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(54) **Title**: ERLOTINIB SALTS

(57) **Abstract**: The invention relates to erlotinib salts selected from the group consisting of the maleic acid salt, salicylic acid salt. L-mandelic acid alt. adipinic acid salt. 1.5-naphthalene-disulfonic acid salt. L-pyroglutamic acid salt. 1 -hydroxy-2-naphthoic acid salt, and mandelic acid salt and amorphous and crystalline forms, hydrates and solvates thereof. The erlotinib salts of the present invention are useful in therapy, particularly for the treatment or prophylaxis of non- small cell lung carcinoma and pancreas rarcinoma.

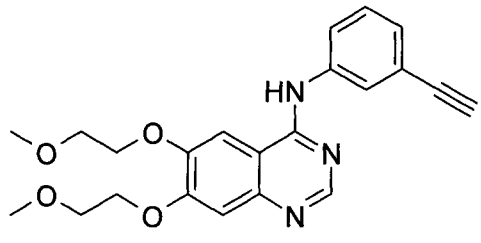
ERLOTINIB SALTS

Subject matter of the invention

The invention relates to new erlotinib salts, anhydrous forms, hydrates and solvates thereof, a process for the preparation thereof, pharmaceutical compositions containing the same and use of said pharmaceutical compositions in therapy.

The state of the art

It is known that [6,7-bis-(2-methoxyethoxy)-4-chinazolinyl](3-ethynyl-phenyl) amine of the Formula 1 is a pharmaceutical active ingredient acting by the tyrosine kinase inhibitor mechanism having the INN erlotinib and which can be preferably used for the treatment of non-small cell lung carcinoma and pancreas cancer. The erlotinib of the Formula **1** was first described in EP 817,775. In this patent the synthesis of the erlotinib hydrochloric acid salt is disclosed and the product is characterized by the melting point.



(1)

EP 1,076,652 relates to the mesylate hydrate of erlotinib and the anhydrous forms (A, B and C) thereof. According to the patent the solubility of the mesylate salt is low.

In WO 2008/122,776 a process is set forth for the preparation of erlotinib salts and the conversion of the erlotinib salts into the base. The acidic conditions cover the following disclosed acids: HCl, HBr, H_2SO_4, p-toluenesulfonic acid, benzoic acid, citric acid, succinic acid, oxalic acid, benzenesulfonic acid, tartaric acid, methanesulfonic acid, phosphoric acid and mixtures thereof. Particularly the preparation of the hydrochloric acid salt from the base by using aqueous hydrochloric acid or a solvent containing hydrochloric acid is described.

In WO 2011/068403 the preparation of new erlotinib salts is described. Namely that of the following salts: ethanesulfonate, isethionate, hydrobromide, malonate, L-lactate and succinate.

The object of the invention

Recently serious demand has occurred in pharmaceutical industry on the reproducible manufacture of morphologically uniform products. This is a fundamental-condition for active ingredients needed to meet the requirements of the formulation of medicines. It is well-known that various salts and polymorphs differ from each other in important properties such as solubility, chemical stability, polymorph stability, bioavailability, filtration, drying and tabletting properties etc.

From the point of view of the economy of the manufacturing process it is highly important that the product should be prepared by a process suitable for industrial scale manufacture in a reproducible manner to provide a morphologically uniform salt free of contaminations.

The object of the present invention is to provide a process for the preparation of morphologically pure new erlotinib salts of high purity which possess more favourable physical-chemical properties than the known salts and have at least as high chemical stability as the known salts and can be prepared in a reproducible manner suitable fore industrial scale manufacture.

Erlotinib hydrochloride is poorly soluble in aqueous medium which restricts the bioavailability thereof. The low solubility also limits the route of administration thereof and the finishing of the active ingredient into solid pharmaceutical compositions.

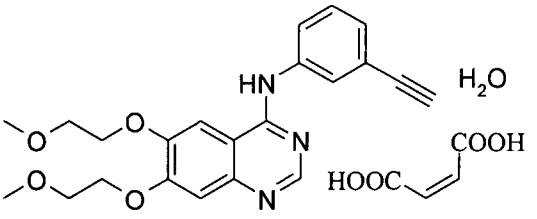
The above object is solved according to the present invention by the preparation of the new salts of erlotinib, namely by salts formed with maleic acid, salicylic acid, L-mandelic acid, adipinic acid, 1,5-naphthalene-disulfonic acid, L-pyroglutamic acid, 1-hydroxy-2-naphthoic acid and DL-mandelic acid.

The common inventive idea of the present invention resides in the preparation of new erlotinib salts which are more soluble in aqueous medium than the erlotinib hydrochloride salt.

Detailed description of the invention

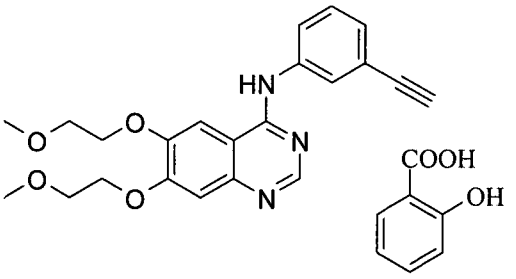
The invention relates to normal or acidic salts of erlotinib and the hydrate and solvate forms thereof.

According to the present invention there is provided the erlotinib maleic acid monohydrate salt of the Formula 2



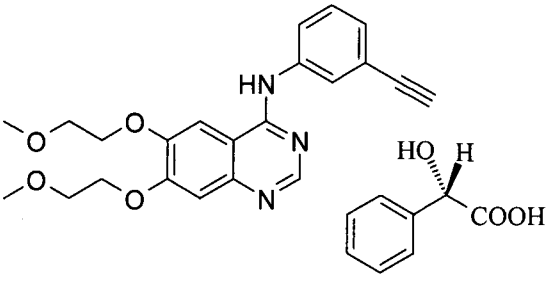
(2)

the L-erlotinib salicylic acid salts of the Formula 3



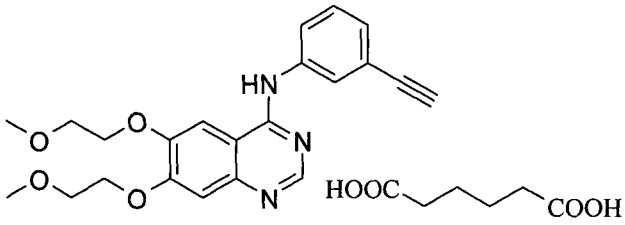
(3)

the L-mandelic acid salt of the Formula 4



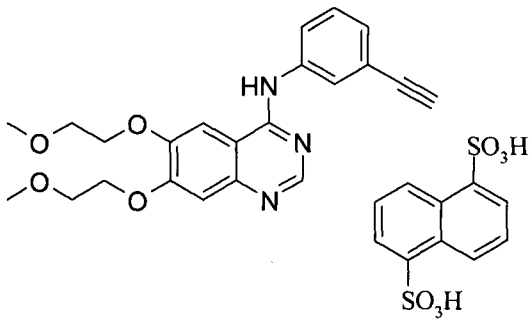
(4)

the erlotinib adipinic acid salt of the Formula 5



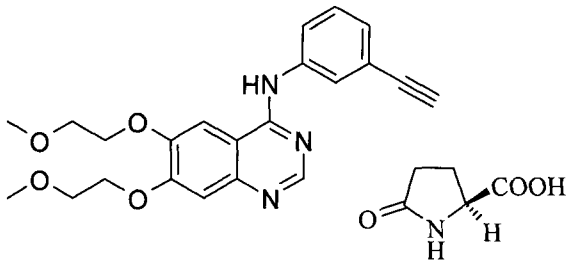
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the erlotinib 1,5-naphthalene-disulfonic acid salt of the Formula 6



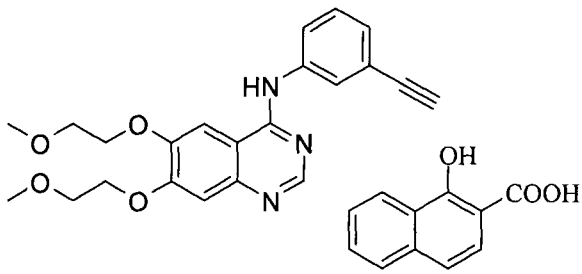
(6)

the erlotinib pyroglutamic acid salt of the Formula 7



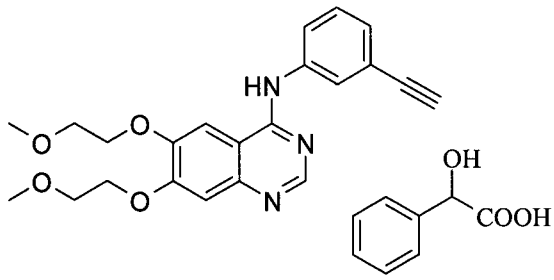
(7)

the erlotinib 1-hydroxy-2-naphthoic acid salt of the Formula 8



(8)

and the erlotinib DL-mandelic acid salt of the Formula 9



(9)

More particularly the invention relates to the M1 polymorph /Form 1/ of the crystalline erlotinib maleate monohydrate salt of the Formula **2** which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.870; 8.190; 8.880; 12.760; 13.740; 16.080; 19.430; 20.850; 21.710; 25.030; 25.740; 26.920; 28.450. More particularly this product can be characterized by the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.870; 8.190; 8.880; 10.690; 12.760; 13.740; 16.080; 17.700; 18.490; 19.110; 19.430; 20.850; 21.170. 21.710; 24.750; 25.030; 25.740; 26.920; 27.720; 28.450; 32.230. The characteristic X-ray powder diffractogram of the product is shown on Figure 1 and the signals having an intensity larger than 6 % are summarized in Table 1

Table 1 /relative intensity >6 %/

Peak	2 Θ	d (Å)	Intensity
1	6.870	12.8560	100
2	8.190	10.7867	87
3	8.880	9.9500	23
4	10.690	8.2690	14
5	11.090	7.9717	7
6	12.760	6.9318	27
7	13.160	6.7220	13
8	13.740	6.4396	23
9	14.360	6.1629	7
10	16.080	5.5073	21
11	17.700	5.0068	13
12	18.490	4.7946	11

13	19.110	4.6404	18
14	19.430	4.5647	61
15	20.340	4.3625	8
16	20.850	4.2569	36
17	21.170	4.1933	20
18	21.710	4.0902	43
19	22.550	3.9397	11
20	23.340	3.8081	8
21	23.810	3.7340	7
22	24.750	3.5943	20
23	25.030	3.5547	32
24	25.740	3.4582	32
25	26.280	3.3884	8
26	26.920	3.3092	19
27	27.720	3.2155	13
28	28.450	3.1347	18
29	31.590	2.8299	7
30	32.230	2.7751	10

The present invention is also concerned with the M2 polymorph /Form 2/ of the crystalline erlotinib maleate monohydrate of the Formula **2** which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.710; 8.018; 8.702; 12.552; 12.951; 13.533; 18.224; 18.859; 19.142; 21.385; 24.395; 25.960. More particularly this product can be characterized by the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.710; 8.018; 8.702; 10.494; 10.891; 12.552; 12.951; 13.533; 17.510; 18.224; 18.859; 19.142; 20.454; 20.843; 21.385; 22.806; 24.395; 25.316; 25.960; 28.979; 30.413; 31.194; 34.408. The characteristic X-ray powder diffractogram of this product is shown on Figure 2 and the signals having an intensity larger than 1 % are summarized in Table 2:

Table 2 /relative signals >1 %/

Peak	2 Θ	d (Å)	Intensity
1	6.710	13.1627	100
2	8.018	11.0179	64
3	8.702	10.1528	29
4	10.494	8.4231	19
5	10.891	8.1168	10
6	12.552	7.0463	17
7	12.951	6.8301	18
8	13.533	6.5376	25
9	13.860	6.3844	7
10	14.180	6.2409	2
11	15.810	5.6008	5
12	16.157	5.4814	4
13	16.505	5.3668	2
14	17.510	5.0607	27
15	18.224	4.8640	37
16	18.859	4.7016	15
17	19.142	4.6329	47
18	20.454	4.3385	14
19	20.843	4.2584	20
20	21.385	4.1517	57
21	21.715	4.0893	11
22	22.806	3.8961	23
23	23.579	3.7701	13
24	24.395	3.6459	32
25	24.765	3.5922	11
26	25.316	3.5152	23
27	25.960	3.4295	29
28	26.524	3.3578	4
29	26.890	3.3130	9
30	28.070	3.1764	8
31	28.609	3.1177	9

32	28.979	3.0787	15
33	29.870	2.9888	3
34	30.413	2.9368	17
35	31.194	2.8650	16
36	31.885	2.8044	4
37	32.809	2.7275	4
38	33.455	2.6764	5
39	33.817	2.6485	3
40	34.408	2.6044	10
41	34.720	2.5817	5
42	35.185	2.5486	4
43	35.400	2.5336	4
44	35.700	2.5130	2
45	36.080	2.4874	2
46	36.675	2.4484	2
47	37.131	2.4193	3
48	37.514	2.3955	4
49	38.262	2.3504	4
50	38.856	2.3158	3
51	39.623	2.2728	4

According to the present invention there is also provided the crystalline erlotinib salicylic acid /1:1/ salt of the Formula **3** which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.830; 6.990; 16.060; 23.490; 26.000. More particularly this product can be characterized by the following X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.830; 6.990; 16.060; 20.220; 22.740; 23.490; 24.930; 26.000. The characteristic X-ray powder diffractogram of this product is shown on Figure 3 and the signals having an intensity larger than 10 % are summarized in Table 3:

Table 3 /relative intensities >10 %/

Peak	2 Θ	d (Å)	Intensity
1	5.830	15.1468	100
2	6.990	12.6355	95
3	16.060	5.5142	42
4	20.220	4.3881	39
5	22.740	3.9072	44
6	23.490	3.7841	46
7	24.930	3.5687	43
8	26.000	3.4242	43

The invention also relates to the crystalline erlotinib L-mandelic acid salt /1:1/ of the Formula **4** which has the following characteristic X-ray powder diffraction peaks 2 Θ (±0.2°. 2 Θ): 6.040; 12.190; 16.200; 17.090; 18.270; 19.230; 20.030; 23.250; 24.870. 26.170. More particularly this product can be characterized by the following X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.040; 8.010; 12.190; 16.200; 18.270; 19.230; 20.030; 21.170; 21.780; 22.630; 23.250; 24.870; 26.170. The characteristic X-ray powder diffractogram of this product is shown on Figure 4 and the signals having an intensity larger than 6 % are summarized in Table 4:

Table 4 /relative intensities >6 %/

Peak	2 Θ	d (Å)	Intensity
1	6.040	14.6206	100
2	8.010	11.0287	7
3	12.190	7.2547	7
4	16.200	5.4668	21
5	18.270	4.8518	11
6	19.230	4.6117	12
7	20.030	4.4293	13
8	21.170	4.1933	13
9	21.780	4.0772	14
10	22.630	3.9259	13
11	23.250	3.8226	16
12	24.870	3.5772	17

13	26.170	3.4024	21
14	28.280	3.1531	8

The invention also relates to the crystalline erlotinib adipinic acid salt /1:1/ of the Formula **5** which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.400; 7.050; 8.990; 12.920; 18.740; 21.820; 22.660; 28.830. More particularly this product can be characterized by the following X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.400; 7.050; 8.990; 12.920; 16.860; 17.350; 18.740; 20.430; 21.240; 21.820; 22.660; 23.370; 28.830. The characteristic X-ray powder diffractogram of this product is shown on Figure 5 and the signals having an intensity larger than 7 % are summarized in Table 5:

Table 5 /relative intensities >7 %/

Peak	2 Θ	d (Å)	Intensity
1	6.400	13.7990	49
2	7.050	12.5281	100
3	8.990	9.8285	9
4	12.920	6.8464	8
5	16.860	5.2543	8
6	17.350	5.1070	10
7	18.740	4.7312	32
8	20.430	4.3435	8
9	21.240	4.1796	15
10	21.820	4.0698	53
11	22.660	3.9208	16
12	23.370	3.8033	8
13	28.830	3.0942	9

The invention also relates to the crystalline erlotinib 1,5-naphthalene-disulfonic acid /2:1/ salt of the Formula **6** which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.310; 12.540; 14.330; 18.750; 19.940; 21.690; 23.230; 25.220. More particularly this product can be characterized by the following X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.310; 12.540; 13.660; 14.330; 17.430; 18.750; 19.070; 19.940;

21.690; 22.640; 23.230; 25.220; 25.770; 27.490; 28.250; 28.860; 29.630; 32.820; 33.400. The characteristic X-ray powder diffractogram of this product is shown on Figure 6 and the signals having an intensity larger than 6 % are summarized in Table 6:

Table 6 /relative intensities >6 %/

Peak	2 Θ	d (Å)	Intensity
1	6.310	13.9956	100
2	12.540	7.0530	10
3	13.660	6.4771	10
4	14.330	6.1757	14
5	17.430	5.0837	8
6	18.750	4.7287	38
7	19.070	4.6500	28
8	19.940	4.4491	25
9	21.690	4.0939	26
10	22.640	3.9242	23
11	23.230	3.8259	30
12	25.220	3.5283	62
13	25.770	3.4543	40
14	27.490	3.2419	14
15	28.250	3.1564	8
16	28.860	3.0911	9
17	29.630	3.0125	7
18	32.820	2.7266	8
19	33.400	2.6805	8

According to the present invention there is also provided the crystalline erlotinib L-pyroglutamic acid /1:1/ salt of the Formula 7 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2°. 2 Θ): 7.180; 13.310; 14.920. 19.590; 20.850; 22.160; 23.100; 24.170; 26.500. More particularly this product can be characterized by the following X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.180; 7.180; 13.310; 14.920; 16.260;

16.610; 18.460; 19.060; 19.590; 20.080; 20.850; 22.160; 23.100; 24.170; 24.580; 25.070; 26.500; 27.360; 28.290; 28.670. The X-ray powder diffractogram of this product is shown on Figure 7 and the signals having an intensity larger than 5% are summarized in table 7:

Table 7 /relative intensities >5 %/

Peak	2 Θ	d (Å)	Intensity
1	5.180	17.0459	6
2	7.180	12.3016	100
3	13.310	6.6466	21
4	14.920	5.9328	13
5	16.260	5.4468	7
6	16.610	5.3328	8
7	18.460	4.8023	8
8	19.060	4.6525	9
9	19.590	4.5278	15
10	20.080	4.4184	12
11	20.850	4.2569	14
12	22.160	4.0081	40
13	23.100	3.8471	24
14	24.170	3.6792	21
15	24.580	3.6187	11
16	25.070	3.5491	10
17	26.500	3.3607	17
18	27.360	3.2570	11
19	28.290	3.1520	7
20	28.670	3.1111	8

The invention also relates to the crystalline erlotinib 1-hydroxy-2-naphthoic acid /1:1/ salt of the Formula **8** which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 4.300; 11.630; 14.340; 17.470; 19.140; 19.850; 22.800; 26.200. More particularly this product can be characterized by the following X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 4.300; 6.760; 11.630; 13.120; 13.750; 14.340; 16.860; 17.470;

18.540; 19.140; 19.850; 21.030; 22.800; 23.660; 24.540; 26.200; 28.580. The characteristic X-ray powder diffractogram of this product is shown on Figure 8 and the signals having an intensity larger than 6 % are summarized in Table 8:

Table 8 /relative intensities >6 %/

Peak	2 Θ	d (Å)	Intensity
1	4.300	20.5322	100
2	6.760	13.0649	7
3	11.630	7.6027	18
4	13.120	6.7424	13
5	13.750	6.4349	10
6	14.340	6.1714	39
7	16.860	5.2543	8
8	17.470	5.0722	18
9	18.540	4.7818	14
10	19.140	4.6332	46
11	19.850	4.4691	13
12	21.030	4.2209	11
13	22.800	3.8971	31
14	23.660	3.7573	15
15	24.540	3.6245	13
16	26.200	3.3985	29
17	28.580	3.1207	9

The invention also relates to the crystalline erlotinib DL-mandelic acid salt of the Formula **9** , which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.400; 9.160; 14.530; 18.140; 21.700; 23.010. More particularly this product can be characterized by the following X-ray powder diffraction peaks. 2 Θ (±0.2° 2 Θ): 5.400; 9.160; 14.530; 15.490; 17.040; 17.360; 18.140; 18.370; 20.190; 21.180; 21.700; 23.010; 23.800; 24.700; 25.230; 25.960; 27.030. The characteristic X-ray powder diffractogram of this

product is shown on Figure 9 and the signals having an intensity larger than 3 % are summarized in Table 9:

Table 9 /relative intensities >3 %/

Peak	2 Θ	d (Å)	Intensity
1	5.400	16.3519	100
2	9.160	9.6465	9
3	14.530	6.0912	8
4	15.490	5.7158	4
5	17.040	5.1992	5
6	17.360	5.1040	6
7	18.140	4.8863	7
8	18.370	4.8256	6
9	20.190	4.3946	6
10	21.180	4.1913	9
11	21.700	4.0920	33
12	23.010	3.8620	11
13	23.800	3.7355	7
14	24.700	3.6014	5
15	25.230	3.5269	5
16	25.960	3.4294	4
17	27.030	3.2960	4

According to a further aspect of the present invention there is provided a process for the preparation of erlotinib salts which comprises reacting an amorphous or crystalline form of erlotinib of the Formula **1** or an anhydrous form, hydrate or solvate thereof in a suitable organic solvent with the desired acid and separating the erlotinib salt formed.

The salts according to the present invention can be prepared by reacting erlotinib free base of the Formula **1** in an organic solvent with the desired acid, separating the crystallized salt and if desired washing with organic solvent.

The salts according to the present invention can also be prepared by reacting the free erlotinib base of the Formula **1** without isolation in an organic solvent with the desired acid, separating the crystallized salt and if desired washing it with an organic solvent.

The salt can be separated by known methods of pharmaceutical industry suitable for the separation of a solid phase and a liquid, such as filtration which is optionally carried out under atmospheric pressure or in vacuo or under pressure or by using a centrifuge.

For the salt formation according to the present invention mono-or polybasic organic or inorganic acids can be used, such as maleic acid, salicylic acid, L-mandelic acid, adipinic acid, 1,5-naphthalene-disulfonic acid, L-pyroglutamic acid ,1-hydroxy-2-naphthoic acid or DL-mandelic acid.

The process can be carried out in an organic solvent, e.g. C_{1-4} aliphatic alcohols, ethers, esters or mixtures thereof. It is preferred to use as organic solvent a C_{1-4} ether, ester or alcohol or a dipolar-aprotic solvent, particularly tetrahydrofurane, diethyl ether, ethyl acetate, acetonitrile, methanol, ethanol or 2-propanol or mixtures thereof.

The salt forming acid is preferably applied in a 0.3-3.0 molar equivalent amount related to the amount of the erlotinib of the Formula 1. One may proceed preferably by using the solution of the organic acid and carrying out the reaction at a temperature between 0°C and the boiling point of the solvent,

One may particularly preferably proceed by reacting the ethanolic solution of erlotinib of the Formula **1** with a solution containing a 0.3-3.0 molar equivalent of the acid at a temperature near to the boiling point of the solvent. The precipitated product is separated by filtration.

One may also proceed by using the acid in solid crystalline form and performing the reaction at a temperature between 0°C and the boiling point of the mixture or at the boiling point of the solvent.

One may proceed particularly preferably by reacting the ethanolic solution of erlotinib of the Formula **1** with a 0.3-3.0 molar equivalent amount of the solid organic acid at a

temperature near to the boiling point of the solvent. The precipitated product is separated by filtration.

The new erlotinib salts of the present invention can be prepared by dissolving erlotinib base of the Formula **1** in a suitable solvent, preferably a C_{1-6} alcohol, particularly ethanol, methanol or isopropanol and adding a 0.5-3.0, preferably a 0.5-1.0 molar equivalent amount of an acid in solid form or as a solution. If the salt precipitates at the temperature of the addition or under cooling it is filtered, if desired purified by digestion or recrystallization and finally filtered, washed and dried. If the precipitation does not spontaneously take place, the solvent is removed in vacuo and the residue is crystallized by adding a suitable solvent or solvent mixture, if desired purified by digestion or recrystallization and finally filtered, washed and dried.

The erlotinib maleic acid /1:1/ salt of the Formula **2** is preferably prepared by stirring the solution of the formed erlotinib base of the Formula **1** with an alcohol type solvent, preferably ethanol and adding the ethanolic solution of maleic acid at a temperature between 0°C and the boiling point of the solvent, preferably at a temperature between 0°C and 80°C, more preferably at 70°C. If necessary the reaction mixture is cooled to 5-25°C, the precipitated crystals are filtered, optionally washed and dried. The product is recrystallized from an alcohol type solvent or a mixture thereof formed with water, preferably from methanol, if necessary. From the erlotinib maleic acid /1:1/ salt of the Formula **2** thus obtained the anhydrous erlotinib maleic acid salt can be prepared by known methods e.g. by drying.

The erlotinib salicylic acid /1:1/ salt of the Formula **3** can be preferably prepared by stirring the erlotinib free base of the Formula **1** in an alcohol type solvent, preferably methanol, adding to the mixture solid crystalline salicylic acid at a temperature between 0°C and the boiling point of the solvent, preferably at a temperature between 0°C and 80°C. more preferably at 70°C. The reaction mixture is cooled to 5-25°C, the precipitated crystals are dried, optionally washed and dried. If desired the product is crystallized from an alcohol type solvent, preferably 2-propanol.

The erlotinib L-mandelic acid /1:1/ salt of the Formula **4** is prepared in an analogous manner to the preparation of the salicylic acid salt except that salicylic acid is replaced by L-mandelic acid.

The erlotinib adipinic acid /1:1/ salt of the Formula **5** can be prepared in an analogous manner to the preparation of the salicylic acid salt except that salicylic acid is replaced by an ethanolic solution of adipinic acid.

The erlotinib 1,5-naphthalene-disulfonic acid /2:1/ salt of the Formula **6** can be preferably prepared by stirring erlotinib free base /**1**/ in an alcohol type solvent, preferably ethanol, adding to the solution solid 1,5-naphthalene-disulfonic acid at a temperature between 0°C and the boiling point of the solvent, preferably between room temperature and 80°C, more preferably at 70°C, then stirring the mixture, preferably at room temperature overnight. The precipitated crystals are filtered, optionally washed and dried. The product is recrystallized from a polar-aprotic solvent, preferably from dimethyl sulfoxide.

The erlotinib L-pyroglutamic acid /1:1/ salt of the Formula **7** can be prepared in an analogous manner to the preparation of the salicylic acid salt except that salicylic acid is replaced by crystalline L-pyroglutamic acid.

The erlotinib 1-hydroxy-2-naphthoic acid /1:1/ of the Formula **8** can be prepared in an analogous manner to the preparation of the salicylic acid salt except that salicylic acid is replaced by crystalline 1-hydroxy-2-naphthoic acid.

The erlotinib DL-mandelic acid /1:1/ salt of the Formula **9** can be prepared in an analogous manner to the preparation of the salicylic acid salt except that salicylic acid is replaced by crystalline DL-mandelic acid.

In course of the thermal stress test and the forced stability test the decompositions in a pharmaceutical composition occurring during storage are constructed essentially in an accelerated manner. The results of these tests have predicted that under normal storage conditions the new erlotinib salts of the present invention would be more stable than the salts used in the marketed pharmaceutical conditions and those known from the prior art. The advantageous properties of the new erlotinib salts of the present invention are significant from

the point of view of the formulation of pharmaceutical compositions, the storage and the minimalization of the harmful effects exerted in the human body.

The stability of the new erlotinib salts of the present invention was subjected to detailed tests. As referent product the Form B erlotinib hydrochloride salt contained in the Tarceva^R medicine of the originator was used.

It has been surprisingly found that the erlotinib salts of the present invention show a higher stability than the salts known from prior art in the storage tests carried out under various conditions. It has been found that from the new salts of the present invention the maleic acid monohydrate and the adipinic acid salts proved to be particularly stable. Said salts are particularly useful in the preparation of pharmaceutical compositions.

The solubility of the new erlotinib salts of the invention was tested in a 0.1 M hydrochloric acid solution. The solubility was tested in said 0.1 M hydrochloric acid solution because the pH of this solution is 1.0 which is suitably similar to the pH value of 0.8-1.5 of the gastric fluid. It has been found in a surprising manner that the new erlotinib salts of the present invention show a better solubility than the hydrochloride salt known from prior art in the 0.1 M hydrochloric acid solution modeling the physiological conditions.

According to a further aspect of the present invention there are provided pharmaceutical compositions comprising a therapeutically effective amount of an erlotinib salt of the present invention and if desired a pharmaceutically active carrier.

According to a further aspect of the present invention there is provided the use of the erlotinib salts of the present invention for the preparation of pharmaceutical compositions.

The pharmaceutical compositions of the invention can be administered preferably orally. Such oral compositions may be e.g. tablets, capsules, dragées, solutions, elixirs, suspensions or emulsions.

The pharmaceutical compositions according to the present invention may contain conventional pharmaceutical carriers and/or auxiliary agents. As carrier e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth,

methyl cellulose, sodium carboxymethyl cellulose, low melting wax, PEG, cocoa butter etc. can be used. In case of capsules the carrier often serves as the capsule wall material so that no additional carrier is required. Chartula and lozenge are further oral pharmaceutical compositions. Particularly preferred oral administration forms are the powders, pirules, chartula and lozenges.

The tablets are prepared by admixing the active ingredient with suitable carriers in an appropriate ratio and from this mixture tablets of desired shape and size are pressed.

The powders are prepared by admixing the finely powdered active ingredient with the carriers. The liquid compositions may be solutions, suspensions and emulsions which can also be sustained release compositions. Aqueous solutions and aqueous propylene glycol solutions proved to be advantageous. Compositions suitable for parenteral administration can be prepared preferably in the form of aqueous polyethylene glycol solutions.

The pharmaceutical compositions of the invention can be preferably prepared in the form of dosage units which contain the desired amount of the active ingredient. The dosage units can be put on the market in the form of packages comprising separated amounts of the compositions e.g. packed tablets, capsules, vials or ampoules which contain the powder. The term "dosage unit" relates to the capsules, chartula, lozenge and also to the package comprising a suitable amount of dosage units.

According to a further aspect of the present invention there is provided a process for the preparation of the above pharmaceutical compositions which comprises admixing an erlotinib salt of the Formula **2, 3, 4, 5, 6, 7, 8** or **9** or a mixture thereof with pharmaceutically acceptable solid or liquid diluents and/or auxiliary agents and bringing the mixture to a galenic composition.

The pharmaceutical compositions of the present invention can be prepared by conventional methods of pharmaceutical industry. The pharmaceutical compositions of the present invention may contain further pharmaceutical active ingredients which are compatible with the new salts of the Formula **2, 3, 4, 5, 6, 7, 8** or **9** or mixtures thereof.

According to a further aspect of the present invention there is provided the use of the compounds of the Formula **2, 3, 4, 5, 6, 7, 8** or **9** as pharmaceutical active ingredient.

According to a further aspect of the present invention there is provided the use of the erlotinib salts of the present invention for the preparation of pharmaceutical compositions for the treatment or prophylaxis of non-small cell lung carcinoma or pancreas carcinoma.

According to a further aspect of the present invention there is provided the use of the salts of the present invention for the treatment or prophylaxis of non-small cell lung carcinoma and pancreas carcinoma.

The advantage of the present invention is that the compounds of the Formulae **2, 3, 4, 5, 6, 7, 8** and **9** are substances of uniform morphology and have an advantageous crystal form. For this reason the salts of the present invention possess preferable and reproducible properties, such as dissolving velocity, bioavailability, chemical stability and processing characteristics e.g. filtration, drying and tabletting properties.

The active ingredients of the Formulae **2, 3, 4, 5, 6, 7, 8** and **9** can be prepared by procedures readily suitable for industrial scale manufacture.

Short description of the Figures

Figure 1 shows the X-ray powder diffractogram of the M1 polymorph /Form 1/ of the erlotinib maleic acid monohydrate of the Formula **2**.

Figure 2 shows the X-ray powder diffractogram of the M2 polymorph /Form 2/ of the erlotinib maleic acid monohydrate salt of the Formula **2**.

Figure 3 shows the X-ray powder diffractogram of the erlotinib salicylic acid salt of the Formula **3**.

Figure 4 shows the X-ray powder diffractogram of the erlotinib L-mandelic acid salt of the Formula **4**.

Figure 5 shows the X-ray powder diffractogram of the erlotinib adipinic acid salt of the Formula **5**.

Figure 6 shows the X-ray powder diffractogram of the erlotinib 1,5-naphthalene-disulfonic acid salt of the Formula **6**.

Figure 7 shows the X-ray powder diffractogram of the erlotinib L-pyroglutamic acid salt of the Formula **7**.

Figure 8 shows the X-ray powder diffractogram of the erlotinib 1-hydroxy-2-naphthoic acid salt of the Formula **8**.

Figure 9 shows the X-ray powder diffractogram of the erlotinib DL-mandelic acid salt of the Formula **9**.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples which serve the purpose of illustration only.

EXAMPLES

The erlotinib base used in the following Examples is prepared from erlotinib hydrochloride by methods well-known for the person skilled in the art. The erlotinib hydrochloride was obtained from the firm Zheijang Jiuzhou /China/.

The NMR spectra of the new salts according to the present invention is registered by use of the following apparatus: VARIAN INOVA 500 /500 MHz/, BRUKER AVANCE III 400/400 MHz/.

The X–ray powder diffraction data of all prepared products are obtained under the following measuring conditions:

Apparatus:	Rigaku Corporation, Miniflex II. powder diffracto-meter
Radiation:	CuKα1 (λ=1.54059 Å)
Accelerating voltage:	30 kV

Anode current:	15 mA
Uptake velocity:	1.5 °/minute
Step interval:	0.02 °
Measuring range:	3.0-40.0° 2θ (continuous θ-θ, reflexion)
Sample holder:	zero background, Si one-crystal
Rotation speed of the sample holder:	1 rotation/sec
Type of detector:	MiniFlex2
Soller:	2,5°
Orifices:	1,25° (divergence, scattered); 0,3 mm (receiving)
Preparatory process of the sample:	without powdering at room temperature
Reference sample:	RSRP-43275 Si plate

Example 1

Preparation of the polymorphs M1 and M2 of the erlotinib maleic acid /1:1/ monohydrate salts Form 1 and Form 2 (compound of the Formula 2).

a) Into an apparatus 10 ml of ethanol are weighed in whereupon 0.496 g /1.26 millimoles/ of erlotinib base is dissolved therein under intensive stirring and under reflux. To the reaction mixture a solution of 0.146 g /1.26 millimoles/ of maleic acid is added at this temperature under stirring. After some seconds the precipitation of crystals begins. Stirring is continued until the reaction mixture cools to room temperature. The precipitated crystalline product is filtered and washed with tertiary butyl methyl ether. The crude product is dried at 50°C under a pressure of 160 mbar for 10 hours.

Yield: 0.63 g (98 %)

Mp.: 164.5-167°C

b) 0.48 g of the crude product thus obtained is recrystallized from 27 ml of methanol. The mixture is allowed to stand in a refrigerator overnight, the precipitated product is filtered, washed with a small amount of cold methanol and tertiary butyl methyl ether.

Thus 0.41 g (85 %) of the M1 polymorph /Form M1/ are obtained as white crystals.

Mp.: 169.4-173°C.

Analysis for the Formula $C_{22}H_{23}N_3O_4 \cdot C_4H_4O_4 \cdot H_2O$ (527,53):

Calc:	C: 59.20	H: 5.54	N: 7.97
Found:	C: 60.01	H: 5.67	N: 7.93

Water content (KF method) 3.79 %.

IR (KBr, cm^{-1}): 3275, 1584, 1524, 1447, 1039.

^{1}H-NMR (DMSO-d_6, 500 MHz): 10.11 (b, 1H), 8.66 (s, 1H), 7.93 (m, 1H), 7.92 (s, 1H),7.82 (m, 1H), 7.46 (m, 1H), 7.32 (m, 1H), 7.22 (s, 1H), 6.19 (s, 2H), 4,30 (m, 4H), 4.17 (s, 1H), 3.80 (m, 2H), 3.77 (m, 2H), 3.37 (s, 3H), 3.37 (s, 3H).

^{13}C-NMR (DMSO-d_6, 125 MHz) 167.07, 157.11, 154.80, 151.20, 148.90, 141.96, 138.74, 132.80, 129.21, 127.90, 126.15, 123.84, 122.11, 108.26, 105.03, 103.84, 83.35, 81.02, 70.11, 68.71, 68.57, 58.55.

c) 3.0 g (5.9 millimoles) of the crude product obtained according to par. a) are recrystallized from 90 ml of a 80:20 mixture of methanol and water whereupon the reaction mixture is cooled to 20-25°C within an hour under stirring. The precipitate is filtered and washed with a 80:20 mixture of methanol and water. The wet solid is dried at room temperature in vacuo until constant weight.

Yield: 2.67 g (89%), A pale fluffy precipitate of the M2 polymorph /Form M2/.

Mp. 167.9-171.5°C.

The ^{1}H-NMR and ^{13}C-NMR data of the product are identical with the values disclosed in point b).

Example 2

Preparation of the erlotinib salicylic acid salt /1:1/ /compound of the Formula 3/

Into an apparatus 25 ml of ethanol are weighed in whereupon 1.3 g (3.3 millimoles) of erlotinib base are dissolved therein under stirring and reflux. To the reaction mixture at this temperature 0.454 g (3.3 millimoles) of salicylic acid are added under stirring; the colour of the solution becomes yellow. The reaction mixture is allowed to cool to room temperature while the precipitation of crystals begins. The precipitated crystalline product is filtered, washed with tert.butyl methyl ether and washed on the air at room temperature for a day.

Yield: 1.51 g (86 %).

The crude product thus obtained is recrystallized from 30 ml of isopropanol. The precipitate is filtered and washed with a small amount of cold isopropanol and tertiary butyl methyl ether.
Yield :0.85 g (57 %), a pale yellow substance.
Mp.: 138.8-142.4°C.
Analysis for the Formula $C_{22}H_{23}N_3O_4 \cdot C_7H_6O_3$ (531.57):

Calc:	C: 65.53	H: 5.50	N: 7.90
Found:	C: 64.47	H: 5.72	N: 7.70

IR (KBr, cm^{-1}): 3266, 3063, 1642, 1588, 1459, 1127.
^{1}H-NMR (DMSO-d_6, 500 MHz): 9.66 (b, 1H), 8.56 (s, 1H), 8.00 (m, 1H), 7.90 (m, 1H), 7.89 (s, 1H), 7.81 (m, 1H), 7.48 (m, 1H), 7.42 (m, 1H), 7.25 (s, 1H), 6.93 (m, 1H), 6.90 (m, 1H), 4.30 (m, 4H), 4.19 (s, 1H), 3.79 (m, 2H), 3.77 (m, 2H), 3.39 (s, 3H), 3.37 (s, 3H).
^{13}C-NMR (DMSO-d_6, 125 MHz) 172.13, 161.43, 156.50, 154.10, 152.44, 148.46, 145.76, 139.66, 135.28, 130.39, 129.03, 126.83, 125.22, 122.98, 121.95, 118.97, 117.07, 113.90, 108.88, 107.50, 103.55, 83.58, 80.69, 70.19, 68.60, 68.30, 58.50.

Example 3

Preparation of the erlotinib L-mandelic acid salt/1:1/ /compound of the Formula 4/

Into an apparatus 10 ml of ethanol are weighed in under intensive stirring, whereupon 0.537 g /1.36 millimoles/ of erlotinib base are dissolved therein under intensive stirring and reflux. To the reaction mixture at this temperature 0.207 g /1.36 millimoles/ of L-mandelic acid are added, whereby the colour of the solution becomes yellow. The reaction mixture is allowed to stand overnight at room temperature under stirring whereby the slow precipitation of crystals begins. The reaction mixture is allowed to stand at room temperature overnight. The precipitated crystalline product is filtered and washed with a small amount of ethanol and tertiary butyl methyl ether.
Yield 0.54 g (72%).

0.325 g of the crude product thus obtained is recrystallized from 25 ml of isopropanol. The suspension is allowed to stand overnight, then filtered and washed with a small amount of cold isopropanol and tertiary butyl methyl ether.

Yield: 0.29 g (89 %).

Mp.: 140.4-141.1°C.

Analysis for the Formula a $C_{22}H_{23}N_3O_4 \cdot C_8H_8O_3$ (545.60):

Calc:	C: 66.04	H: 5.73	N: 7.70
Found:	C: 66.26	H: 5.72	N: 7.65

IR (KBr, cm^{-1}): 3231, 2927, 1636, 1583, 1515, 1448, 1365, 1327, 1278.

^{1}H-NMR (DMSO-d_6, 500 MHz): 9.48 (b, 1H), 8.02 (m, 1H), 7.92 (m, 1H), 7.87 (s, 1H), 7.42 (m, 2H), 7.41 (m, 1H), 7.35 (m, 2H), 7.29 (m, 1H), 7.24 (s, 1H), 7.23 (m, 1H), 5.05 (s, 1H), 4.30 (m, 4H), 4.18 (s, 1H), 3.80 (m, 2H), 3.76 (m, 2H), 3.39 (s, 3H), 3.36 (s, 3H).

^{13}C-NMR (DMSO-d_6, 125 MHz) 174.26, 156.32, 153.90, 152.90, 148.34, 147.05, 140.43, 139.97, 129.03, 128.26, 127.77, 126.79, 126.53, 124.95, 122.74, 121.93, 109.10, 108.33, 103.46, 83.68, 80.62, 72.60, 70.30, 70.23, 68.60, 68.24, 58.56.

Example 4

Preparation of the erlotinib adipinic acid salt /1:1/ /compound of the Formula 5/

Into an apparatus 10 ml of ethanol are weighed in under intensive stirring whereupon 0.604 g /1.54 millimoles/ of erlotinib base are dissolved therein under reflux. To the reaction mixture at this temperature a solution of 0.225 g /1.54 millimoles/ of adipinic acid in 5 ml of ethanol is added under stirring. The reaction mixture is allowed to cool to room temperature under stirring while the precipitation of crystals begins already in the warm solution, The precipitated product is filtered and washed with tertiary butyl methyl ether. The product is dried at room temperature on the air for a day.

Yield: 0.70 g (84 %).

The crude product thus obtained is recrystallized from 25 ml of isopropanol. The precipitate is filtered and washed with a small amount of cold isopropanol and tertiary butyl methyl ether. Thus 0.55 g (78 %) of a white crystalline product is obtained.

Mp.: 150.3-154.0°C

Analysis for the Formula $C_{22}H_{23}N_3O_4 \cdot C_6H_{10}N_3O_4$ (539.59):

Calc:	C: 62.33	H: 6.16	N: 7.79
Found:	C: 62.63	H: 6.29	N: 7.69

IR (KBr, cm^{-1}): 3254, 2929, 2456, 1606, 1574, 1515, 1446, 1327, 1286, 1128, 1073, 1035.

^{1}H-NMR (DMSO-d_6, 400 MHz): 12.00 (b, 2H), 9.46 (b, 1H), 8.51 (s, 1H), 8.01 (m, 1H), 7.92 (m, 1H), 7.87 (s, 1H), 7.41 (m, 1H), 7,23 (s, 1H), 7.22 (m, 1H), 4.30 (m, 4H), 3.80 (m, 2H), 3.76 (m, 2H), 3.39 (s, 3H), 3.37 (s, 3H), 2.21 (m, 4H), 1.52 (m, 4H).

^{13}C-NMR (DMSO-d_6, 100 MHz): 174.46, 156.29, 153.88, 152.93, 148.33, 147.17, 139.98, 129.02, 126.49, 124.91, 122.70, 121.92, 109.11, 108.40, 103.45, 83.67, 80.61, 70.31, 70.24, 68.59, 68.23, 58.56, 33.56, 24.21.

Example 5

Preparation of the erlotinib 1,5-naphthalene-disulfonic acid salt /2:1/ /compound of the Formula 6/

Into an apparatus 10 ml of ethanol are weighed in under vigorous stirring whereupon 0.730 g /1.86 millimoles/ of erlotinib base are dissolved therein under stirring and reflux. To the reaction mixture 0.335 g /0.93 millimoles/ of 1,5-naphthalene-disulfonic acid is added under stirring and the reaction mixture is stirred overnight without heating. The precipitated crystalline product is filtered, washed with a small amount of cold ethanol and tert.butyl methyl ether.

Yield 0.83 g (78 %) white crystals.

1,06 g of the crude product thus obtained are recrystallized from 20 ml of dimethyl sulfoxide. The precipitate is filtered, washed with a small amount of cold dimethyl sulfoxide and tertiary butyl methyl ether.

Yield: 0.85 g (80 %), ochre colored substance.

Mp.: >290°C (decomposition)

Analysis for the Formula $(C_{22}H_{23}N_3O_4)_2 \cdot C_{10}H_8S_2O_6$ (1075.59):

Calc:	C: 60.32	H: 5.06	N: 7.82	S: 5.96
Found:	C: 59.96	H: 4.96	N: 7.82	S: 5.89

IR (KBr, cm^{-1}): 3269, 1637, 1575, 1451, 1165, 1029, 607.

^{1}H-NMR (DMSO-d_6, 500 MHz): 14.53 (b), 8.88 (m, 1H), 8.86 (s, 1H), 8.06 (s, 1H), 7.95 (m, 1H), 7.83 (m, 1H), 7.71 (m, 1H), 7.51 (m, 1H), 7.43 (m, 1H), 7.39 (m, 1H), 7.29 (s, 1H), 4.31 (m, 4H), 4.27 (s, 1H), 3.76 (m, 2H), 3.36 (s, 3H), 3.35 (s, 3H).

^{13}C-NMR (DMSO-d_6, 125 MHz): 158.26, 156.01, 149.66, 149.25, 143.95, 137.26, 135.81, 129.66, 129.63, 129.50, 129.16, 127.69, 125.27, 124.15, 123.98, 122.35, 107.34, 104.56, 101.12, 82.94, 81.57, 69.98, 69.96, 69.01, 68.92, 58.56.

Example 6

Preparation of the erlotinib L-pyroglutamic acid salt /1:1/ /compound of the Formula 7/

Into an apparatus 20 ml of ethanol are weighed in under intensive stirring whereupon 1.000 g (2.54 millimoles) of erlotinib base are dissolved therein under stirring and reflux. To the reaction mixture at this temperature 0.328 g /2.54 millimoles/ of L-pyroglutamic acid is added under stirring. The reaction mixture is allowed to cool to room temperature under stirring whereby the slow precipitation of crystals begins. The reaction mixture is allowed to stand at room temperature for an hour, the precipitated crystalline product is filtered and washed with a small amount of cold ethanol and thereafter with tertiary butyl methyl ether.
Yield 0.87 g (65 %)

0.717 g of the crude product is recrystallized from 25 ml of isopropanol. The suspension obtained is allowed to stand in a refrigerator overnight, filtered and washed with a small amount of cold isopropanol and thereafter with tertiary butyl methyl ether.
Yield: 0.51 g (72 %).
Mp.: 158.3-160.7°C.
Analysis for the Formula $C_{22}H_{23}N_3O_4 \cdot C_5H_7NO_3$ (522.56):

Calc:	C: 62.06	H: 5.79	N: 10.72
Found:	C: 60.97	H: 6.08	N: 10.65

IR (KBr, cm^{-1}): 3319, 1691, 1628, 1520, 1447, 1279, 1129.
^{1}H-NMR (DMSO-d_6, 500 MHz): 12.74 (b), 9.47 (b, 1H), 8.35 (s, 1H), 8.01 (m, 1H), 7.92 (m, 1H), 7.90 (b, 1H), 7.87 (s, 1H), 7.41 (m, 1H), 7.23 (s, 1H), 7.22 (m, 1H), 4.30 (m, 4H), 4.18 (s, 1H), 4.09 (m, 1H), 3.80 (m, 2H), 3.76 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 2.34 (m, 1H), 2.14 (m, 2H), 1.99 (m, 1H).
^{13}C-NMR (DMSO-d_6, 125 MHz) 177.11, 174.57, 156.29, 153.88, 152.91, 148.32, 147.12, 139.97, 129.02, 126.50, 124.92, 122.70, 121.91, 109.10, 108.37, 103.44, 83.67, 80.62, 70.31, 70.23, 68.59, 68,23, 58.56, 58.50, 54.93, 29.22, 24.77.

Example 7

Preparation of erlotinib 1-hydroxy-2-naphthoicc acid salt /1:1/ /compound of the Formula 8/

Into an apparatus 15 ml of ethanol are weighed in under vigorous stirring, whereupon 0.704 g /1.79 millimoles/ of erlotinib base are dissolved therein under stirring and reflux. To the reaction mixture at this temperature 0.336 g /1.79 millimoles/ of 1-hydroxy-2-naphthoic acid are added under stirring. A dark yellow solution is obtained. The reaction mixture is allowed to cool to room temperature under stirring whereby a slow precipitation of crystals can begin. The reaction mixture is allowed to stand in a refrigerator overnight the precipitated product is filtered and washed with a small amount of cold ethanol and thereafter with tertiary butyl methyl ether.

Yield: 0.77 g (74 %)

0.700 g of the crude product thus obtained is recrystallized from 10 ml of ethanol. The suspension obtained is allowed to stand in a refrigerator overnight and washed with a small amount of cold isopropanol and thereafter with tertiary butyl methyl ether.

Yield: 0.47 g (67 %)

Mp.:144.2-147°C.

Analysis for the Formula $C_{22}H_{23}N_3O_4 \cdot C_{11}H_8O_3$ (581.63):

Calc:	C: 68.15	H: 5.37	N: 7.22
Found:	C: 67.39	H: 5.46	N: 7.22

IR (KBr, cm^{-1}): 3258, 1648, 1583, 1439, 1403, 775.

^{1}H-NMR (DMSO-d_6, 500 MHz): 12-10 (b), 9.74 (b, 1H), 8.58 (s, 1H), 8.29 (m, 1H), 8.00 (m, 1H), 7.89 (m, 3H), 7.78 (d, J=8.7 Hz, 1H), 7.65 (m, 1H9, 7.56 (m, 1H), 7.43 (m, 1H), 7.34 (d, J=8.7 Hz, 1H), 7.27 (m, 1H), 7.25 (s, 1H), 4.30 (m, 4H), 4.21 (s, 1H), 3.78 (m, 4H), 3.39 (s, 2H), 3.37 (s,3H).

^{13}C-NMR (DMSO-d_6, 125 MHz) 173.06, 160.68, 156.54, 154.14, 152.36, 148.49, 145.53, 139.60, 129.22, 129.05, 127.69, 126.91, 125.80, 125.28, 125.23, 124.43, 123.22, 123.04, 121.96, 117.88, 108.84, 107.35, 106.93, 103.57, 83.56, 80.73, 70.24, 70.18, 68.60, 68.31, 58.53, 58.49.

Example 8

Preparation of erlotinib DL-mandelic acid salt /1:1/ /compound of the Formula 9/

Into an apparatus 20 ml of ethanol are weighed in whereupon 1.00 g /2.54 millimoles/ of erlotinib base are dissolved therein under intensive stirring and reflux. To the reaction mixture at this temperature 0.387 g /2.54 millimoles/ of DL-mandelic acid are added. The colour of the solution becomes yellow. The reaction mixture is allowed to cool to room temperature whereby a slow precipitation of crystals begins on rubbing. The reaction mixture is allowed to stand at room temperature overnight the precipitated product is filtered and washed with a small amount of cold ethanol and tertiary butyl methyl ether.

Yield.: 0.80 g (80 %)

The crude product thus obtained is recrystallized from 10 ml of isopropanol. The suspension obtained is allowed to stand in a refrigerator, filtered and washed with a small amount of cold isopropanol and thereafter with tertiary butyl methyl ether.

Yield: 0.60 g (75 %)

Mp.: 138.6-140.9°C.

Analysis for the Formula $C_{22}H_{23}N_3O_4 \cdot C_8H_8O_3$ (545.60):

Calc:	C: 66.04	H: 5.73	N: 7.70
Found:	C: 65.24	H: 5.73	N: 7.73

IR (KBr, cm^{-1}): 3284, 2933, 1583, 1513, 1448, 1128, 946, 861, 731, 699.

^{1}H-NMR (DMSO-d_6, 500 MHz): 9.48 (b, 1H), 8.02 (m, 1H), 7.92 (m, 1H), 7.87 (s, 1H), 7.42 (m, 2H), 7.41 (m, 1H), 7.35 (m, 2H), 7.29 (m, 1H), 7.24 (s, 1H), 7.23 (m, 1H), 5.05 (s, 1H), 4.30 (m, 4H), 4.18 (s, 1H), 3.80 (m, 2H), 3.76 (m, 2H), 3.39 (s, 3H), 3.36 (s, 3H).

^{13}C-NMR (DMSO-d_6, 125 MHz) 174.26, 156.32, 153.90, 152.90, 148.34, 147.05, 140.43, 139.97, 129.03, 128.26, 127.77, 126.79, 126.53, 124.95, 122.74, 121.93, 109.10, 108.33, 103.46, 83.68, 80.62, 72.60, 70.30, 70.23, 68.60, 68.24, 58.56.

Example 9

Determination of the solubility of erlotinib maleate and erlotinib adipinate salts in 0.1 M hydrochloric acid solution

Erlotinib maleate monohydrate salt: 10 mg of erlotinib maleate monohydrate are weighed in a 25 ml round-bottomed flask whereupon a 0.1 M hydrochloric acid solution /exact titre/ is added under continuous stirring /Heidolph 3001 mixer, 1000 rpm/ After addition of 10 ml of the hydrochloric acid solution immediately a clear solution is obtained.

Erlotinib adipinate salt: 10 mg of erlotinib adipinate are weighed in a 25 ml round-bottomed flask whereupon a 0.1 M hydrochloric acid solution /exact titre/ is added under continuous stirring /Heidolph 3001 mixer. 1000 rpm/. After addition of 2 ml of the hydrochloric acid solution immediately a clear solution is obtained.

Erlotinib hydrochloride: 10 mg of erlotinib hydrochloride salt are weighed into a 50 ml round-bottomed flask whereupon a 0.1 M hydrochloric acid solution /exact titre/ is added under continuous stirring. After addition of 50 ml of the hydrochloric acid solution no clear solution is obtained even after stirring for two hours /according to visual observation the mixture still contains insoluble particles/.

Solubility in a 0.1 M hydrochloric acid solution	
Erlotinib maleate monohydrate salt M1 polymorph /Form M1/	≥1 mg/cm^3
Erlotinib adipinate salt	≥5 mg/cm^3
Erlotinib hydrochloride salt	<0.4 mg/ml (pure solution was not obtained)
Erlotinib maleate monohydrate salt M2 polymorph /Form M2/	≥0.53 mg/cm^3

Example 10

Preparation of erlotinib maleate monohydrate /compound of the Formula 2/ and erlotinib adipinate /compound of the Formula 5/ without isolating the erlotinib base

3.0 g /6.98 millimoles/ of erlotinib hydrochloride are intensively stirred in the mixture of 100 ml of ethyl acetate, 60 ml of water and 30 ml of a concentrated ammonium hydroxide solution

for 30 minutes /Heidolph MR 3001, 1000 rpm/ at 50°C. The phases are separated and the strongly alkaline aqueous layer is washed twice with 80 ml of ethyl acetate each and thereafter with 50 ml ethyl acetate at 50°C the solution layers are well separated and are completely clear. The united ethyl acetate phases are washed four times with 100 ml of water each at the above temperature /the duration of each washing step is 15 minutes/. After each washing step clear well-separated phases are obtained. Finally the ethyl acetate phase is washed with 100 ml of a saturated sodium chloride solution, which is then dried over sodium sulfate and the drying agent is filtered off. Thus 310 ml /total volume/ of a solution are obtained which can be used in the salt forming reactions.

a) Salt formation with maleic acid /preparation of the compound of the Formula 2/

To the 310 ml of the ethyl acetate solution thus obtained a solution of 0.81 g (6.98 millimoles) of maleic acid and 10 ml of ethanol is added under intensive stirring /Heidolph MR 3001, 1000 rpm/ at room temperature. The precipitation of crystals begins, whereupon the mixture is stirred for a further period of 24 hours, the precipitated crystals are filtered, washed with 20 ml of tert. butyl methyl ether and dried at 50°C under a pressure of 160 mbar for 20 hours.
Yield: 3.17 g (89 %).

b) Salt formation with adipinic acid /preparation of the compound of the Formula 5/

One proceeds according to point a) except that to the ethyl acetate solution 1.02 g (6.98 millimoles) of adipinic acid in 20 ml of ethanol is added. Crystallization is started by using a seeding crystals and external ice-water cooling. After the beginning of the crystal precipitation the mixture is stirred for a further period of 24 hours. The precipitated crystals are filtered, washed with 20 ml of tert. butyl methyl ether and dried at 50°C under a pressure of 160 mbar for 20 hours.
Yield 2.71 g (72 %).

The further advantage of the above salt formation procedures is that as a result of the aqueous washing steps the precipitated salt contains no residual inorganic contaminations /e.g. sodium chloride/ contrary e.g. to the precipitation of the base carried out from an alcoholic solution with sodium acetate.

Claims

1. Erlotinib salt selected from the group consisting of the maleic acid salt, salicylic acid salt, L-mandelic acid salt, adipinic acid salt, 1,5-naphthalene-disulfonic acid salt, L-pyroglutamic acid salt, 1-hydroxy-2-naphthoic acid salt and (D,L) mandelic acid salt and amorphous and crystalline forms, hydrates and solvates thereof.

2. M1 polymorph /Form M1/ of erlotinib maleic monohydrate acid salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.870; 8.190; 8.880; 12.760; 13.740; 16.080; 19.430; 20.850; 21.710; 25.030; 25.740; 26.920; 28.450.

3. M1 polymorph /Form M1/ of erlotinib maleic acid salt monohydrate according to Claim 2 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.870; 8.190; 8.880; 10.690; 12.760; 13.740; 16.080; 17.700; 18.490; 19.110; 19.430; 20.850; 21.170. 21.710; 24.750; 25.030; 25.740; 26.920; 27.720; 28.450; 32.230.

4. M2 polymorph /Form M2/ of erlotinib maleic acid salt monohydrate according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.710; 8.018; 8.702; 12.552; 12.951; 13.533; 18.224; 18.859; 19.142; 21.385; 24.395; 25.960.

5. M2 polymorph /Form M2/ of erlotinib maleic acid salt monohydrate according to Claim 4 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.710; 8.018; 8.702; 10.494; 10.891; 12.552; 12.951; 13.533; 17.510; 18.224; 18.859; 19.142; 20.454; 20.843; 21.385; 22.806; 24.395; 25.316; 25.960; 28.979; 30.413; 31.194; 34.408.

6. Erlotinib salicylic acid /1:1/ salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.830; 6.990; 16.060; 23.490; 26.000.

7. Erlotinib salicylic acid /1:1/ salt according to Claim 6 which has the following characteristic X-ray powder diffraction peaks: (±0.2° 2 Θ): 5.830; 6.990; 16.060; 20.220; 22.740; 23.490; 24.930; 26.000.

8. Erlotinib L-mandelic acid /1:1/ salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2°. 2 Θ): 6.040; 12.190; 16.200; 17.090; 18.270; 19.230; 20.030; 23.250; 24.870. 26.170.

9. Erlotinib L-mandelic acid /1:1/ salt according to Claim 8 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.040; 8.010; 12.190; 16.200; 18.270; 19.230; 20.030; 21.170; 21.780; 22.630; 23.250; 24.870; 26.170.

10. Erlotinib adipinic acid salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.400; 7.050; 8.990; 12.920; 18.740; 21.820; 22.660; 28.830.

11. Erlotinib adipinic acid salt according to Claim 10 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.400; 7.050; 8.990; 12.920; 16.860; 17.350; 18.740; 20.430; 21.240; 21.820; 22.660; 23.370; 28.830.

12. Erlotinib 1.5-naphthalene-disulfonic acid salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.310; 12.540; 14.330; 18.750; 19.940; 21.690; 23.230; 25.220.

13. Erlotinib 1.5-naphthalene-disulfonic acid salt according to Claim 12 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 6.310; 12.540; 13.660; 14.330; 17.430; 18.750; 19.070; 19.940; 21.690; 22.640; 23.230; 25.220; 25.770; 27.490; 28.250; 28.860; 29.630; 32.820; 33.400.

14. Erlotinib L-pyroglutamic acid salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2°. 2 Θ): 7.180; 13.310; 14.920. 19.590; 20.850; 22.160; 23.100; 24.170; 26.500.

15. Erlotinib L-pyroglutamic acid salt according to Claim 14 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.180; 7.180; 13.310; 14.920; 16.260; 16.610; 18.460; 19.060; 19.590; 20.080; 20.850; 22.160; 23.100; 24.170; 24.580; 25.070; 26.500; 27.360; 28.290; 28.670.

16. Erlotinib 1-hydroxy-2-naphthoic acid salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2°. 2 Θ): 4.300; 11.630; 14.340; 17.470; 19.140; 19.850; 22.800; 26.200.

17. Erlotinib 1-hydroxy-2-naphthoic acid salt according to Claim 16 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 4.300; 6.760; 11.630; 13.120; 13.750; 14.340; 16.860; 17.470; 18.540; 19.140; 19.850; 21.030; 22.800; 23.660; 24.540; 26.200; 28.580.

18. Erlotinib DL-mandelic acid salt according to Claim 1 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2°. 2 Θ): 5.400; 9.160; 14.530; 18.140; 21.700; 23.010.

19. Erlotinib DL-mandelic acid salt according to Claim 18 which has the following characteristic X-ray powder diffraction peaks: 2 Θ (±0.2° 2 Θ): 5.400; 9.160; 14.530; 15.490; 17.040; 17.360; 18.140; 18.370; 20.190; 21.180; 21.700; 23.010; 23.800; 24.700; 25.230; 25.960; 27.030.

20. Process for the preparation of erlotinib salts according to any of Claims 1 to 19, characterized in that it comprises reacting erlotinib base with an organic acid in an organic solvent or a mixture of an organic solvent and water and separating the erlotinib salt formed.

21. Process according to Claim 20 characterized in that it comprises using the acid in a 0.3-3.0 molar equivalent amount. preferably in a 0.5-1.0 molar equivalent amount.

22. Process according to any of Claims 20 and 21 characterized in that the used organic solvent is a C_{1-4} alcohol. an ether. ester or a dipolar aprotic solvent or a mixture thereof.

23. Process according to Claim 22 which characterized in that used solvent is tetrahydrofurane. diethyl ether. ethyl acetate. acetonitrile. methanol. ethanol. 2-propanol or a mixture thereof.

24. Process according to any of Claims 20 to 23 characterized in that the reaction is carried out at a temperature between 0°C and the boiling point of the solvent. preferably between room temperature and 80°C.

25. Pharmaceutical composition comprising an erlotinib salt according to any of Claims 1 to 19 in an admixture with conventional pharmaceutical auxiliary agents.

26. Process for the preparation of pharmaceutical compositions according to Claim 25 characterized in that it comprises admixing a therapeutically effective amount of an erlotinib salt according to any of Claims 1 to 19 with a pharmaceutically acceptable carrier and optionally with further pharmaceutically acceptable auxiliary agents and bringing the mixture into a galenic form.

27. Erlotinib salts according to any of Claims 1 to 19 for use in medicine.

28. Erlotinib salts according to any of Claims 1 to 19 for use in the treatment or prophylaxis of non-small cell lung carcinoma or pancreas carcinoma.

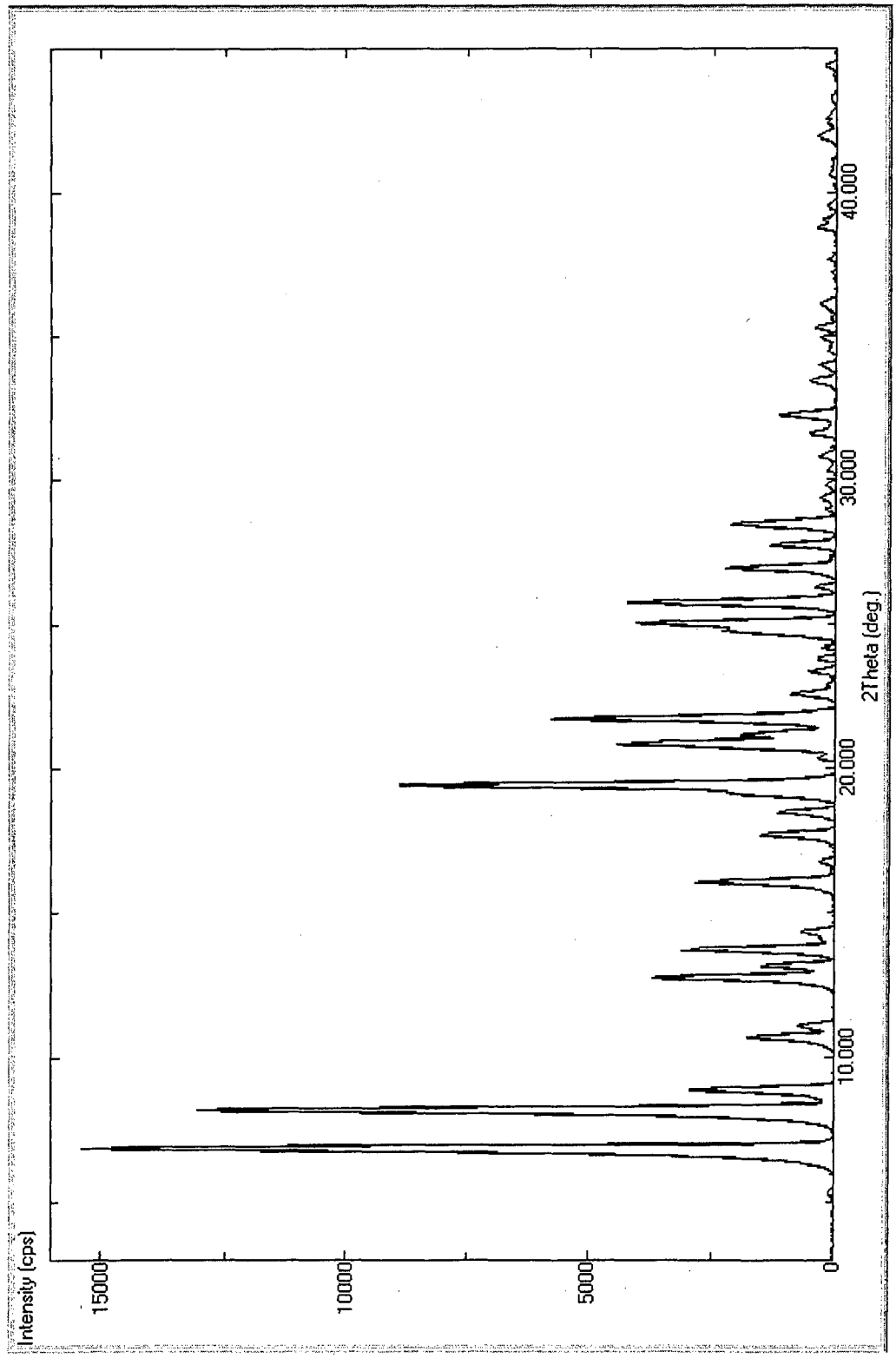

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Fig. 1.

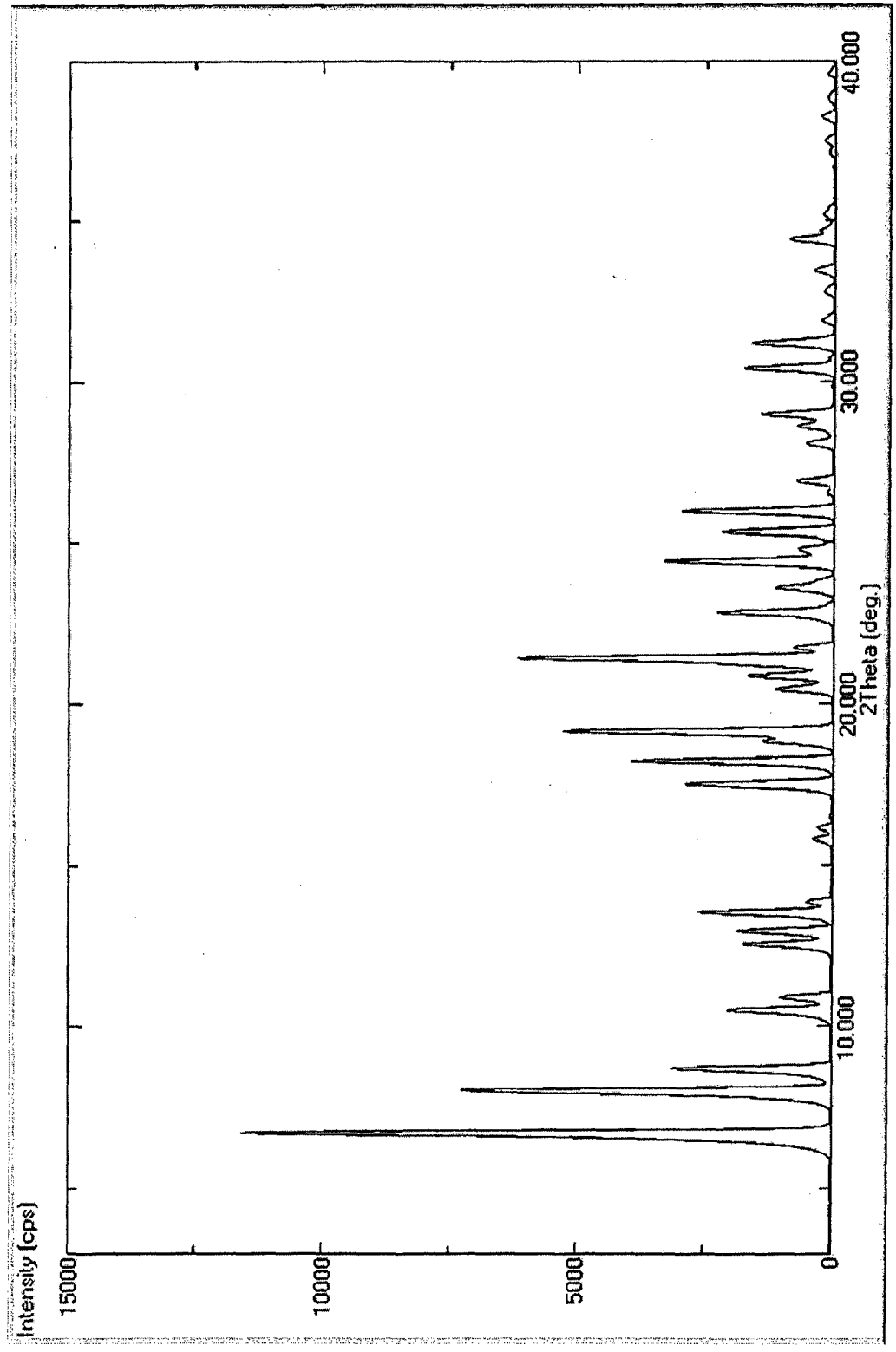

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Fig. 2.

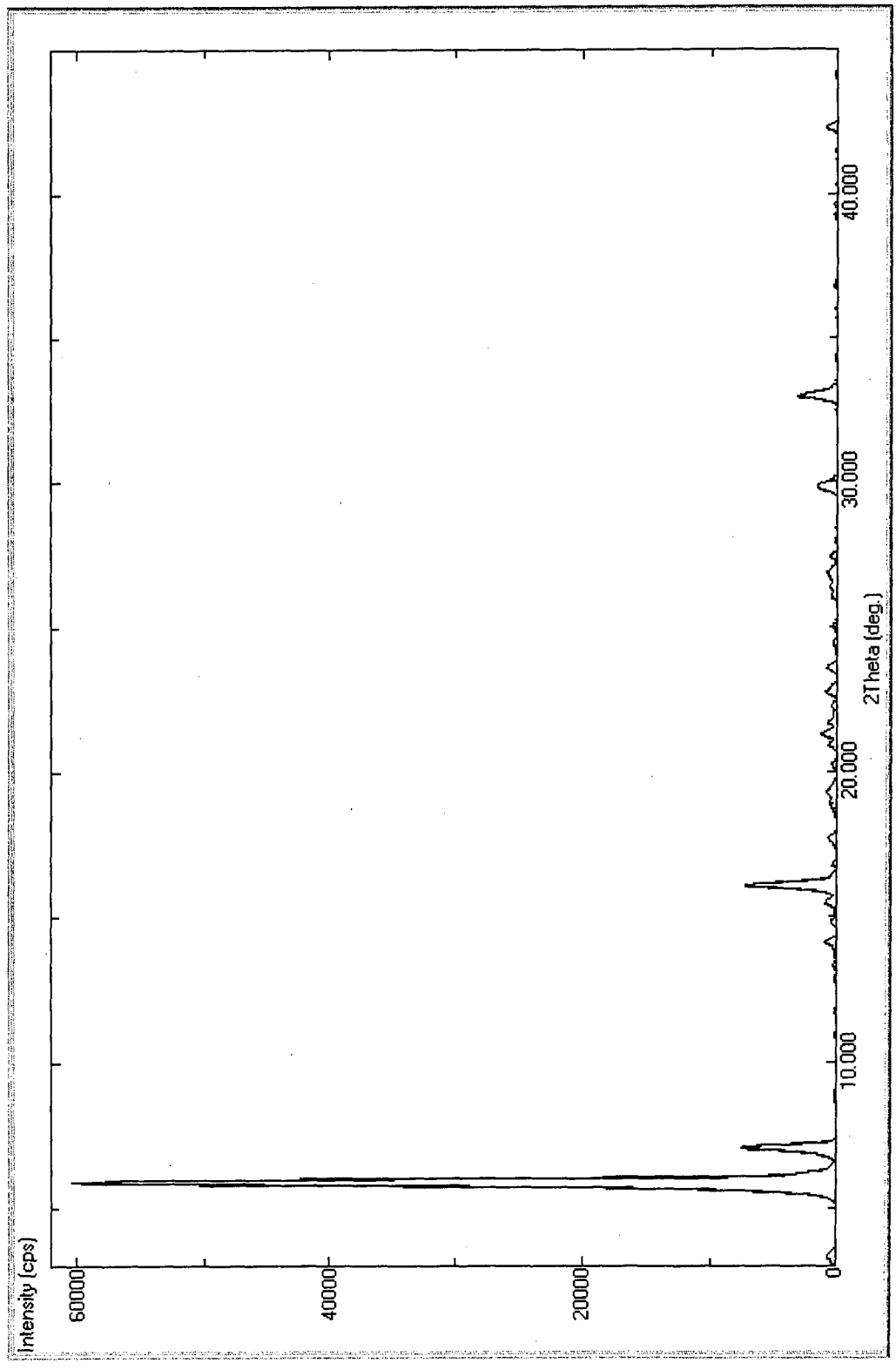

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Fig. 3.

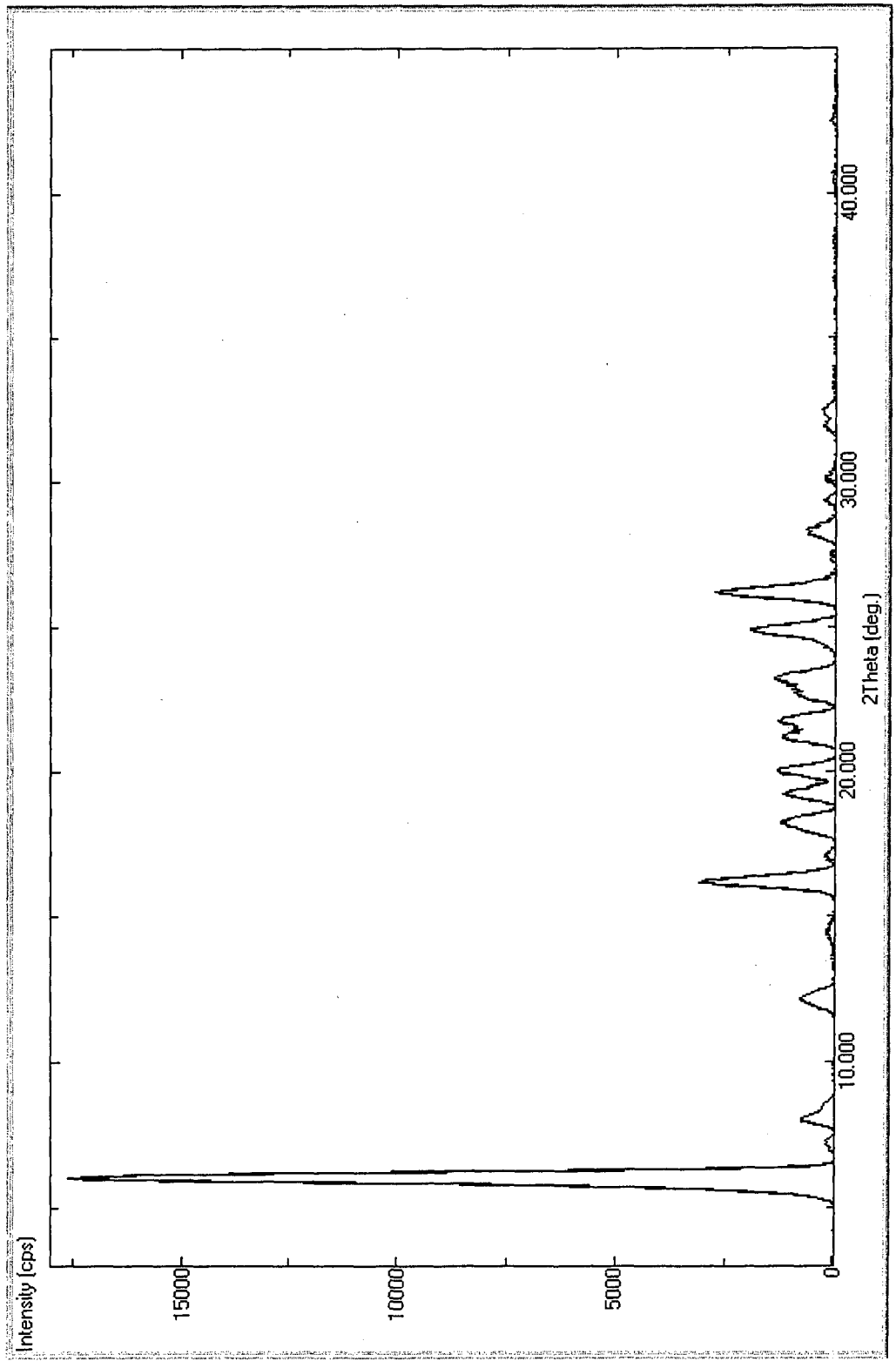

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Fig. 4.

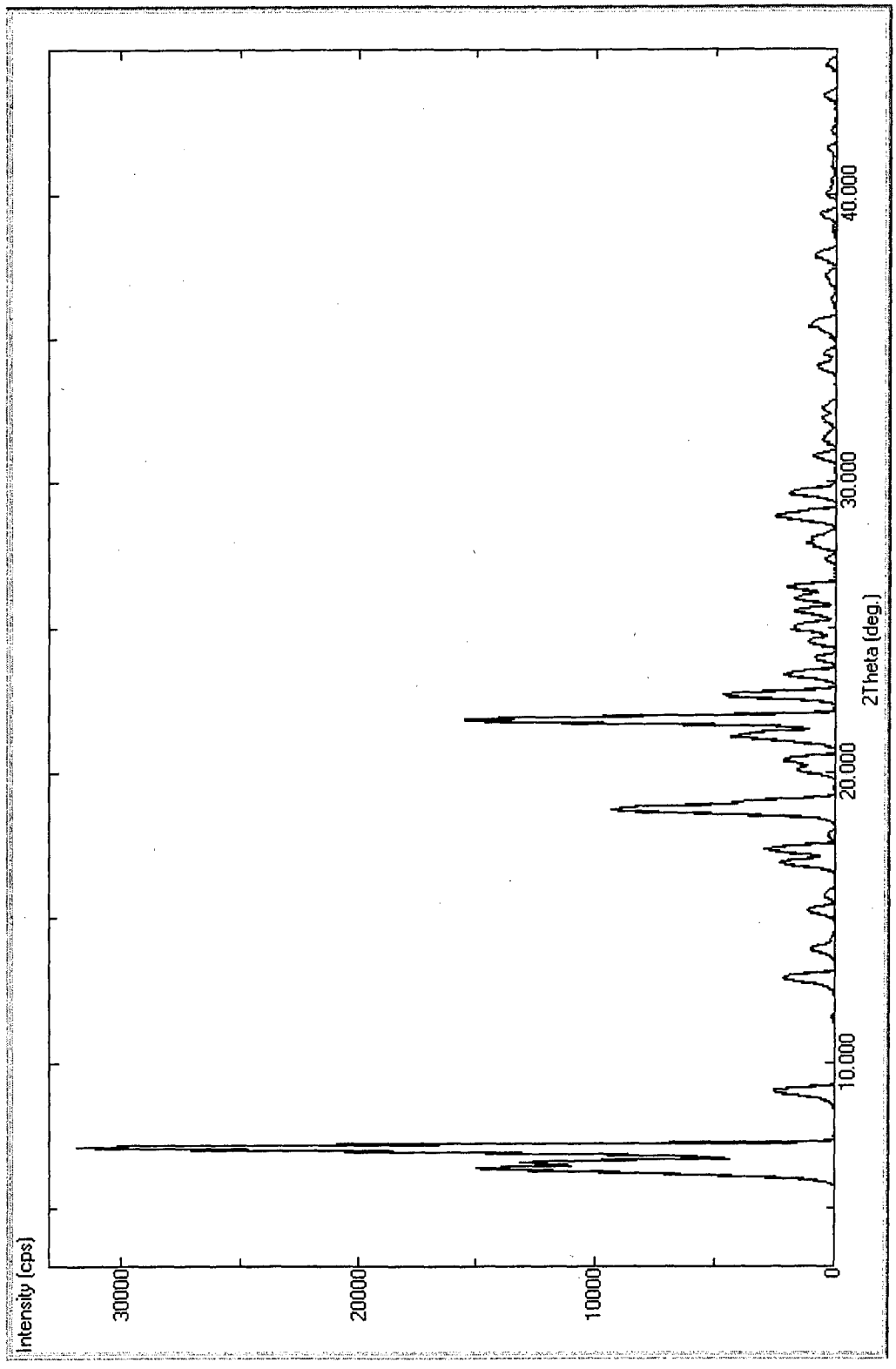

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Fig. 5.

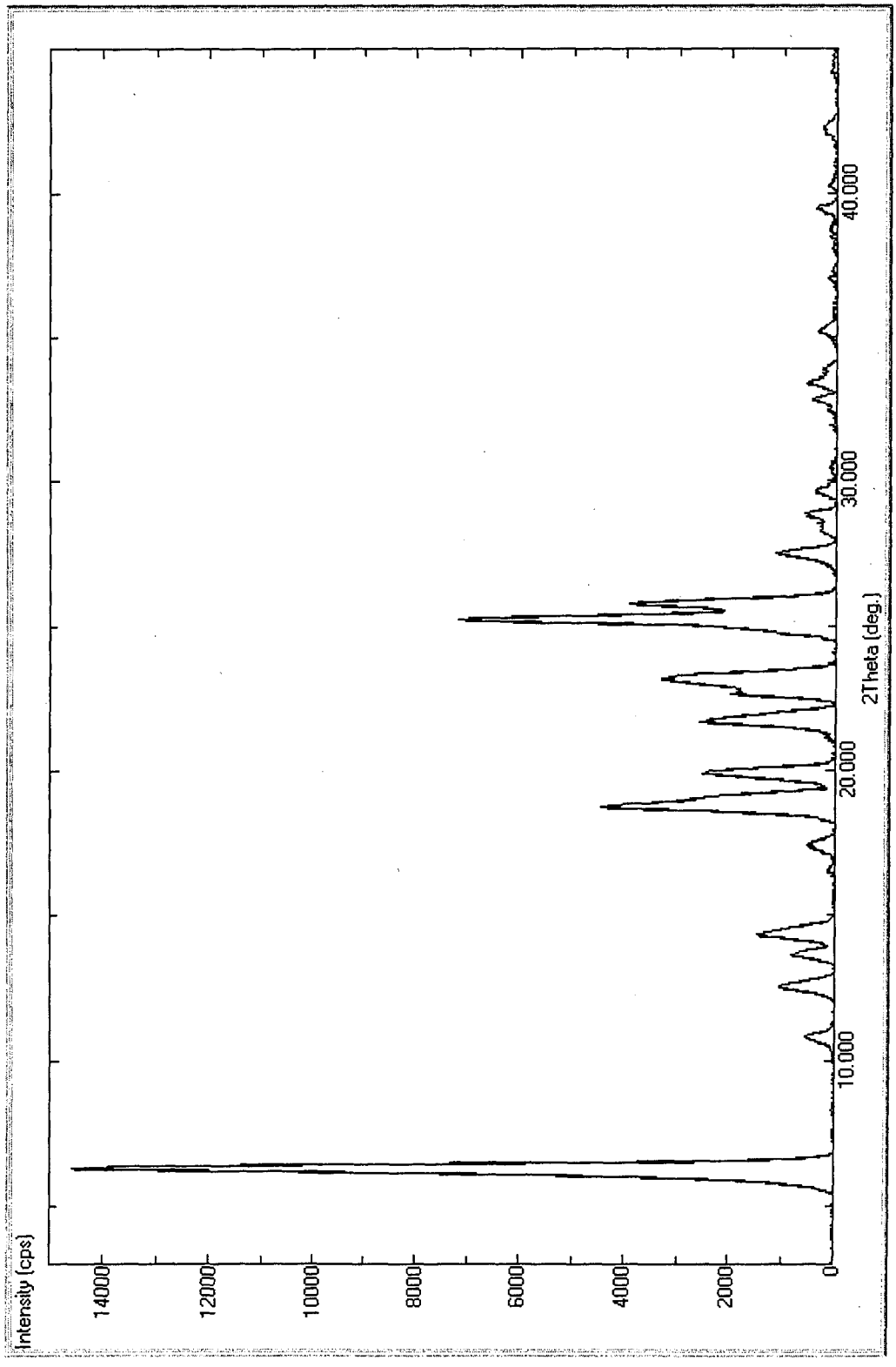

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Fig. 6.

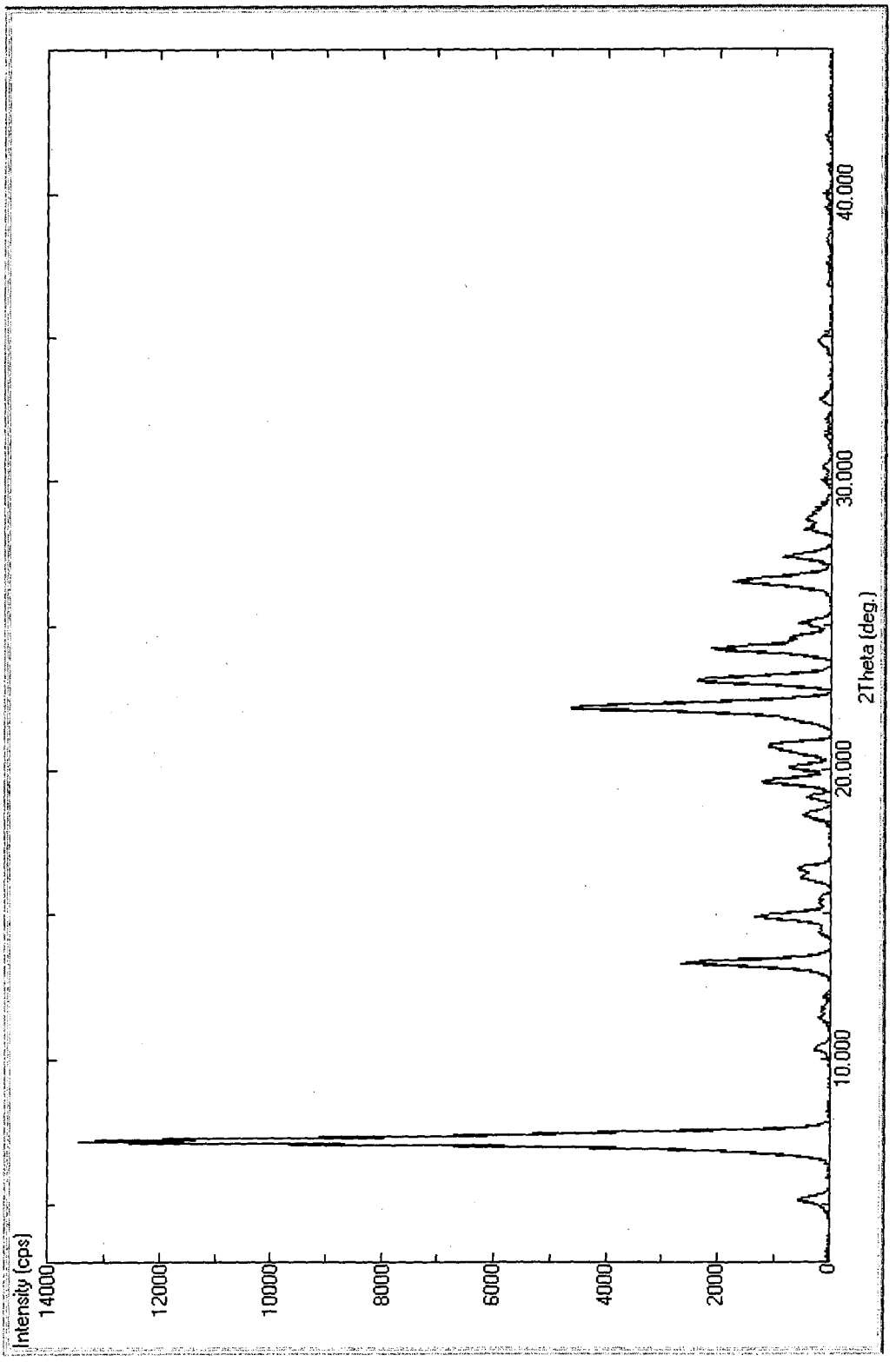

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Fig. 7.

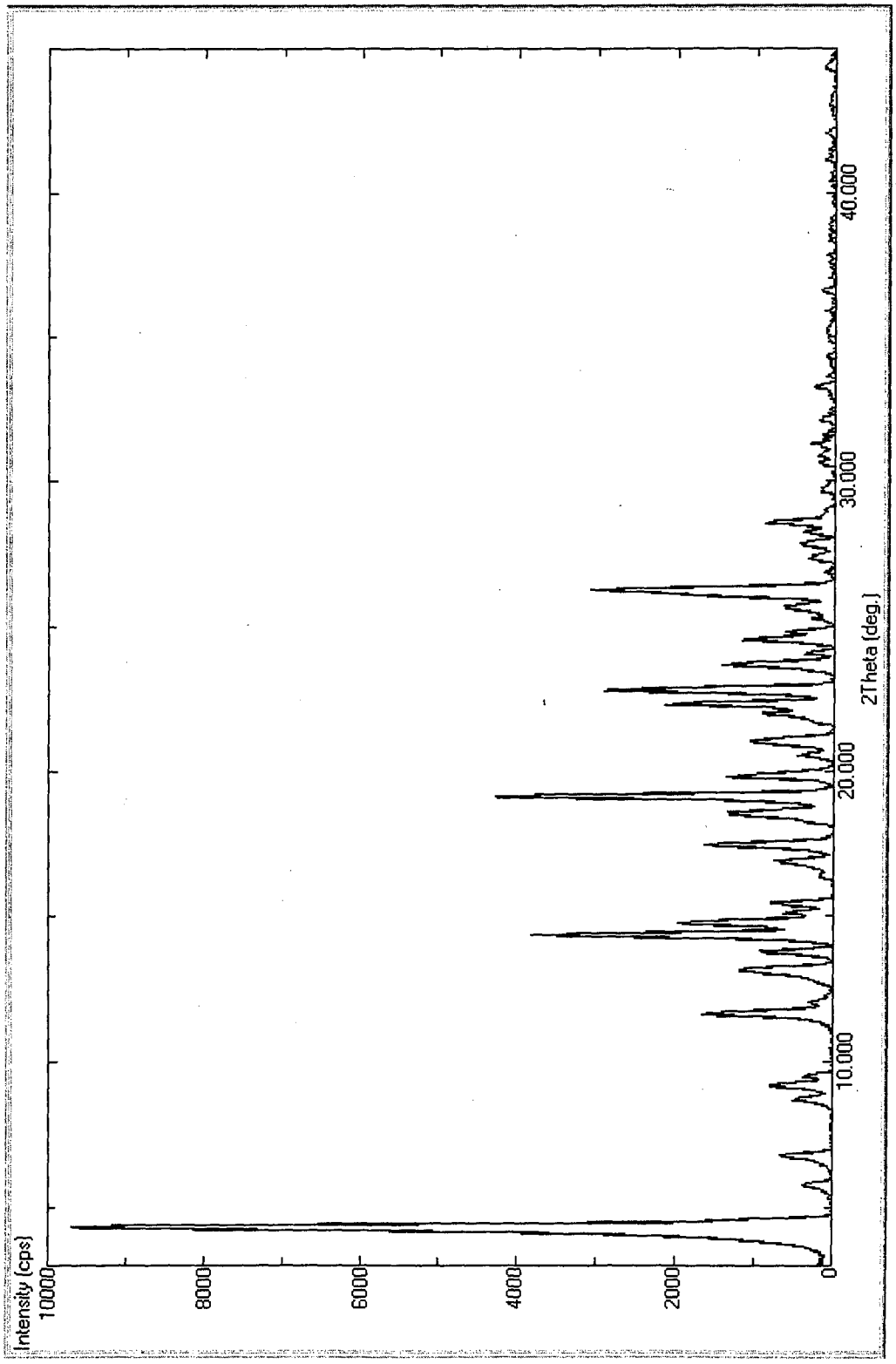

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Fig. 8.

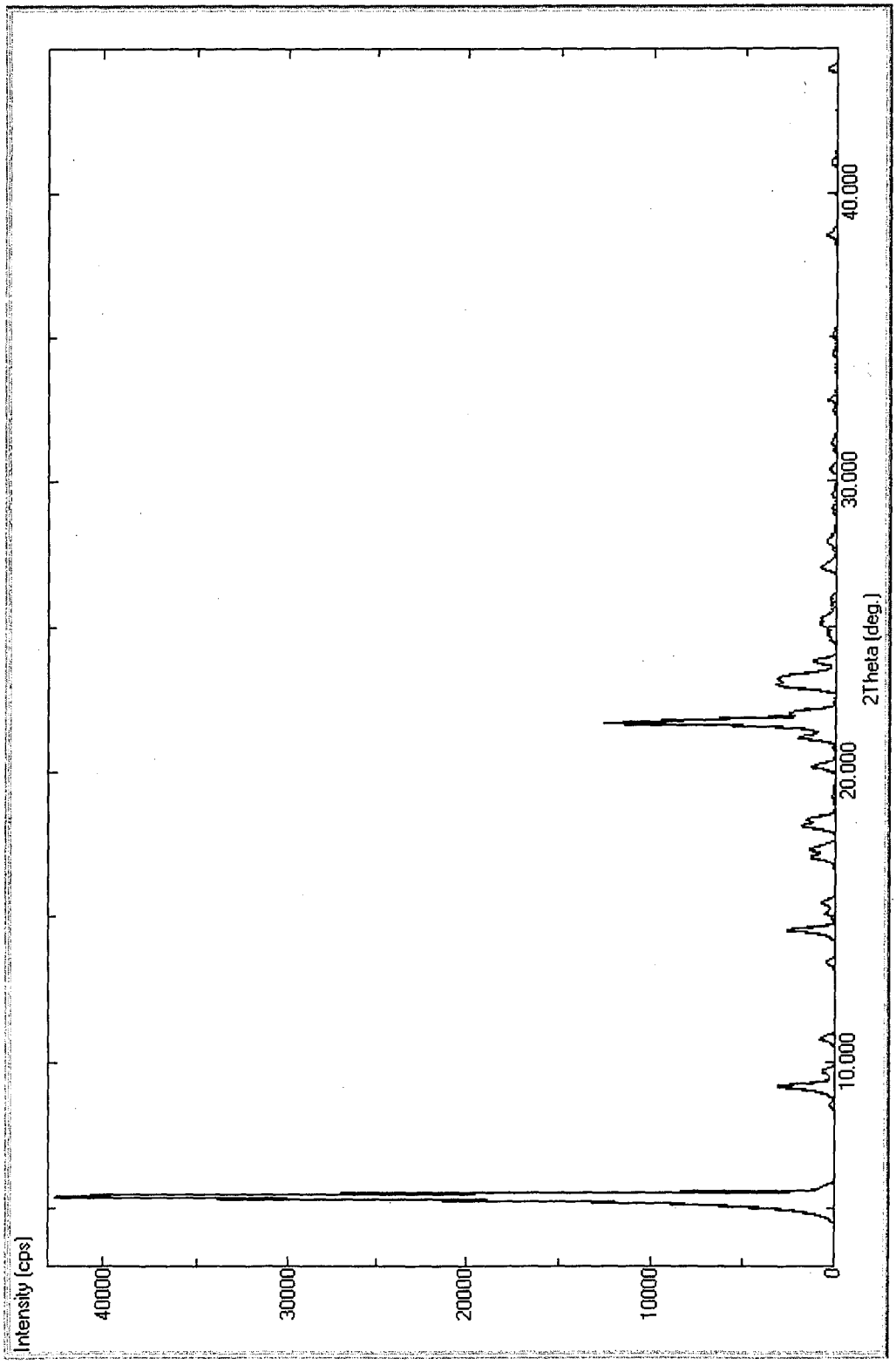

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Fig. 9.