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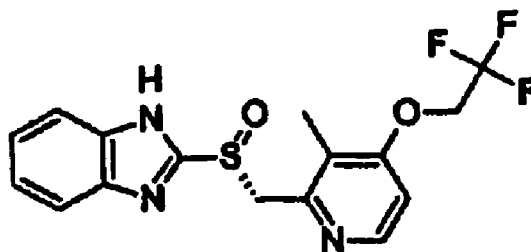
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(54) Title: PROCESS FOR THE PREPARATION OF DEXLANSOPRAZOLE



(57) Abstract: The present invention relates to a process for the preparation of crystalline dexlansoprazole.

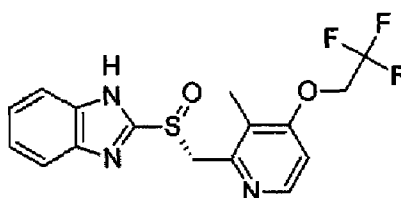
PROCESS FOR THE PREPARATION OF DEXLANSOPRAZOLE

Field of the Invention

The present invention relates to a process for the preparation of crystalline dexlansoprazole.

Background of the Invention

Dexlansoprazole is chemically described as 2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole as represented by Formula I.



FORMULA I

Dexlansoprazole is useful for healing of all grades of erosive esophagitis (EE) for up to 8 weeks, to maintain healing of EE for up to 6 months, and for the treatment of heartburn associated with non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

U.S. Patent Nos. 6,462,058 and 7,285,668 and U.S. Patent Application No. 2007/0004779 describe the processes for preparing crystalline forms of dexlansoprazole and its hydrates. WO 2009/117489 describes the process for the preparation of amorphous dexlansoprazole.

According to U.S. Patent No. 7,271,182, sodium salt, magnesium salt, lithium salt, potassium salt, calcium salt, or barium salt of dexlansoprazole are obtained by reacting dexlansoprazole with a metal hydroxide, a metal alkoxide or a metal amide.

WO 2010/095144 describes the process for the preparation of crystalline dexlansoprazole from amorphous dexlansoprazole using acetone and n-heptane solvent mixture. It also describes the preparation of crystalline dexlansoprazole sesquihydrate using acetone and aqueous ammonia.

Summary of the Invention

The present inventors have found that the crystalline dextralansoprazole prepared by using acetone and heptane mixture is not stable. The color of this material deteriorates on stability. The present inventors have found that the salts of dextralansoprazole can be converted into crystalline dextralansoprazole which is stable and the color and consistency of the material remains stable on storage. By employing the present invention, crystalline dextralansoprazole can also be obtained as chirally and chemically pure material in a consistent manner. Thus, the present invention provides a simple, efficient and industrially preferable process for the preparation of crystalline dextralansoprazole.

Detailed Description of the Invention

One aspect of the present invention provides a process for the preparation of crystalline dextralansoprazole which comprises:

- a) treating a salt of dextralansoprazole with an agent capable of liberating dextralansoprazole as a free base in the presence of a solvent;
- b) treating the dextralansoprazole obtained in step a) with a solvent selected from the group consisting of water, halogenated hydrocarbon, C₄₋₆ alkanol, and a mixture thereof;
- c) treating the mixture obtained in step b) with aliphatic hydrocarbon or cyclic aliphatic hydrocarbon or a mixture thereof; and
- d) isolating crystalline dextralansoprazole from the mixture thereof.

Another aspect of the present invention provides a process for the preparation of crystalline dextralansoprazole which comprises:

- a) treating dextralansoprazole with a solvent selected from the group consisting of water, halogenated hydrocarbon, C₄₋₆ alkanol, and a mixture thereof;
- b) treating the mixture obtained in step a) with aliphatic hydrocarbon or cyclic aliphatic hydrocarbon or a mixture thereof; and
- c) isolating crystalline dextralansoprazole from the mixture thereof.

The salt of dextansoprazole used as a starting material may be in any solid form and prepared according to the methods described in U.S. Patent No. 7,271,182 or our co-pending Indian Patent Application Nos. 197/DEL/2010; 795/DEL/2010; and 796/DEL/2010. The salt may be, for example, an alkali metal, alkaline earth metal, ammonium or an amine salt of dextansoprazole. The salt of dextansoprazole is treated with an agent capable of liberating dextansoprazole as a free base in the presence of a solvent. The agent capable of liberating dextansoprazole as a free base may be an alkali or alkaline metal hydroxide, for example, sodium or potassium hydroxide, or both. The solvent may be selected from the group consisting of water, halogenated hydrocarbon, ketone, and a mixture thereof. The liberation of dextansoprazole as a free base may be effected by stirring the reaction mixture. The dextansoprazole obtained as a free base may optionally be isolated by solvent removal.

The dextansoprazole is treated with a solvent selected from the group consisting of water, halogenated hydrocarbon, C₄₋₆ alkanol, and a mixture thereof. Halogenated hydrocarbon may be, for example, dichloromethane. C₄₋₆ alkanol may be, for example, butanol, pentanol and hexanol. The butanol may be, for example, n-butanol or t-butanol. The dextansoprazole may be optionally treated with organic amines, for example, diisopropylethylamine. The solution may be further treated with aliphatic hydrocarbon or cyclic aliphatic hydrocarbon, or a mixture thereof. Aliphatic hydrocarbon may be, for example, n-heptane. Cyclic aliphatic hydrocarbon may be, for example, cyclohexane. The treatment with the solvent may be carried out at a temperature of about -30°C to about 60°C, for example, about 15°C to about 45°C. The crystalline dextansoprazole may be isolated by filtration, distillation, decantation, vacuum drying, evaporation, or a combination thereof.

Brief Description of the Drawings

Figure 1 depicts the X-ray powder diffraction pattern (XRPD) of the crystalline dextansoprazole obtained according to Example 3.

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

Figure 2 depicts the X-ray powder diffraction pattern (XRPD) of the crystalline dextansoprazole obtained according to Example 4.

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

Figure 3 depicts the X-ray powder diffraction pattern (XRPD) of the crystalline dextansoprazole obtained according to Example 5.

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

5 Figure 4 depicts the X-ray powder diffraction pattern (XRPD) of the crystalline dextansoprazole obtained according to Example 6.

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

Figure 5 depicts the X-ray powder diffraction pattern (XRPD) of the crystalline dextansoprazole obtained according to Example 7.

10 Figure 5A provides the table of values for the XRPD pattern depicted in Figure 5.

Figure 6 depicts the X-ray powder diffraction pattern (XRPD) of the crystalline dextansoprazole obtained according to Example 8.

Figure 6A provides the table of values for the XRPD pattern depicted in Figure 6.

XRPD of the samples were determined by using Panalytical X'Pert Pro X-Ray
15 Powder Diffractometer in the range 3-40 degree 2 theta and under tube voltage and current of 45 Kv and 40 mA, respectively. Copper radiation of wavelength 1.54 angstrom and Xceletor detector was used.

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
20 art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of Dextansoprazole

Dextansoprazole sodium (300 g) was dissolved in de-ionized water (15 L) at 45°C
to 50°C. The pH of the reaction mixture was adjusted to 12.6 to 12.8 using sodium
25 hydroxide (102 g). The reaction mixture was filtered through a Celite-bed and was cooled
to 35°C to 38°C. The filtrate was extracted with dichloromethane (2×900 mL). The pH of
the aqueous reaction mixture was adjusted to 7.4 to 7.8 with dropwise addition of 2N
hydrochloric acid (1480 mL). The reaction mixture was filtered, washed with water (1500

mL) and added to acetone (900 mL). De-ionized water (300 mL) and aqueous ammonia (22.8 mL) were added to the reaction mixture and heated to 35°C to 38°C. De-ionized water (4.8 L) was added dropwise over a period of 45 minutes to 60 minutes. The reaction mixture was stirred for 3 hours to 4 hours at 35°C to 38°C and the precipitate obtained was
5 filtered and washed with water (600 mL). The precipitate was again added to acetone (900 mL) followed by addition of de-ionized water (300 mL) and aqueous ammonia (22.8 mL). The reaction mixture was heated to 35°C to 38°C. De-ionized water (4.8 L) was added dropwise over a period of 45 minutes to 60 minutes. The reaction mixture was stirred for 3 hours to 4 hours at 35°C to 38°C and the precipitate obtained was filtered and
10 washed with water (600 mL) to obtain the title product.

Yield: 530 g

Chromatographic Purity = 99.75%.

Deoxylansoprazole = 0.03%.

Lansoprazole Sulphone = 0.02%.

15 Example 2: Preparation of Dexlansoprazole

Dexlansoprazole sodium (300 g) was dissolved in de-ionized water (15 L) at 26°C to 30°C and the pH of the reaction mixture was adjusted to 12.4 to 12.6 using sodium hydroxide (100 g). The reaction mixture was heated to 45°C to 50°C, stirred for 30 minutes and filtered through a Celite-bed and filtrate was cooled to 35°C to 38°C. The
20 filtrate was extracted with dichloromethane (2×1200 mL). The pH of the aqueous reaction mixture was adjusted to 7.4 to 7.8 with dropwise addition of 2N hydrochloric acid (1485 mL). The reaction mixture was filtered, washed with water (1500 mL) and added to acetone (900 mL). De-ionized water (300 mL) and aqueous ammonia (22.8 mL) were added to this reaction mixture and heated to 35°C to 38°C. De-ionized water (4.8 L) was
25 added dropwise over a period of 45 minutes to 60 minutes. The reaction mixture was stirred for 3 hours to 4 hours at 35°C to 38°C and the precipitate obtained was filtered and washed with water (600 mL). The precipitate was again added to acetone (900 mL) followed by addition of de-ionized water (300 mL) and aqueous ammonia (22.8 mL). The reaction mixture was heated to 35°C to 38°C. De-ionized water (4.8 L) was added to the
30 reaction mixture drop-wise over a period of 45 minutes to 60 minutes. The reaction

mixture was stirred for 3 hours to 4 hours at 35°C to 38°C and the precipitate obtained was filtered and washed with water (600 mL) to obtain the title product.

Yield: 402 g

Chromatographic Purity = 99.77%.

5 Deoxylansoprazole = 0.02%.

Lansoprazole Sulphone = 0.081%.

Example 3: Preparation of Crystalline Dexlansoprazole

Dexlansoprazole (37 g) prepared according to Example 1 was dissolved in dichloromethane (125 mL) and washed with 5% aqueous sodium chloride solution (150 mL). The layers obtained were separated. The organic layer was washed with de-ionized water (150 mL). The organic layer was separated and diisopropylethylamine (0.025 g) was added to the organic layer. Dichloromethane was recovered completely under vacuum at 30°C to 35°C to obtain the residue. Ethanol (25 mL) and cyclohexane (50 mL) were added to the residue. Solvents were recovered completely under vacuum at 30°C to 35°C to obtain the residue. Ethanol (37.5 mL) was added to the residue and heated to 38°C to 40°C. n-Heptane (375 mL) was added to the reaction mixture dropwise and the solution was stirred for 3 hours to 4 hours. The reaction mixture was filtered and washed with n-heptane (25 mL). n-Heptane (150 mL) was added to the solid material and the reaction mixture was heated to 40°C to 45°C. The reaction mixture was stirred for 1 hour at 40°C to 45°C, filtered, washed with n-heptane (25 mL) and dried under vacuum at 35°C to 38°C for 10 hours to 12 hours to obtain the title compound having the X-ray powder diffraction pattern (XRPD) as shown in Figure 1.

Yield = 12.4 g

Chromatographic Purity = 99.94

25 Moisture = 0.09%

Example 4: Preparation of Crystalline Dexlansoprazole

Dexlansoprazole (10 g) prepared according to Example 1 was dissolved in dichloromethane (50 mL) and washed with water (40 mL). t-Butanol (20 mL) and activated carbon (1.0 g) were added to the dichloromethane layer (50 mL) and stirred for

30 minutes. The reaction mixture was filtered and washed with dichloromethane (25 mL). Dichloromethane was recovered completely under vacuum at 30°C to 35°C to obtain the residue. Cyclohexane (20 mL) was added to the residue. The cyclohexane was recovered completely from the reaction mixture under vacuum at 35°C to 38°C to obtain the residue.
5 n-Heptane (200 mL) was added dropwise to the residue in 10 minutes to 15 minutes. The reaction mixture was stirred for 3 hours to 4 hours, filtered and washed with n-heptane (25 mL). n-Heptane (120 mL) was added to the solid material and the reaction mixture was heated to 40°C to 45°C and stirred for 1 hour at 40°C to 45°C. The reaction mixture was filtered, washed with n-heptane (25 mL) and dried under vacuum at 35°C to 38°C for 10
10 hours to 12 hours to obtain the title compound having the X-ray powder diffraction pattern (XRPD) as shown in Figure 2.

Yield = 8.9 g

Chromatographic Purity = 99.89

Moisture = 0.13%

15 Example 5: Preparation of Crystalline Dexlansoprazole

Dexlansoprazole (10 g) prepared according to Example 1 was dissolved in dichloromethane (50 mL) and washed with water (40 mL). n-Butanol (20 mL) and activated carbon (1.0 g) were added to the dichloromethane layer (50 mL) and stirred for 30 minutes. The reaction mixture was filtered and washed with dichloromethane (25 mL).
20 Dichloromethane was recovered completely under vacuum at 30°C to 35°C to obtain the residue. Cyclohexane (20 mL) was added to the residue. The cyclohexane was recovered completely from the reaction mixture under vacuum at 35°C to 38°C to obtain the residue. n-Heptane (200 mL) was added dropwise to the residue in 10 minutes to 15 minutes. The reaction mixture was stirred for 3 hours to 4 hours, filtered and washed with n-heptane (25
25 mL). n-Heptane (120 mL) was added to the solid material and the reaction mixture was heated to 40°C to 45°C and stirred for 1 hour at 40°C to 45°C. The reaction mixture was filtered, washed with n-heptane (25 mL) and dried under vacuum at 35°C to 38°C for 10 hours to 12 hours to obtain the title compound having the X-ray powder diffraction pattern (XRPD) as shown in Figure 3.

30 Yield = 8.5 g

Chromatographic Purity = 99.95

Moisture = 0.12%

Example 6: Preparation of Crystalline Dexlansoprazole

Dexlansoprazole (10 g) prepared according to Example 1 was dissolved in
5 dichloromethane (50 mL) and washed with water (40 mL). n-Butanol (20 mL) and
activated carbon (1.0 g) were added to the dichloromethane layer (50 mL) and stirred for
30 minutes. The reaction mixture was filtered and washed with dichloromethane (25 mL).
Dichloromethane was recovered completely under vacuum at 30°C to 35°C to obtain the
residue. Cyclohexane (20 mL) was added to the residue. The cyclohexane was recovered
10 completely from the reaction mixture under vacuum at 35°C to 38°C to obtain the residue.
Cyclohexane (200 mL) was added dropwise to the residue in 10 minutes to 15 minutes.
The reaction mixture was stirred for 3 hours to 4 hours, filtered and washed with n-
heptane (25 mL). n-Heptane (120 mL) was added to the solid material and the reaction
mixture was heated to 40°C to 45°C and stirred for 1 hour at 40°C to 45°C. The reaction
15 mixture was filtered, washed with n-heptane (25 mL) and dried under vacuum at 35°C to
38°C for 10 hours to 12 hours to obtain the title compound having the X-ray powder
diffraction pattern (XRPD) as shown in Figure 4.

Yield = 7.8 g

Chromatographic Purity = 99.95

20 Moisture = 0.13%

Example 7: Preparation of Crystalline Dexlansoprazole

Dexlansoprazole (25 g) prepared according to Example 1 was dissolved in
dichloromethane (250 mL) and washed with water (300 mL). n-Butanol (50 mL) and
activated carbon (2.5 g) were added to the dichloromethane layer (250 mL) and stirred for
25 30 minutes. The reaction mixture was filtered and washed with dichloromethane (50 mL).
Diisopropylethylamine (50 mg) and cyclohexane (600 mL) were added to the solid
material and water was removed azeotropically under vacuum at 45°C to 50°C.
Dichloromethane was recovered completely under vacuum and the reaction mixture was
cooled to 20°C to 25°C. The reaction mixture was stirred at 20°C to 25°C for 3 hours to 4
30 hours. The reaction mixture was filtered, washed with cyclohexane (50 mL) and dried

under vacuum. Cyclohexane (300 mL) was added to the solid and the reaction mixture was heated to 40°C to 45°C. The reaction mixture was stirred for 1 hour at 40°C to 45°C, filtered, washed with cyclohexane (25 mL) and dried under vacuum at 35°C to 38°C for 10 hours to 12 hours to obtain the title compound having the X-ray powder diffraction pattern (XRPD) as shown in Figure 5.

Yield = 18 g

Chromatographic Purity = 99.96%

Moisture = 0.08%

Example 8: Preparation of Crystalline Dexlansoprazole

Dexlansoprazole (402 g) prepared according to Example 2 was dissolved in dichloromethane (1500 mL) and washed with 5% aqueous sodium chloride solution (1800 mL). The layers obtained were separated and washed with de-ionized water (1800 mL). The organic layer was separated and filtered through a Celite bed followed by washing with dichloromethane (300 mL). Diisopropylethylamine (0.3 g) was added to the combined dichloromethane layer (1800 mL). n-Butanol (360 mL) and activated carbon were added to the reaction mixture and stirred for 30 minutes. The reaction mixture was filtered through celite and a bed of molecular sieve (120 g) to get moisture of organic layer not more than 0.25% w/w. Solvents were recovered completely under vacuum at less than 35°C to get the residue. Cyclohexane (2x360 mL) was added to the residue. The cyclohexane was recovered completely from the reaction mixture under vacuum at less than 35°C to get the residue. Cyclohexane (4300 mL) was added to the residue dropwise and the solution was stirred for 4 hours at 25°C to 30°C. The reaction mixture was filtered. Cyclohexane (600 mL) was added to the solid material and the reaction mixture was stirred for 30 minutes at 25°C to 30°C, filtered under nitrogen atmosphere and dried under vacuum at 35°C to 38°C for 10 hours to 12 hours to obtain the title compound having the X-ray powder diffraction pattern (XRPD) as shown in Figure 6.

Yield: 138 g

Moisture: 0.14%

We claim:

- 1 1. A process for the preparation of crystalline dextansoprazole, which comprises:
 - 2 a) treating a salt of dextansoprazole with an agent capable of liberating
3 dextansoprazole as a free base in the presence of a solvent;
 - 4 b) treating the dextansoprazole obtained in step a) with a solvent selected from
5 the group consisting of water, halogenated hydrocarbon, C₄₋₆ alkanol, and a
6 mixture thereof;
 - 7 c) treating the mixture obtained in step b) with aliphatic hydrocarbon or cyclic
8 aliphatic hydrocarbon, or a mixture thereof; and
 - 9 d) isolating crystalline dextansoprazole from the mixture thereof.
- 1 2. A process according to claim 1, wherein the salt of dextansoprazole is an alkali
2 metal, alkaline earth metal, ammonium or an amine salt.
- 1 3. A process according to claim 1, wherein the agent capable of liberating
2 dextansoprazole as a free base is an alkali or alkaline metal hydroxide.
- 1 4. A process according to claim 3, wherein the agent capable of liberating
2 dextansoprazole as a free base is sodium or potassium hydroxide, or both.
- 1 5. A process according to claim 1, wherein the solvent used in step a) is water,
2 halogenated hydrocarbon, ketone, or a mixture thereof.
- 1 6. A process according to claim 1, wherein the halogenated hydrocarbon solvent used
2 in step b) is dichloromethane.
- 1 7. A process according to claim 1, wherein the C₄₋₆ alkanol solvent used in step b) is
2 butanol, pentanol or hexanol.
- 1 8. A process according to claim 7, wherein the butanol solvent is n-butanol or t-
2 butanol.
- 1 9. A process according to claim 1, wherein the dextansoprazole obtained in step b) is
2 optionally treated with organic amines.
- 1 10. A process according to claim 1, wherein the aliphatic hydrocarbon solvent used in
2 step c) is n-heptane.

- 1 11. A process according to claim 1, wherein the cyclic aliphatic hydrocarbon solvent
2 used in step c) is cyclohexane.
- 1 12. A process for the preparation of crystalline dextansoprazole, which comprises:
2 a) treating dextansoprazole with a solvent selected from the group consisting of
3 water, halogenated hydrocarbon, C₄₋₆ alkanol, and a mixture thereof;
4 b) treating the mixture obtained in step a) with aliphatic hydrocarbon or cyclic
5 aliphatic hydrocarbon, or a mixture thereof; and
6 c) isolating crystalline dextansoprazole from the mixture thereof.
- 1 13. A process according to claim 12, wherein the halogenated hydrocarbon solvent
2 used in step a) is dichloromethane.
- 1 14. A process according to claim 12, wherein the C₄₋₆ alkanol solvent used in step a) is
2 butanol, pentanol or hexanol.
- 1 15. A process according to claim 14, wherein the butanol solvent is n-butanol or t-
2 butanol.
- 1 16. A process according to claim 12, wherein the aliphatic hydrocarbon solvent used in
2 step b) is n-heptane.
- 1 17. A process according to claim 12, wherein the cyclic aliphatic hydrocarbon solvent
2 used in step b) is cyclohexane.
- 1 18. A process according to claim 12, wherein the dextansoprazole obtained in step a) is
2 optionally treated with organic amines.

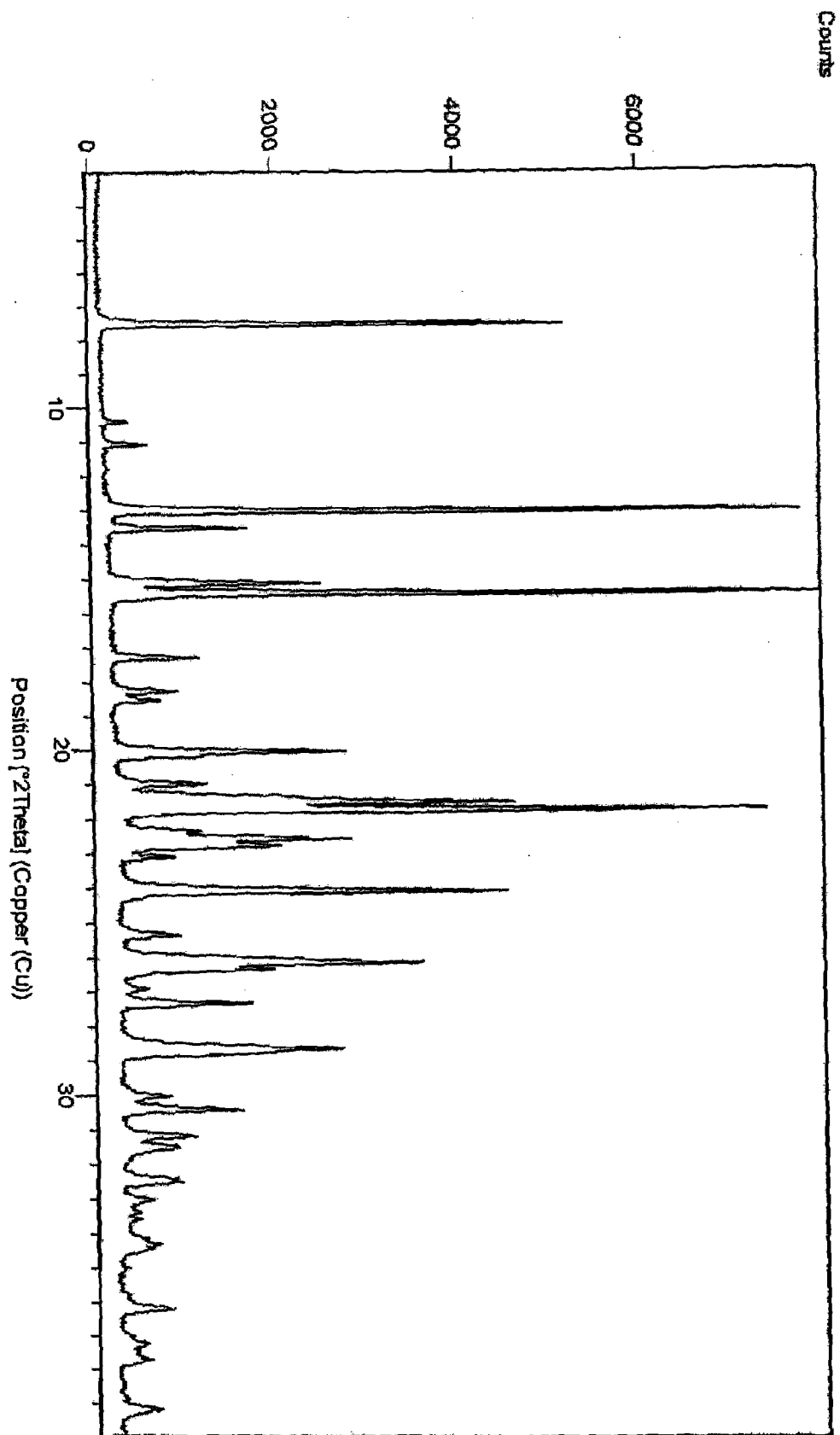


FIGURE 1

FIGURE 1A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 1

Pos [° 2Th]	d-spacing [Å]	Rel. Int [%]
7.54	11.71	63.90
11.09	7.97	6.04
13.05	6.78	98.63
13.55	6.54	20.86
15.15	5.85	29.80
15.43	5.74	100.00
17.29	5.13	13.55
18.26	4.86	10.51
18.54	4.78	8.08
20.04	4.44	33.28
20.46	4.40	13.38
20.94	4.24	14.19
21.29	4.17	24.76
21.46	4.14	57.79
21.69	4.10	92.50
22.29	3.99	11.85
22.54	3.94	34.52
22.75	3.91	24.40
23.06	3.86	9.62
24.04	3.70	55.57
25.31	3.52	10.27
26.11	3.41	43.70
26.29	3.39	23.61
26.87	3.32	5.88
27.30	3.27	20.28
28.62	3.12	33.20
28.73	3.10	19.63
30.02	2.98	8.81
30.39	2.94	18.66
31.16	2.87	12.11
31.50	2.84	9.57
32.50	2.75	10.29
33.06	2.71	6.34
34.38	2.61	6.17
36.22	2.48	8.69
37.23	2.44	5.16
37.74	2.38	5.75
39.18	2.30	6.92

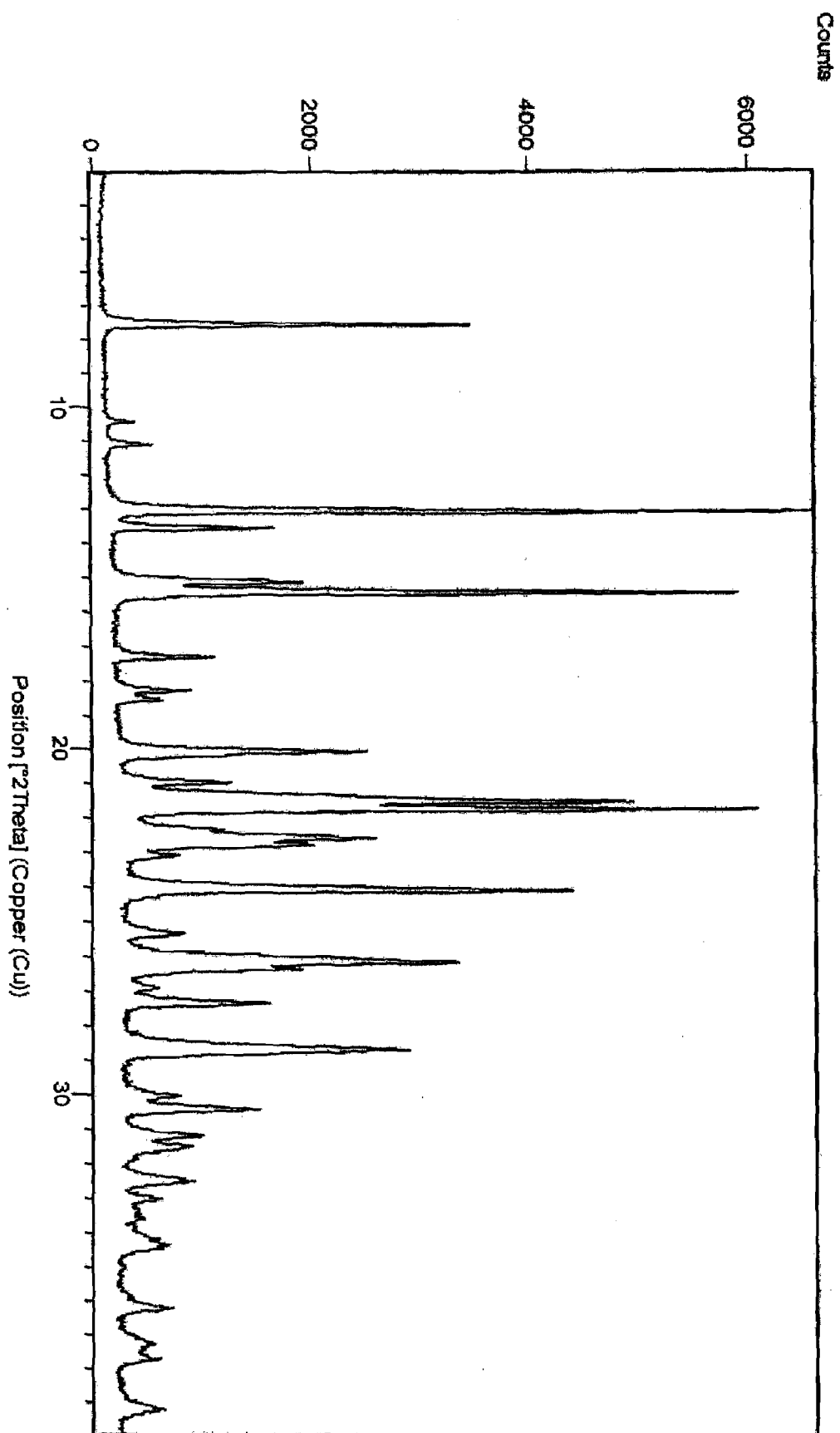


FIGURE 2

FIGURE 2A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 2

Pos [° 2Th]	d-spacing [Å]	Rel. Int [%]
7.57	11.67	52.96
10.43	8.48	4.64
11.11	7.96	6.69
13.08	6.77	100.00
13.57	6.52	24.41
15.18	5.84	28.63
15.45	5.73	92.22
17.33	5.12	14.74
18.28	4.85	12.3
18.58	4.77	7.25
20.04	4.43	38.15
20.95	4.24	17.98
21.48	4.14	75.40
21.71	4.09	93.95
22.57	3.94	37.49
22.79	3.90	28.80
23.08	3.85	10.45
24.05	3.70	67.91
25.32	3.52	11.39
26.12	3.41	50.77
26.32	3.39	28.48
26.88	3.32	7.61
27.32	3.26	24.07
28.64	3.12	43.89
30.04	2.97	10.70
30.41	2.94	22.24
31.47	2.87	13.98
31.48	2.84	12.47
32.51	2.75	12.48
33.01	2.71	7.65
34.33	2.61	8.24
36.21	2.48	9.45
37.25	2.41	6.63
37.76	2.38	6.80
39.20	2.30	7.73

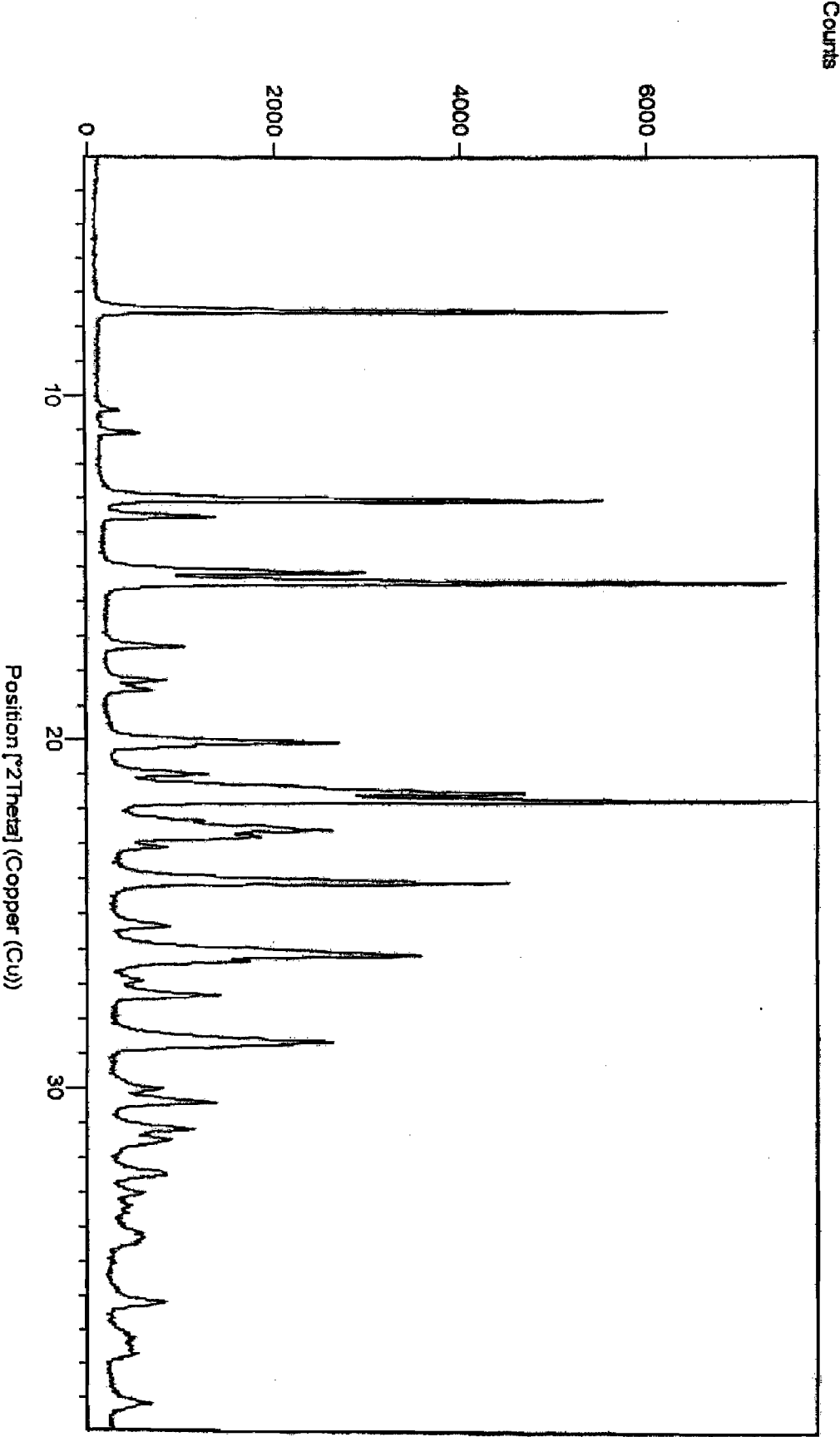


FIGURE 3

FIGURE 3A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 3

Pos [° 2Th]	d-spacing [Å]	Rel. Int [%]
7.57	11.68	80.08
11.10	7.97	5.68
13.07	6.77	69.83
13.56	6.53	16.37
15.17	5.84	36.38
15.45	5.73	95.82
17.31	5.12	12.37
18.28	4.85	9.29
18.56	4.78	7.79
20.03	4.43	33.12
20.18	4.40	13.27
20.96	4.24	15.39
21.30	4.17	28.67
21.48	4.14	58.80
21.71	4.09	100.00
22.31	3.98	14.65
22.56	3.94	32.86
22.79	3.90	21.87
23.09	3.85	8.75
24.06	3.70	54.46
25.33	3.52	10.10
26.44	3.41	44.55
26.31	3.39	20.57
26.87	3.35	6.13
27.31	3.27	16.38
28.63	3.12	32.88
30.01	2.98	8.75
30.41	2.94	16.23
31.17	2.87	13.24
31.48	2.84	9.51
32.48	2.76	9.27
33.02	2.71	6.32
33.42	2.68	4.16
34.40	2.61	5.68
36.20	2.48	9.04
37.20	2.42	4.57
37.76	2.38	5.03
39.19	2.30	7.10

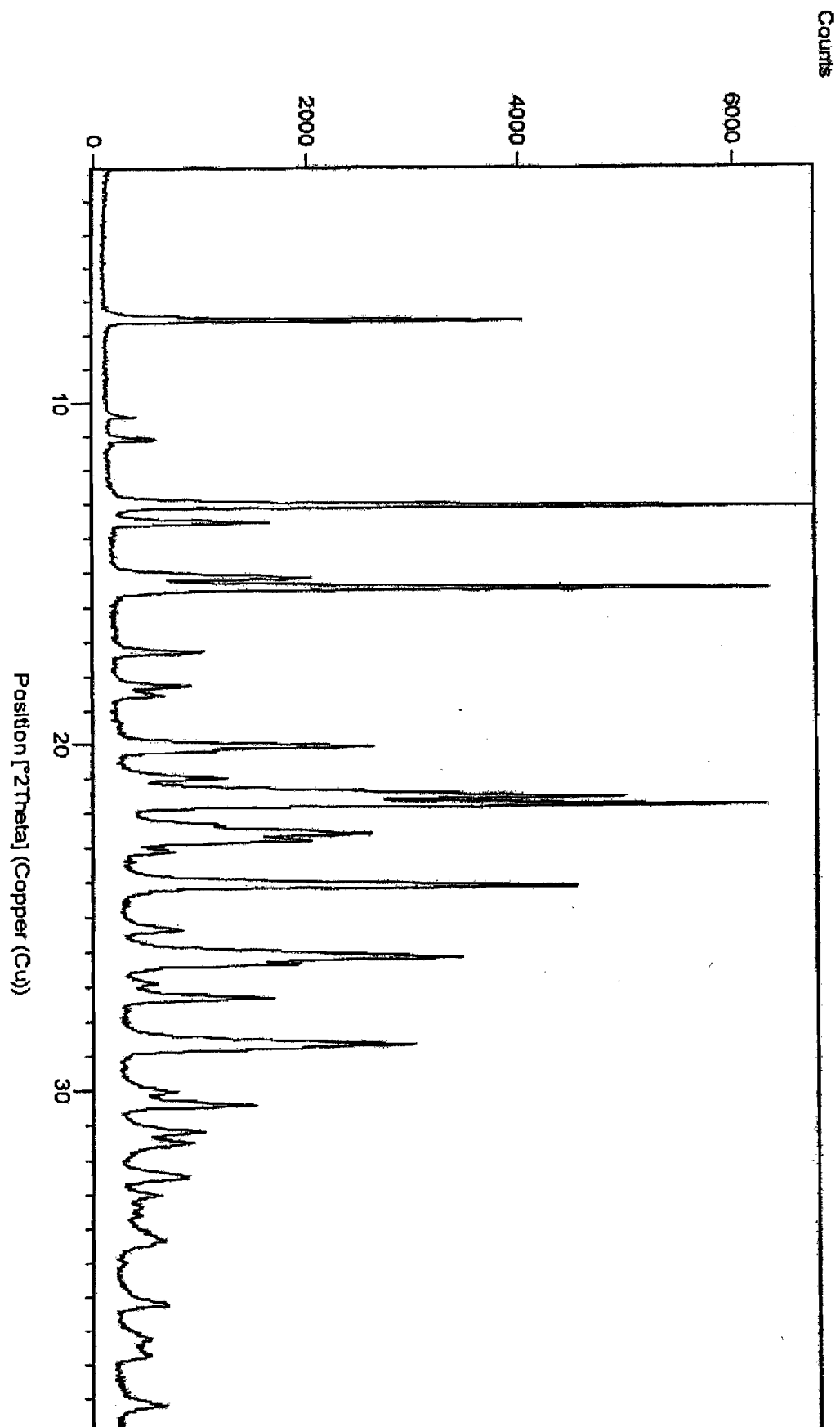


FIGURE 4

FIGURE 4A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 4

Pos [° 2Th]	d-spacing [Å]	Rel. Int [%]
7.56	11.69	59.09
11.10	7.97	7.39
13.07	6.78	100.00
13.55	6.53	23.02
15.16	5.84	29.22
15.44	5.74	93.29
17.29	5.43	13.78
18.27	4.86	12.04
18.55	4.78	8.46
20.03	4.43	38.09
20.18	4.40	14.92
20.95	4.24	16.89
21.28	4.17	30.35
21.47	4.14	72.72
21.70	4.09	94.42
22.28	3.99	15.00
22.55	3.94	37.88
22.76	3.91	29.05
23.09	3.85	9.29
24.05	3.70	66.23
25.32	3.52	10.80
26.10	3.41	50.45
26.30	3.39	26.94
26.88	3.32	6.76
27.30	3.27	23.69
28.63	3.12	43.68
30.01	2.98	10.19
30.40	2.94	21.15
31.16	2.87	13.84
31.48	2.84	11.34
32.47	2.76	10.85
32.99	2.71	7.36
34.37	2.61	7.49
36.23	2.48	8.61
37.22	2.42	6.12
37.74	2.38	6.26
39.20	2.30	8.26

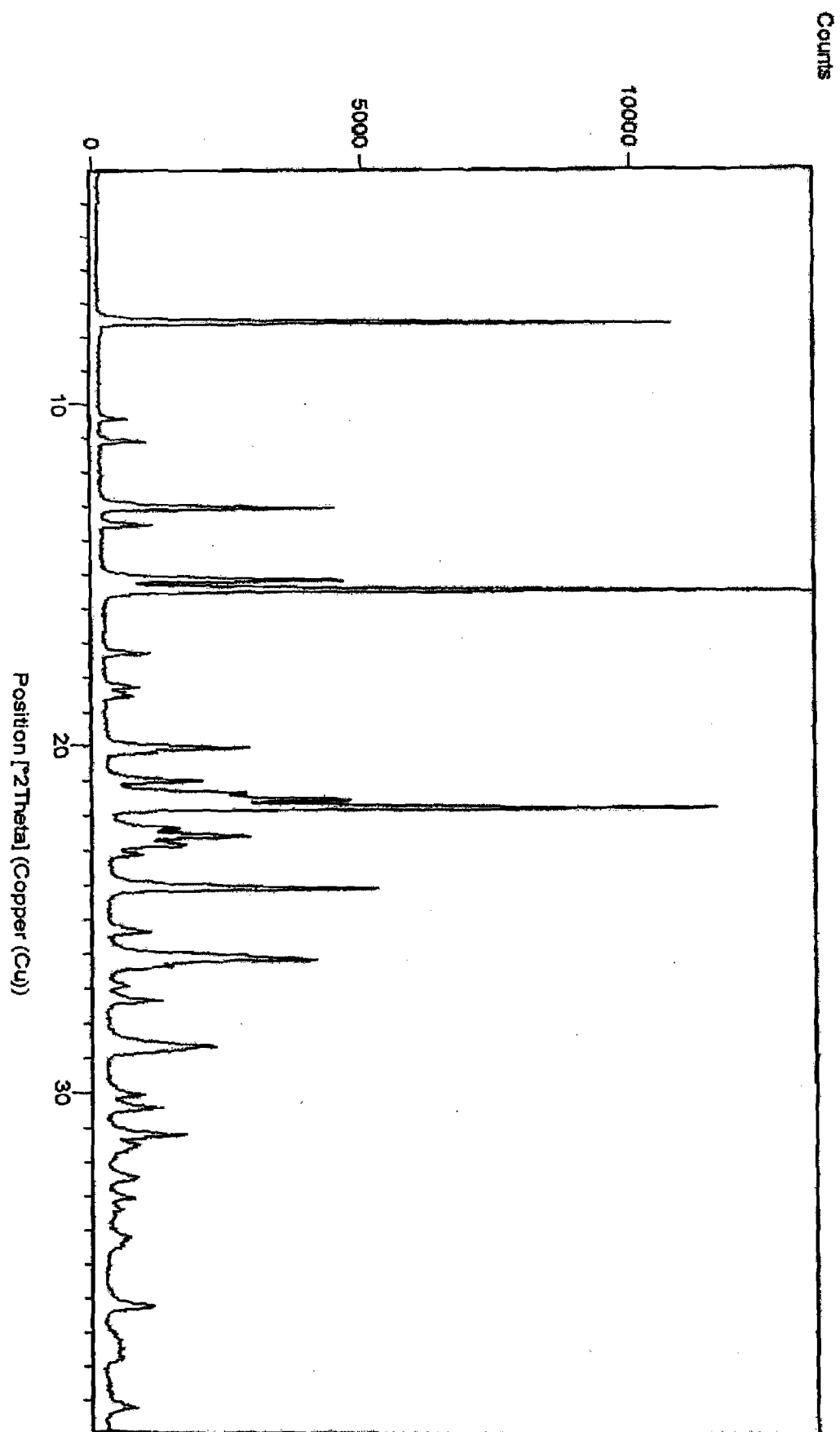


FIGURE 5

FIGURE 5A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 5

Pos [° 2Th]	d-spacing [Å]	Rel. Int [%]
7.57	11.68	80.30
11.11	7.96	6.60
13.07	6.77	32.74
13.57	6.53	7.32
15.17	5.84	34.45
15.46	5.73	100.00
17.31	5.42	6.92
18.29	4.85	5.46
18.56	4.78	4.59
20.03	4.43	20.64
20.18	4.40	7.50
20.98	4.23	14.12
21.31	4.17	18.75
21.49	4.13	34.99
21.71	4.09	86.66
22.32	3.98	10.92
22.56	3.94	20.54
22.83	3.89	11.87
23.08	3.85	5.89
24.06	3.70	39.01
25.33	3.52	6.97
25.98	3.43	18.72
26.12	3.41	30.24
26.31	3.39	9.98
26.89	3.31	4.01
27.32	3.26	8.44
28.64	3.11	15.85
30.03	2.98	5.96
30.41	2.94	8.56
31.19	2.87	11.74
31.48	2.84	5.09
32.45	2.76	4.85
33.04	2.71	4.54
36.24	2.48	6.63
39.21	2.30	4.55

11/12

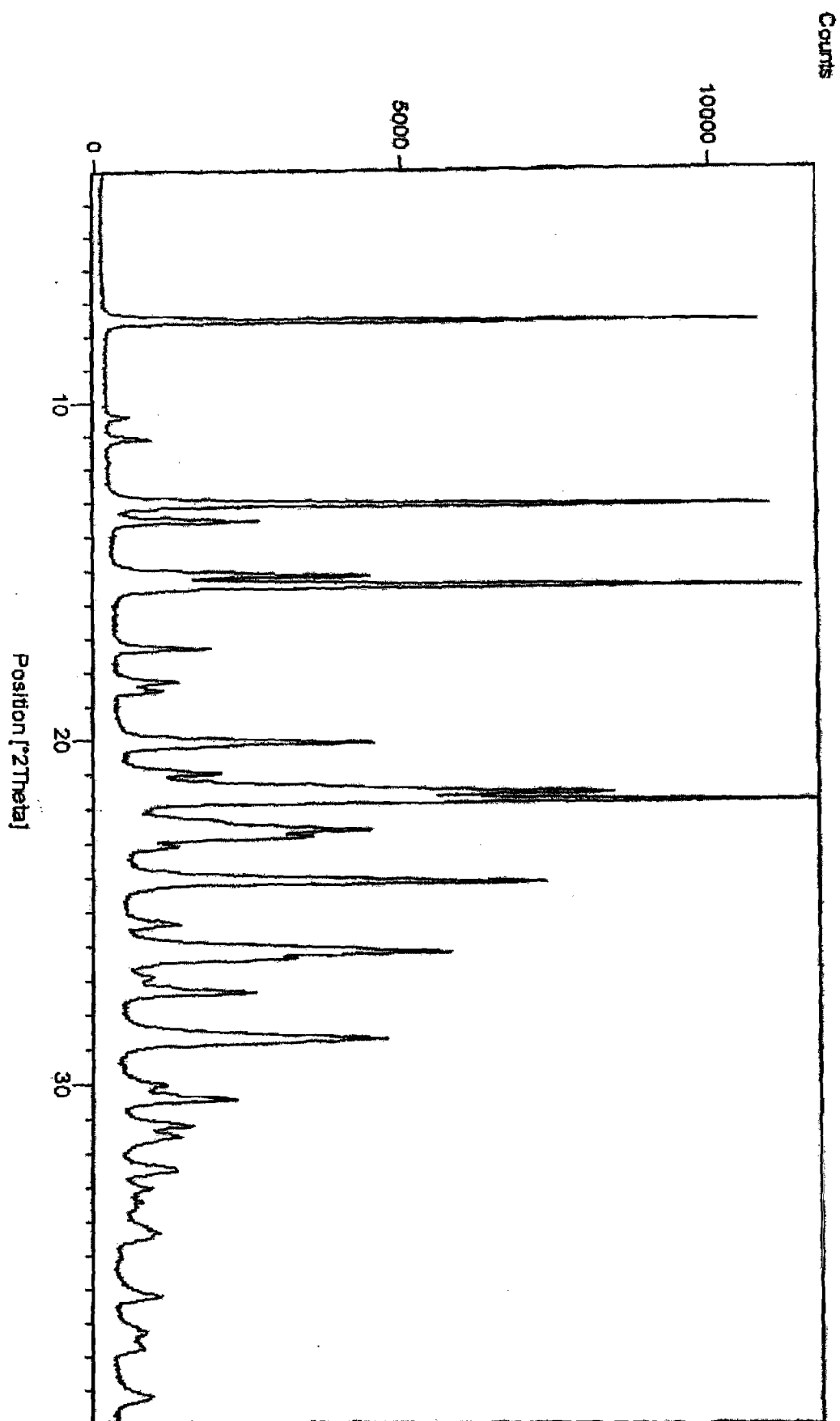


FIGURE 6

FIGURE 6A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 6

Pos [° 2Th]	d-spacing [Å]	Rel. Int [%]
7.59	11.65	91.45
11.12	7.96	7.13
13.09	6.76	92.55
13.58	6.52	21.62
15.18	5.83	38.35
15.47	5.73	97.71
17.32	5.12	14.79
18.29	4.85	10.56
18.58	4.78	8.35
20.05	4.43	37.83
20.98	4.23	16.25
21.49	4.13	71.55
21.73	4.09	100.00
22.58	3.94	37.39
22.79	3.90	28.72
23.11	3.85	10.70
24.07	3.70	62.39
25.35	3.51	11.10
26.13	3.41	48.72
26.33	3.38	26.97
26.89	3.31	7.27
27.33	3.26	21.39
28.66	3.11	39.48
30.03	2.98	8.84
30.42	2.94	18.61
31.20	2.87	12.60
31.50	2.84	11.35
32.52	2.75	10.66
33.04	2.71	6.87
34.35	2.61	7.95
36.25	2.48	7.99
37.30	2.41	6.24
37.77	2.38	5.98
39.21	2.30	7.25

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/050481

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 216 333 A2 (DIPHARMA FRANCIS SRL [IT]) 11 August 2010 (2010-08-11)	12,
Y	Crystallisation from ethanol and toluene/	14-16,18
A	ethanol and heptane; page 6; claims 10, 11, 13; examples 5, 6	1-5,7-10
	-----	6,11
Y	"Isolation and Purification Techniques 2.18 General Considerations" In: Vogel, A.I., Tatchell A.R., Furnis B.S., Hannaford A.J., Smith P.W.G.: "Vogel's Textbook of Practical Organic Chemistry", 1996, Prentice Hall, XP002672724, ISBN: 0582462363 pages 131-133, page 132, paragraph 4th	1-5,7-10
	----- -/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

3 April 2012

Date of mailing of the international search report

18/04/2012

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/050481

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 2011/028728 A1 (VLADISKOVIC CHIARA [IT] ET AL) 3 February 2011 (2011-02-03) claims 1-11; examples 1-4 -----	12,14-17
X,P	WO 2011/092665 A1 (RANBAXY LAB LTD [IN]; RAY ANMOL KUMAR [IN]; KHANNA MAHAVIR SINGH [IN];) 4 August 2011 (2011-08-04) page 7; example 1 -----	12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/050481

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			US 2010204479 A1	12-08-2010

US 2011028728	A1	03-02-2011	NONE	

WO 2011092665	A1	04-08-2011	NONE	
