml acetone at 50 - 55°C, clarified, and distilled off solvent completely under vacuum. To this 25 ml of ethanol was added and solution was stirred at 25 - 30°C for 1 hour. The solution was cooled to 0 - 5°C, filtered and then dried under vacuum at 40 - 45°C to obtain esomeprazole potassium Form C (18 g).

Yield = 68 %

Purity = 99.4 %

Residual ethanol content – 10 – 20% (determined by gas chromatography)

Water content – Not more than 3.0%

Tap and Bulk density – 0.41 g/mL

Example 4 -

Toluene (125 ml), D-(-)-diethyl tartrate (4.7 g) and titanium (IV) isopropoxide (3.2 g) were charged in reaction vessel and stirred for 15 minutes. To this up to 0.4% water based on the moisture content was added and stirring continued for 30 minutes at 25 - 30°C to form a chiral titanium complex. Further, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]thio]-1H-benzimidazole (25 g) was added to the mass and contents were heated to

70°C over a period of 1 hour and maintained at 70 - 75°C for 30 minutes. After cooling the reaction mass to 10 - 15°C, cumene hydroperoxide (28.5 g) was slowly added at 10 - 15°C over a period of 3 hours.

After reaction completion, an ethanolic solution of potassium hydroxide (5 g of potassium hydroxide dissolved in 50 ml of ethanol) was added to the reaction mass at 10 - 15°C, content was stirred at 25 - 30°C for 2 hours and chilled to 10°C. The precipitated product was filtered and dissolved in 125 ml acetone at 50 - 55°C, clarified, and the solvent was distilled off completely under vacuum. To this 25 ml of ethanol was added and solution was stirred at 25 - 30°C for 1 hour. The solution was cooled to 0 - 5°C, filtered and then dried under vacuum at 40 - 45°C to obtain esomeprazole potassium Form C (18.2 g).

Yield = 69%

Purity = 99.7%

Residual ethanol content – 10 – 20% (determined by gas chromatography)

Water content – Not more than 3.0%

Tap and Bulk density – 0.39 g/mL

It will be appreciated that the invention may be modified within the scope of the appended claims.

CLAIMS

1. Form C esomeprazole potassium ethanol solvate.

2. Form C according to claim 1, characterised by having an X-ray powder diffraction pattern comprising peaks at 13.1 and 14.0 °2θ ± 0.2 °2θ.

3. Form C according to claim 2, wherein the X-ray powder diffraction pattern further comprises peaks at 6.3, 14.8, 16.0 and 16.3 °2θ ± 0.2 °2θ.

4. Form C according to claim 3, wherein the X-ray powder diffraction pattern further comprises peaks at 8.0 and 12.7 °2θ ± 0.2 °2θ.

5. Form C according to claim 4, wherein the X-ray powder diffraction pattern further comprises peaks at 18.0, 18.8, 23.0, 23.9 and 25.7 °2θ ± 0.2 °2θ.

6. Form C according to claim 5, wherein the X-ray powder diffraction pattern further comprises peaks at 20.0, 24.4, 25.0, 27.0, 28.3, 29.7, 30.3 and 34.8 2θ ± 0.2 °2θ.

7. Form C according to claim 1, characterised by having an X-ray powder diffraction pattern as shown in Figure 1.

8. Form C according to any preceding claim, characterised by having an FTIR spectrum as shown in Figure 2.

9. Form C according to any preceding claim, characterised by having a DSC thermogram exhibiting a significant exothermic peak at 112.71^{0}C and endothermic peak at 206.99^{0}C.

10. Form C according to any preceding claim, characterised by having a DSC thermogram as shown in Figure 3.

11. Form C according to any preceding claim, wherein the amount of ethanol in the polymorph ranges from about 10% to about 20% by weight of the esomeprazole potassium.

12. A process for preparing Form C of esomeprazole potassium ethanol solvate according to any preceding claim, the process comprising reacting esomeprazole with a potassium source to obtain the esomeprazole potassium salt, dissolving the salt in a first solvent, adding ethanol and isolating the Form C.

13. A process according to claim 12, wherein the process comprises concentrating the solution of the salt in the first solvent to obtain a residue, adding the ethanol to the residue, and isolating the Form C.

14. A process according to claim 12 or 13, wherein the potassium source is selected from methanolic potassium hydroxide, ethanolic potassium hydroxide or methanolic potassium methoxide.

15. A process according to claim 12, 13 or 14, wherein the first solvent is a polar aprotic solvent.

16. A process according to any one of claims 12 to 15, wherein the first solvent is selected from dichloromethane, tetrahydrofuran, acetonitrile, acetone, methyl isobutyl ketone and methyl ethyl ketone

17. A process according to claim 16, wherein the first solvent is acetone.

18. Form C of esomeprazole potassium ethanol solvate prepared according to a process defined in any one of claims 12 to 17.

19. A pharmaceutical composition comprising Form C esomeprazole potassium ethanol solvate according to any one of claims 1 to 11 and 18, together with one or more pharmaceutically acceptable excipients.

20. Form C esomeprazole potassium ethanol solvate according to any one of claims 1 to 11 and 18 for use in medicine

21. Form C esomeprazole potassium ethanol solvate according to any one of claims 1 to 11 and 18 for use as a gastric acid secretion suppressant.

22. Form C esomeprazole potassium ethanol solvate according to any one of claims 1 to 11 and 18 for use in suppressing gastric acid secretion.

23. A method of suppressing gastric acid secretion, the method comprising administering a therapeutically effective amount of Form C esomeprazole potassium ethanol solvate according to any one of claims 1 to 11 and 18 to a patient in need thereof.

24. Form C esomeprazole potassium ethanol solvate substantially as herein described with reference to the Figures.

25. Form C esomeprazole potassium ethanol solvate substantially as herein described with reference to the Examples.

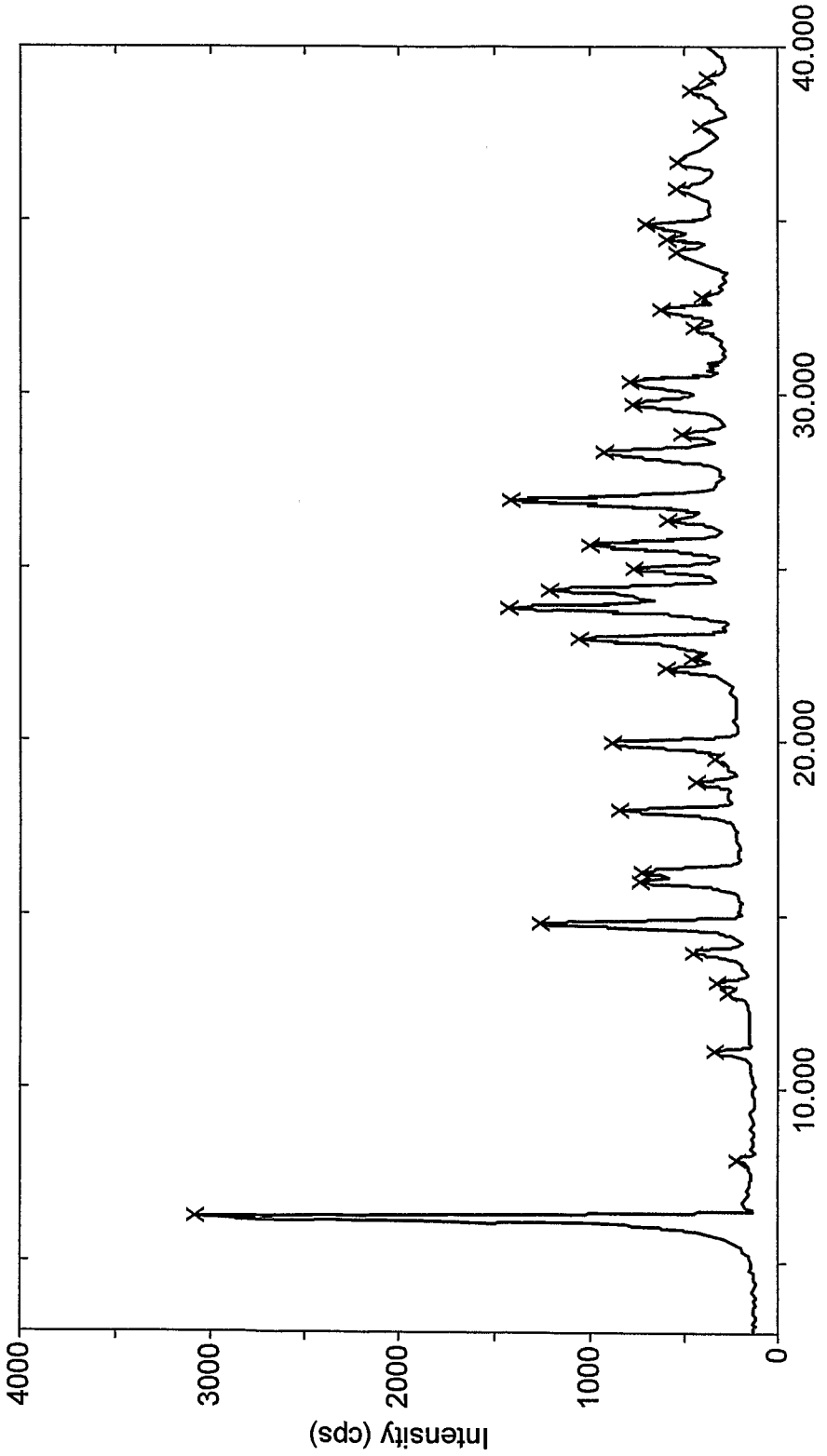
Intensity (cps)
4000
3000
2000
1000
0
10.000
20.000
30.000
40.000
2theta (deg.)

FIG. 1

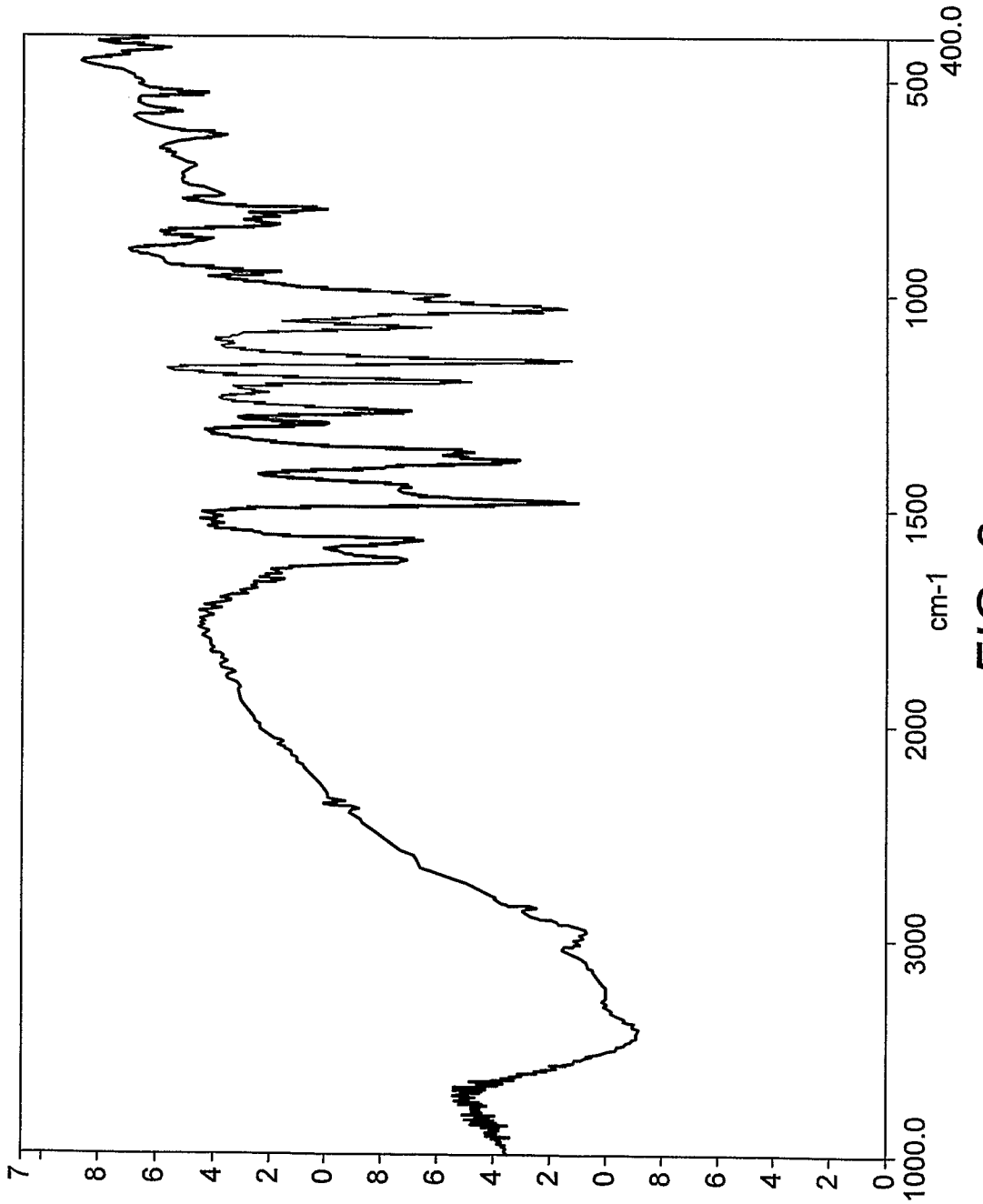

FIG. 2

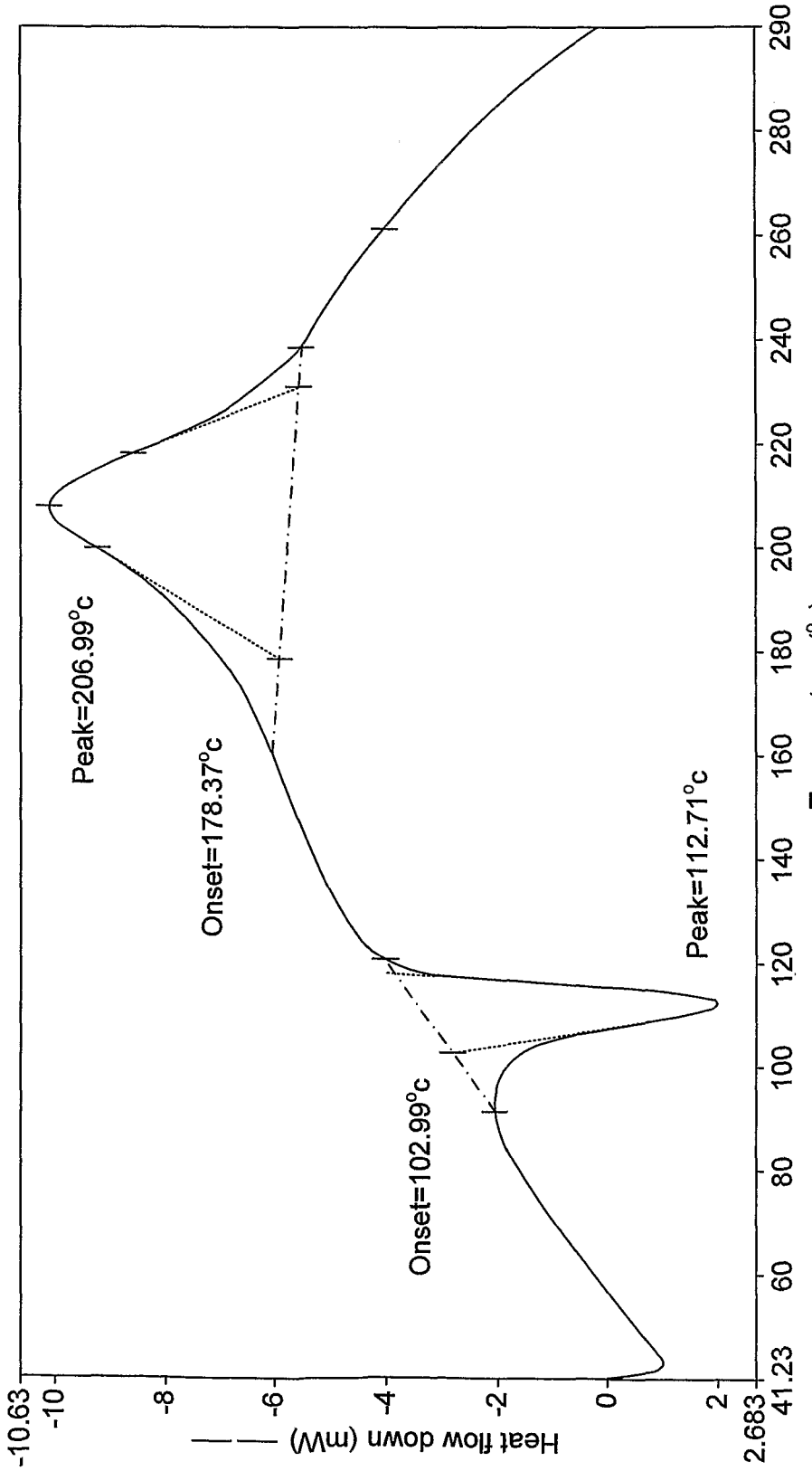
Peak=206.99°c
Onset=178.37°c
Onset=102.99°c
Peak=112.71°c
Heat flow down (mW)
Temperature (°c)
-10.63
-10
-8
-6
-4
-2
0
2
2.683
41.23
60
80
100
120
140
160
180
200
220
240
260
280
290

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000333

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/4439 A61P1/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/027614 A2 (UNIVERSITE DE ROUEN, FR.) 5 March 2009 (2009-03-05) page 17; figure 4; example 10; table 1	1-12, 18-25
Y	WO 2007/148213 A2 (GLENMARK PHARMACEUTICALS LTD [IN]; KUMAR BOBBA VENKATA SIVA [IN]; KULK) 27 December 2007 (2007-12-27) cited in the application page 10 - page 11; claim 1	1-25
Y	WO 2008/102145 A2 (CIPLA LTD [IN]; CURTIS PHILIP ANTHONY [GB]; RAO DHARMARAJ RAMACHANDRA) 28 August 2008 (2008-08-28) page 7; claim 29	1-25

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2010	09/04/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Skulj, Primoz

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000333

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No
PCT/GB2010/000333

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