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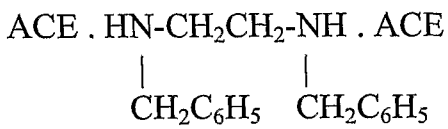
(54) Title: NEW BENZATHINE SALTS OF ACE INHIBITORS, PROCESS FOR THEIR PREPARATION AND THEIR USE FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

(57) Abstract: The present invention describes new salts of ACE inhibitors with N5N'-dibenzylethylenediamine (abbr.: benzathine salts), a process for their preparation in crystal and amorphous forms by the reaction of two moles of ACE inhibitors with one mole of N,N'-dibenzylethylenediamine, a process for the preparation of pharmaceutical formulations containing these salts and their use for the treatment of cardiovascular diseases.

New Benzathine Salts of ACE Inhibitors, Process for Their Preparation and Their Use for the Treatment of Cardiovascular Diseases

Technical Field

The present invention belongs to the field of pharmaceutical chemistry and relates to new stable salts of ACE inhibitors with N,N'-dibenzylethylenediamine in amorphous and crystal forms of the general formula:



wherein ACE means a molecule of ACE inhibitor,
a process for the preparation thereof and the use thereof for the preparation of a pharmaceutical form for the treatment of cardiovascular diseases associated with hypertension.

Technical Problem

In the practical application of hitherto known salts of ACE inhibitors, one often encounters an insufficient stability of pharmaceutical preparations. A marked example thereof are preparations containing perindopril erbumine and therefore their use has lately been increasingly discontinued.

Thus, there existed a need for new salts with better stability so that the prepared pharmaceutical preparations would also be applicable in countries with higher average day temperatures and an increased air humidity and will have a sufficiently long shelf-life.

Prior Art

ACE (**A**ngiotensin **C**onverting **E**nzyme) inhibitors are very useful in the treatment of cardiovascular diseases, especially those associated with hypertension and weakened heart muscle function. There are known numerous ACE inhibitors such as enalapril, quinapril, perindopril, trandolapril, ramipril, fosinopril, spirapril, moexipril, lisinopril, cilazapril and others.

For the production of a pharmaceutical form suitable for application, they can be used in the basic form (free acid), as a hydrate, but mostly in the form of a suitable salt, particularly due to the better solubility in water.

Enalapril is used in the form of maleate as described in US 4,374,829 or as sodium salt described in SI 9111842.

Perindopril is usually a salt with tert-butylamine (erbumine) in various polymorph crystal forms: alpha, beta, gamma, delta, epsilon, eta and D, disclosed in EP-A 0 308 341, EP 1 296 947 B1, EP 1 294 689 A1, EP 1 296 948, WO 2007/02009A1, as erbumine in hydrated form disclosed in EP 1 647 547 and WO 2004/46172 and as a salt with amino acid arginine disclosed in EP 1 354 873.

Perindopril and also other ACE inhibitors are often combined with diuretics e.g. with hydrochlorothiazide, indapamide and others as described in WO 2007/099217A1.

Ramipril obtained according to patents EP 0097022 and US 6,541,635 is known in the forms of acid, hydrochloride and of other salts, e.g with alkali metals and alkaline earth metals such as sodium, potassium and calcium (USPTO 20070098782). Zinc salts as well as a combination with diuretics, statines, antidiabetics etc. are known from WO 2008/065421.

WO 2008/065424 discusses an interesting salt of ramipril with amlodipine that is supposed to be used for preventing cardiovascular abnormalities, renal failure, ischemic conditions, diabetes mellitus and post-stroke condition.

US 6,086,919 discusses a combination of ramipril with dihydropiridine compounds such as nifedipine, nitrendipine and lacidipine.

Cilazapril is mostly in the form of hydrate and, due to its sensibility, it is formulated by dry granulation as described in EP 1 603 916, also in combination with diuretics according to EP 1 889 629.

Fosinopril contains phosphor in the molecule and is used in the form of sodium salt (EP 0408273 and US 7,078,532) and also as calcium or zinc salt in different polymorph forms as described in EP 0442378 B1.

The main problem with the majority of ACE inhibitors is a relatively low stability of the compounds. Several chemical reactions take place, which lead to a decomposition of the molecule, to the formation of new impurities and to a decrease of activity. In the first place is certainly the elimination of water followed by internal cyclization and the formation of diketopiperazine impurities. Diketopiperazine compounds are inactive and decrease the effectiveness of the basic compound.

A second undesired reaction is the hydrolytic cleavage of the ester group under formation of dicarboxylic acid such as ramiprilat or perindoprilat. These are compounds that are several times more reactive than the basic compound, yet their transport within the organism is more difficult. The cleavage of the ester bond is stimulated by strong alkaline ions and a higher water content in the preparation and by esterase enzymes within the organism.

The problem of stability is predominantly solved by precisely performed methods of preparation of the pharmaceutical form, granulation (dry or wet), and also by several additives for increased stability. With perindopril erbumine mostly bicarbonates or carbonates of alkali metals or alkaline earth metals are added (US 2003/0215526A1).

Certainly, the stability of a pharmaceutical preparation with ACE inhibitors also strongly depends upon the basic stability of the salt containing ACE inhibitor. In the case of perindopril, it is known that other salts such as calcium, sodium or argininium salt are substantially more stable than erbumine.

Brief Description of the Figures

Fig. 1. X-ray powder diffractogram of benzathine perindopril, polymorph form A.
Fig. 2. X-ray powder diffractogram of benzathine perindopril, polymorph form B.
Fig. 3. X-ray powder diffractogram of benzathine fosinopril.
Fig. 4. X-ray powder diffractogram of benzathine enalapril.
Fig. 5. X-ray powder diffractogram of benzathine ramipril.
Fig. 6. X-ray powder diffractogram of benzathine cilazapril.
Fig. 7. FTIR spectrum of benzathine perindopril, polymorph form A.
Fig. 8. FTIR spectrum of benzathine perindopril, polymorph form B.
Fig. 9. FTIR spectrum of benzathine fosinopril.
Fig. 10. FTIR spectrum of benzathine enalapril.
Fig. 11. FTIR spectrum of benzathine ramipril.
Fig. 12. FTIR spectrum of benzathine cilazapril.

The Technical Solution

The main technical problem associated with the stability of ACE inhibitors and salts thereof is solved in several ways. Primarily, it is necessary to prevent the hydrolysis of the ester group and the internal cyclization to diketopiperazine products. This can be

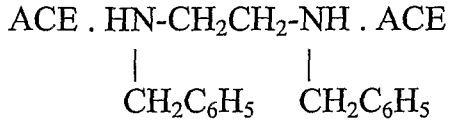
affected by the selection of an appropriate cation of the salt, by steric conditions in the salt, by the selection of appropriate inert additives necessary for the preparation of the granulate for tabletting, by various secondary additives for the increase of stability and by the method of the preparation of the pharmaceutical form.

In the case of peridopril erbumine it has turned out that tert-butylamine, which is a component of the addition salt, is linked in a relatively weak manner. After the elimination of tert-butylamine from the salt, a free perindopril acid is formed, which is highly susceptible to nucleophilic attack and internal cyclization. This can be partly solved by the formation of a ionic salt, e.g. with potassium, sodium or calcium cations as described in WO 2008/150245A2.

The conformational analysis of perindopril salt structure by ^{1}H-NMR spectroscopy has shown that the molecule exists in cis and trans forms. The trans form is more present with perindopril erbumine. However, it is characteristic that just in the cis conformer an intermolecular formation of a hydrogen bond between the carboxylate group and the NH group is present, which substantially stabilizes the molecule! Suprisingly, it has been found that with the salts of ACE inhibitors with N,N'-dibenzylethylenediamine (abbr. benzathine) generally a greater part of the cis conformer is present, which is the reason for a greater stability of synthetized benzathine salts of ACE inhibitors.

Another possible reason for the low stability of some salts of ACE inhibitors is the hydrolysis of the ester bond. It is stimulated by a higher water content, a higher temperature and in the presence of substances with a strong alkaline action such as tert-butylamine or Na ions. Also from this aspect, the selection of N,N'-dibenzylethylenediamine as a component of the salt is very appropriate.

An object of the present invention are the salts of ACE inhibitors with N,N'-dibenzylethylenediamine (abbr. benzathine) of the general formula:



wherein the molar ratio of the ACE inhibitor to benzathine is 2 : 1.

The advantages of benzathine salts of ACE inhibitors are as follows:

- the salts possess a very good stability at ageing since almost no hydrolysis of ester groups and no formation of diketopiperazine impurities occur;
- the salts crystalize excellently from usual solvents and some also from water;
- by crystalization the product purifies itself very well of synthesis admixtures and very pure active substances are obtained;
- crystallized compounds have a higher melting point than amorphous ones and also surpass them in stability;
- benzathine is a nontoxic component and is well known in the field of penicillin antibiotics.

Otherwise, benzathine salts of ACE inhibitors can also be prepared in an amorphous form if the salt solutions are frozen and then lyophilized. The yields of the synthesis are higher, yet the salts are slightly less pure.

According to the invention, the benzathine salts of ACE inhibitors are prepared by the reaction of both components in a molar ratio of 2 moles of ACE inhibitor in the form of a free acid to 1 mole of benzathine and crystallization in appropriate solvents that are defined separately for each case.

As an exception, benzathine perindopril can also be obtained by wet granulation so that onto the inert components – granulating mass ingredients – a solution of perindopril erbumine and benzathine is sprayed and it is dried in a counterflow of warm air. Thereby tert-butylamine evaporates and benzathine perindopril remains included on the granulate. The granulate is then tabletted.

As an other exception, benzathine perindopril can also be obtained in industrial production immediately after step of catalytic debenzylation with activated charcoal.

The obtained perindopril (acid) is isolated in pure form, recrystallized if necessary, then directly reacted with N,N'-dibenzylethylenediamine and converted into benzathine salt.

As the starting substance for the preparation of benzathine salts of ACE inhibitors there is used an ACE inhibitor in the form of a free acid, a hydrate or in the form of a salt with a volatile alkaline component such as the already mentioned perindopril erbumine.

Crystallization is very selective so that also a starting substance of inferior quality can be used, e. g. also with 10 % of diketopiperazine impurity, and nevertheless a product of high purity is obtained. Namely, diketopiperazine impurity does not have a free carboxylic group, therefore it does not crystallize with benzathine and is removed with crystallization mother liquor.

Said method is generally applicable for the preparation of benzathine salts of all known ACE inhibitors having free carboxylic group and is not limited only to the concrete stated examples of ACE inhibitors.

The crystal structure of the compounds was determined by X-ray powder diffractograms (abbr.: XRD) recorded on X'Pert PRO X-ray difractometer with alpha configuration, CuKα radiation, in a range 3–35° 2Θ. FTIR spectra were recorded by Perkin Elmer 727B IR spectrometer.

Benzathine salt of perindopril (abbr: benzathine perindopril) is obtained by the reaction of perindopril and benzathine in a molar ratio 2 : 1 and crystallization from hot ethyl acetate or from water, in a polymorph form A with a characteristic X-ray powder diffractogram represented in Table 1. Therein only signals higher than 15 % of relative intensity are stated.

Table 1

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	5.8949	14.98041	25.01
2	6.5122	13.56185	100.00
3	10.7061	8.25681	24.99
4	12.0797	7.32081	17.38
5	14.8462	5.96227	20.12
6	16.0810	5.50712	18.65
7	16.6625	5.31622	24.27
8	17.6098	5.03231	17.22
9	17.8417	4.96743	45.19
10	19.0928	4.64466	47.09
11	15.5830	4.52949	32.66
12	20.5267	4.32333	18.58
13	21.3166	4.16487	31.09
14	21.4948	4.13075	20.08
15	22.0069	4.03576	28.04
16	22.6724	3.91880	15.78
17	23.9340	3.71500	43.77
18	25.0831	3.54736	18.66
19	25.5437	3.48442	16.50
20	28.1560	3.16680	18.30
21	29.6824	3.00733	28.99
22	35.0811	2.55590	20.18

Benzathine perindopril in a polymorph form B is obtained by the reaction of perindopril and benzathine in a molar ratio 2 : 1 and crystallization from ethanol subsequent to the addition of methyl tert-butyl ether. It has a characteristic X-ray

powder diffractogram, represented in Table 2, wherein only signals with relative intensity higher than 10 % are stated.

Table 2

No.	Position [2Θ/°]	Spacing [*d*/Å]	Rel. intensity [%]
1	6.5142	13.55760	100.00
2	11.5531	7.65333	28.99
3	12.1045	7.30591	15.95
4	14.8847	5.94695	14.10
5	16.0939	5.50275	13.61
6	17.6270	5.02743	13.85
7	19.6125	4.52273	47.32
8	20.1330	4.40696	14.26
9	20.5802	4.31221	23.59
10	20.4838	4.13283	10.67
11	22.0327	4.03110	22.73
12	23.1710	3.83558	21.40
13	24.0011	3.70477	26.78
14	26.1996	3.39866	11.24
15	26.6917	3.00640	14.75
16	30.5506	2.92381	12.96
17	36.6578	2.44950	13.62

Benzathine salt of fosinopril (benzathine fosinopril) is obtained by the reaction of fosinopril and benzathine in a molar ratio of 2 : 1. The compound crystallizes well from acetonitrile, acetone or ethyl acetate in needle crystals. XRD diffractogram shows signals stated in Table 3 (only signals over 15 % of relative intensity are stated).

Table 3

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	5.2077	16.95574	41.12
2	12.2576	7.21499	65.38
3	16.3771	5.40822	37.00
4	16.8437	5.25944	100.00
5	17.3788	5.09870	47.64
6	18.3355	4.83474	73.92
7	19.0872	4.64601	56.65
8	19.6200	4.52103	38.92
9	20.4326	4.34303	37.21
10	20.8643	4.25413	57.53
11	21.5937	4.11204	26.29
12	22.0858	4.02152	21.83
13	22.7456	3.90634	19.16
14	23.4929	3.78374	15.57
15	24.4831	3.63291	15.47
16	24.8190	3.58449	22.19
17	25.8486	3.44601	22.72
18	27.6789	3.22028	15.09
19	28.7615	3.10148	55.69
20	29.4269	3.03285	31.20
21	30.0668	2.96975	46.72
22	32.5029	2.75251	19.68
23	33.9593	2.63772	19.01
24	35.6444	2.51679	15.83

Depending on the crystallization solvent there occur minor variations in the intensity of signals at positions (5.2, 17.5 and 12.5) 2Θ due to different orientations of the needle crystals.

Benzathine salt of enalapril (benzathine enalapril) is prepared by the reaction of enalapril and benzathine in a molar ratio of 2 : 1 and crystallization from acetone or methyl tert-butyl ether. The salt crystallizes in needle crystals, which in XRD diffractogram give the signals stated in Table 4 (only signals over 10 % of relative intensity are stated).

Table 4

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	5.7194	15.43988	100.00
2	13.7934	6.41492	28.44
3	16.5103	5.36489	54.37
4	17.7514	4.99251	17.00
5	18.7449	4.73007	60.88
6	19.0720	4.64968	10.32
7	19.4392	4.56266	13.07
8	20.5924	4.30967	14.80
9	21.1680	4.19377	33.97
10	23.3380	3.80850	26.51
11	24.9277	3.56911	10.42
12	25.2710	3.52141	23.54
13	27.9803	3.18628	29.46
14	35.2158	2.54643	11.94

Benzathine salt of ramipril (benzathine ramipril) is obtained by the reaction of ramipril and benzathine in a molar ratio of 2 : 1 and crystallization from water,

acetone or ethyl acetate in the form of needle crystals with a characteristic XRD diffractogram represented in Table 5 (only signals over 10 % of relative intensity are stated).

Table 5

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	5.6472	15.63699	100.00
2	11.2714	7.84394	41.27
3	13.9095	6.36162	14.47
4	15.0119	5.89683	10.67
5	16.5107	5.36477	49.26
6	17.0071	5.20928	37.15
7	17.6850	5.01109	14.42
8	19.8578	4.46743	10.16
9	20.4361	4.34229	39.35
10	20.7197	4.28348	36.94
11	22.5331	3.94442	89.77
12	24.2194	3.67187	10.98
13	25.6742	3.46701	18.31
14	27.5848	3.23106	26.25
15	33.3840	2.68185	14.44
16	34.1824	2.62102	12.71
17	35.7393	2.51032	10.31

Benzathine salt of cilazapril (benzathine cilazapril) is prepared by the reaction of cilazapril hydrate with benzathine in a molar ratio of 2 : 1 and crystallization from ethyl acetate by the addition of n-hexane or from methyl tert-butyl ether, in needle crystals with a characteristic XRD diffractogram represented in Table 6 (only signals higher than 10 % are stated).

Table 6

No.	Position [2Θ/°]	Spacing [*d*/Å]	Rel. intensity [%]
1	5.4139	16.31028	41.24
2	11.7645	7.51623	12.54
3	13.2925	6.65550	26.78
4	14.2868	6.19446	50.55
5	17.2822	5.12697	100.00
6	21.3132	4.16553	11.51
7	23.2854	3.81700	8.00
8	24.8299	3.58295	10.59

New salts of ACE inhibitors that are an object of the present invention can be used as therapeutical active substances, which, together with an inert pharmaceutically acceptable carrier, can be transformed into a suitable form such as tablets, which are then used for treatment of cardiovascular diseases, hypertension and heart muscle weakness.

An object of the present invention is also a pharmaceutical formulation containing new benzathine salts of ACE inhibitors. As pharmaceutically acceptable adjuvants, substances generally known to those skilled in the art are used.

Inert ingredients or pharmaceutical adjuvants are selected from the following groups:
- fillers such as anhydrous lactose, microcrystalline cellulose, starch, calcium phosphate, calcium carbonate, different sugars and the others;
- binders such as microcrystalline cellulose, hydroxyalkyl celluloses, povidone, cellulose esters, starch or a mixture thereof;
- disintegrants such as starch, cross-linked croscarmellose sodium, crospovidone, microcrystalline cellulose, sodium carboxymethyl cellulose and the others, mostly in an amount of 1–10 % ;

- substances for lubrication and improvement of gliding at tabletting such as talc, magnesium stearate, stearic acid, potassium stearate and colloidal silica. These substances are usually added to the other ingredients in final phase.

Pharmaceutical formulations are prepared according to known processes such as direct mixing, dry granulation, wet granulation and tabletting or spraying of a solution of the benzathine salt of ACE inhibitor onto inert pharmaceutical substances under simultaneous drying in counterflow of warm air. To the granulate obtained, if necessary, also other ingredients are added, it is homogenized and tabletted in a usual manner.

The benzathine component in the discussed new salts is the cause of a greater hydrophobicity of active substances in this form. Therefore it is realistic to expect a better passage through biological membranes, which also makes possible the manufacture of preparations acting through the skin like creams, ointments or patches.

The transdermal system comprises a back layer unpermeable for the active substance, a polymer layer that serves as a reservoir for the active substance and is pressure-sensitive and a protection foil that is perforated in several sites so that the active substance can permeate through it.

According to the invention, also other single active substances can be added, which improve the basic action of perindopril or act sinergistically. These substances are from the following groups:

- diuretics such as indapamide or hydrochlorothiazide and salts thereof;
- substances with antitrombotic action such as clopidogrel and acetylsalicylic acid;
- substances with anti-hyperlipoproteinemic action such as rosuvastatin and atorvastatin;
- inhibitors of calcium ion influx from the group of dihydropiridines such as amlodipine and lacidipine and salts thereof;

- substances with antioxidative action such as dry green tea extract, coenzyme Q_{10}, idebenone, curcumin and others.

Of special interest is the combination with coenzyme Q_{10} or ubiquinone, which is very active antioxidant and free radical scavenger and, in addition, it can be used at heart diseases associated with a decreased blood flow and too high blood pressure and at indications of heart failure. Recently, also curcumin has turned out to be a very important antioxidant with a strong anti-cancer action.

As expected, benzathine salts of ACE inhibitors are surprisingly stable in ageing. Experimentally, a higher stability of benzathine perindopril in comparison with some other known salts of perindopril was determined so that these salts were incubated at 50 °C and 65 % relative humidity in phials with a PE lid. The content within time intervals was determined by HPLC method:
Kromasil C18 column, 5 μm, 150 × 4.6 mm;
mobile phase A: 30 % acetonitrile/70 % buffer pH = 2.0;
mobile phase B: 90 % acetonitrile/10 % buffer pH = 2.0;
gradient from 100 % A to 57 % A within 20 min;
buffer composition: 0.92 g sodium heptane sulphonate and 1 mL of triethylamine/1000 mL water, pH 2.0 with $HClO_4$;
temperature: 20 °C;
flow: 1mL/min;
detection: UV at 210 nm.

Table 7. The decrease of perindopril salt content at incubation at 50 °C and 65 % relative humidity:

Type of salt:	initial state	30 days	60 days	90 days
Benzathine perindopril	99.8	99.2	98.7	98.1
Perindopril arginine	99.8	98.9	98.5	97.9
Perindopril erbumine	99.6	98.6	97.6	96.5

The present invention is illustrated by the following Examples, which do not limit it in any way.

EXAMPLE 1. Benzathine perindopril - polymorph form A

Perindopril (1.97 g, 5.35 mmol) was disolved in 7 mL of water at 50–60 °C and thereto benzathine (0.6 g, 2.5 mmol) was added dropwise under stirring. It was stirred and slowly cooled to room temperature, then it was left to stay at +5 °C over night. The crystal broth was filtered, washed with ice-cold water and dried in vacuum at 50 °C. 2.32 g (90.3 %) of a white crystal salt with a melting point at 84–89 °C (Kofler) were obtained. The XRD powder diffractogram is represented in Table 1 and corresponds to the polymorph form A. The elementary analysis (C, H, N) corresponded to a compound with empirical formula $(C_{19}H_{32}N_2O_5)_2 \cdot C_{16}H_{20}N_2$ = $C_{54}H_{84}N_6O_{10}$ and with molecular weight 977.3.

EXAMPLE 2. Benzathine perindopril - polymorph form A

Perindopril erbumine (2.0 g, 4.53 mmol) was dissolved in 20 mL of ethyl acetate, during stirring benzathine (0.6 g, 2,5 mmol) was added thereto and ethyl acetate was evaporated to dryness in a vacuum at 60 °C. The dry substance was dissolved again in 25 mL of ethyl acetate, ethyl acetate was again evaporated and the dry substance was well dried in vacuum (thereby tert-butlyamine was removed). Subsequently, the dry substance was dissolved in 10 mL of ethyl acetate at 70 °C and 5 mL of n-hexane were added. After cooling the desired benzathine perindopril in the form of fine crystals with a melting point of 82–86 °C was separated. There were obtained 1.97 g (88.9 %) of a substance with XRD diffractogram as stated in Table 1 and corresponding to polymorph form A.

EXAMPLE 3. Benzathine perindopril - amorphous

Perindopril (1.97 g, 5.35 mmol) was dissolved in 30 mL of water and thereto benzathine (0.64 g, 2.675 mmol) was added dropwise under stirring at 35 °C. It was

rapidly dried with dry ice and lyophilized. 2.61 g (100 %) of amorphous benzathine perindopril with a melting point of 80–87 °C were obtained.

EXAMPLE 4. Benzathine perindopril - polymorph form B

Perindopril (1.0 g, 2.71 mmol) was dissolved in 4 mL of ethanol and thereto benzathine (0.33 g, 1.33 mmol) was added. During stirring 7 mL of methyl tert-butyl ether were added stepwise and it was left for the salt to crystallize over night at +5 °C. It was filtered, washed with methyl tert-butyl ether and dried in vacuum. The crystals (0.67 g, 51.5 %) melt at 84-87 °C (Kofler) and have an XRD powder diffractogram as represented in Table 2, which corresponds to polymorph form B.

EXAMPLE 5. Benzathine perindopril - polymorph form A

In this Example as a starting substance perindopril of inferior quality (content: 91.5 %, impurity B: 1.4 %, impurity F: 3.1 %) was used. Perindopril (32.4 g, 87.9 mmol) was dissolved in 100 mL of ethyl acetate at 70–75 °C and benzathine (10.4 g, 43.3 mmol) was added during stirring. Then stepwise another 100 mL of n-heptane were added to start the crystallization of the salt. During cooling to room temperature, another 50 mL of n-heptane were added and it was cooled to –15 °C for 4 hours. The salt was filtered and washed well with a mixture of ethyl acetate/n-heptane 1 : 3 and additionally with pure n-heptane. It was dried in a vacuum at 50 °C. There were obtained 40.11 g (93.3 %) of crystals with a melting point of 87–91 °C and XRD diffractogram characteristic for polymorh form A.

The obtained salt was very pure: content 99.8 %, impurity B 0 %, impurity F 0.09 %.

This benzathine perindopril was used for the production of test tablets.

EXAMPLE 6. Benzathine enalapril

Enalapril (2.24 g, 5.95 mmol) was dissolved in 22 mL of acetone, thereto benzathine (0.69 g, 2.87 mmol) was added and it was crystallized at room temperature for 24 hours. The crystals of salt were filtered off and dried in vacuum. There were obtained 2.33 g (81.75 %) of benzathine enalapril with a melting point of 128–130 °C (Kofler)

and XRD powder diffractogram represented in Table 4. The elementary analysis (C, H, N) corresponded to a compound of empiric formula $(C_{20}H_{28}N_2O_5)_2 \cdot C_{16}H_{20}N_2$ = $C_{56}H_{76}N_6O_{10}$ and molecular weight 993.26.

EXAMPLE 7. Benzathine enalapril

Enalapril (0.46 g, 1.22 mmol) was dissolved in 20 mL of methyl tert-butyl ether and slowly benzathine (0.15 g, 0.62 mmol) was admixed. In the first phase a gelatinous solvate formed, which by heating and stirring transformed to fibrous crystals. After filtering and drying, 0.59 g (96.7 %) of benzathine enalapril with a melting point of 128–130 °C were obtained.

EXAMPLE 8. Benzathine ramipril

a) Crystallization from water

Ramipril (1.0 g, 2.4 mmol) was dissolved in 15 mL of water, benzathine (0.28 g, 1.17 mmol) was added during stirring and it was heated to 60 °C. After cooling, benzathine ramipril (1.16 g, 90 %) with a melting point of 83–85 °C and a characteristic XRD powder diffractogram represented in Table 5 was crystallized.

b) Crystallization from ethyl acetate

Ramipril (1.0 g, 2.4 mmol) was dissolved in 15 mL of ethyl acetate at 60 °C and benzathine (0.28 g, 1.17 mmol) was added. During stirring slowly 15 mL of n-heptane for the crystallization of the salt was added. There were obtained 1.17 g (90.8 %) of benzathine ramipril with a melting point of 83–84 °C and XRD diffractogram represented in Table 5.

c) Crystallization from acetone

Ramipril (1.0 g, 2.4 mmol) was dissolved in 7 mL of acetone containing benzathine (0.28 g, 21.17 mmol) and n-heptane was added thereto up to the first turbidity. The salt was crystallized at room temperature overnight. There were obtained 1.13 g (87.7 %) of benzathine ramipril with a melting point of 83–85 °C and XRD diffractogram represented in Table 5. The elementary analysis (C, H, N) corresponded to a

compound of empiric formula $(C_{23}H_{32}N_2O_5)_2 \cdot C_{16}H_{20}N_2 = C_{62}H_{84}N_6O_{10}$ and of molecular weight 1073.4.

EXAMPLE 9. Benzathine ramipril, another crystallization method

Sodium salt of ramipril (2.1 g, 4.8 mmol) was dissolved in 20 mL of water and then a solution of N,N'-dibenzylethylendiamine diacetate (0.865 g, 2.4 mmol) in 10 mL of water was added during stirring and it was heated to 60 °C. During stirring and cooling at +5 °C, benzathine ramipril crystallized. The obtained salt was filtered, washed with ice-cold water and dried. There were obtained 2.22 g (86.1 %) of a salt with melting point 83–85 °C.

EXAMPLE 10. Benzathine fosinopril

Fosinopril (1.49 g, 2.64 mmol) was dissolved in 20 mL of ethyl acetate and benzathine (0.314 g, 1.31 mmol) dissolved in 10 mL of ethyl acetate was added thereto. After crystallization at room temperature, 1.30 g (72 %) of benzathine fosinopril with melting point 136–137 °C were obtained.

XRD diffractogram is represented in Table 3. The compound has empiric formula $(C_{30}H_{46}NO_7P)_2 \cdot C_{16}H_{20}N_2 = C_{76}H_{112}N_4O_{14}P_2$ and molecular weight 1367.66.

EXAMPLE 11. Benzathine cilazapril

Cilazapril hydrate (1.5 g, 3.31 mmol) was dissolved in 40 mL of methyl tert-butyl ether and heated to boiling point, benzathine (0.39 g, 1.63 mmol) was added thereto and it was crystallized at +5 °C for at least 10 hours. There were obtained 1.56 g (85.2 %) of crystal benzathine cilazapril with melting point 107–108 °C.

XRD powder diffractogram is represented in Table 6. The elementary analysis (C, H, N) corresponded to a compound of empiric formula $(C_{22}H_{33}N_3O_6) \cdot C_{16}H_{20}N_2 = C_{60}H_{86}N_8O_{12}$ and of molecular weight 1111.4.

EXAMPLE 12. Tablets with benzathine perindopril - variant I

Ingredients:	mg/tablet:
Benzathine perindopril	4.43
Lactose DCL 21	59.70
Celullose Avicel 102	19.87
Corn starch	5.00
Magnesium stearate	1.00
Tablet weight	90.00 mg

The tablets were prepared by dry mixing and direct tabletting.

EXAMPLE 13. Tablets with benzathine perindopril – variant II

Ingredients :	mg/tablet:
Benzathine perindopril	4.43
Lactose DCL21	59.70
Celullose Avicel 102	18.87
Corn starch	4.00
Sodium croscarmellose	2.00
Magnesium stearate	1.00
Tablet weight	90.00 mg

EXAMPLE 14. Tablets with benzathine perindopril – variant III

Ingredients:	mg/tablet:
Benzathine perindopril	4.50
Lactose monohydrate	42.58
Celullose Avicel 102	20.42
Sodium hydrogen carbonate	6.50
Corn starch	15.00
Magnesium stearate	1.00
Tablet weight	90.00 mg

EXAMPLE 15. Tablets with benzathine perindopril and indapamide

Ingredients:	mg/tablet:
Benzathine perindopril	4.50
Lactose monohydrate	42.58
Celullose Avicel	20.67
Sodium hydrogen carbonate	5.00
Corn starch	15.00
Indapamide	1.25
Magnesium stearate	1.00
Tablet weight	90.00 mg

EXAMPLE 16. Tablets with benzathine perindopril and amlodipine besylate

Ingredients:	mg/tablet:
Benzathine perindopril	4.50
Amlodipine besylate	5.00
Lactose monohydrate	42.58
Celullose Avicel	20.67
Corn starch	15.00
Silica	1.25
Magnesium stearate	1.00
Tablet weight	90.00 mg

EXAMPLE 17. Formulation with benzathine ramipril and diuretic

Ingredients:	mg/capsule:
Benzathine ramipril	4.8
Hydrochlorothiazide	12.5

EXAMPLE 18. Formulation with benzathine enalapril and lacidipine

Ingredients:	mg/tablet:
Benzathine enalapril	10.00
Lactose monohydrate	65.28
Corn starch	6.50
Lacidipine	4.00
Colloidal silica	0.22
Crospovidone	3.00
Magnesium stearate	1.00
Tablet weight	90.00 mg

EXAMPLE 19. Benzathine perindopril with antioxidant

Ingredients:	mg/tablet:
Benzathine perindopril	8.86
Lactose DCL21	53.77
Microcrystalline celullose	35.57
Curcumin	35.00
Crospovidone	4.00
Talc	1.80
Magnesium stearate	1.00
Tablet weight	140.00 mg

EXAMPLE 20. Preparation of patch for transdermal application

In a solvent consisting of monomethyl ester of glutaric acid (5 g), ethanol (5 g), butanone (5 g) and 1-dodecanole (7 g), benzathine cilazapril (5.5 g) was dissolved. Separately, 66 g of a cross-linked acrylate polymer consisting of 2-ethyl-hexylacrylate, vinyl acetate and acrylic acid in a solvent mixture ethyl acetate/n-hexane/isopropanol/acetyl acetone/toluene = 40/25/25/1/4 (parts by volume) was prepared and during vigorous stirring this solution was added to the previously prepared solution of benzathine cilazapril. This was stirred well, another 0.7 g of

aluminium acetylacetonate were added and it was stirred at 20 °C for 4 hours to achieve the polymerisation of mixture. Then the resinous sticky substance was spread in a thickness of 0.35 mm on siliconized polyethylene foil and the solvent was removed by drying at 55 °C. The adhesive film was then covered with a thin polyester foil of a thickness of 0.15 mm, which was perforated by a special tool at defined sites.

EXAMPLE 21. Industrial preparation of benzathine perindopril

a) Perindopril (in acid form) was isolated from the solution after catalytic debenzylation by removing the solvent by distillation until an oily product formed, then heptane was added thereto and the obtained mixture was stirred to obtain a free solid, which was filtered and dried.

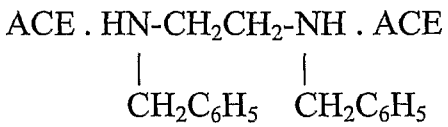
b) Purification of perindopril: the crude residue – perindopril in acid form – (172 g) was dissolved in ethyl acetate (516 mL), heated to 35 °C to obtain a clear solution, which was filtered in order to remove insoluble particles. Heptane (2580 mL) was slowly added to this filtrate, which was stirred for 3 hours at 25–30 °C. The solid was filtered, washed with heptane and dried to a constant weight in vacuum. 137 g (79.65 %) of very pure perindopril were obtained.

c) Crystallization of benzathine perindopril: benzathine (34.08 g) was charged in absolute ethanol (143 mL), perindopril (100 g) was slowly added while stirring to obtain a clear solution. This solution was heated at 65–70 °C for 30 minutes and then methyl tert-butyl ether (1842 mL) was slowly added. The solution was cooled to 25–30 °C, stirred for 4 hours, cooled down to 10 °C and then benzathine perindopril (1 g) was added (to initiate the process of crystallization) and the solution was then cooled to –15 °C for 8 hours. The solid was filtered off and washed with cooled methyl tert-butyl ether. After drying of the solid at 50 °C to a constant weight benzathine perindopril (94 g) was obtained.

After concentration of collected filtrates in vacuum, an addition of methyl tert-butyl ether and crystallization, a second yield (16 g) of benzathine perindopril was obtained. The purity of the final product exceeded 99.7 % (by HPLC).

Claims

1. Salts of ACE inhibitors with N,N'-dibenzylethylenediamine (benzathine) of the general formula:



wherein ACE means a molecule of ACE inhibitor and the salts exist in amorphous or crystal forms.

2. Benzathine salt of perindopril in crystal polymorph form A with the following X-ray powder diffractogram:

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	5.8949	14.98041	25.01
2	6.5122	13.56185	100.00
3	10.7061	8.25681	24.99
4	12.0797	7.32081	17.38
5	14.8462	5.96227	20.12
6	16.0810	5.50712	18.65
7	16.6625	5.31622	24.27
8	17.6098	5.03231	17.22
9	17.8417	4.96743	45.19
10	19.0928	4.64466	47.09
11	15.5830	4.52949	32.66
12	20.5267	4.32333	18.58
13	21.3166	4.16487	31.09
14	21.4948	4.13075	20.08
15	22.0069	4.03576	28.04
16	22.6724	3.91880	15.78

17	23.9340	3.71500	43.77
18	25.0831	3.54736	18.66
19	25.5437	3.48442	16.50
20	28.1560	3.16680	18.30
21	29.6824	3.00733	28.99
22	35.0811	2.55590	20.18

3. Benzathine salt of perindopril in crystal polymorph form B with the following X-ray powder diffractogram:

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	6.5142	13.55760	100.00
2	11.5531	7.65333	28.99
3	12.1045	7.30591	15.95
4	14.8847	5.94695	14.10
5	16.0939	5.50275	13.61
6	17.6270	5.02743	13.85
7	19.6125	4.52273	47.32
8	20.1330	4.40696	14.26
9	20.5802	4.31221	23.59
10	20.4838	4.13283	10.67
11	22.0327	4.03110	22.73
12	23.1710	3.83558	21.40
13	24.0011	3.70477	26.78
14	26.1996	3.39866	11.24
15	26.6917	3.00640	14.75
16	30.5506	2.92381	12.96
17	36.6578	2.44950	13.62

4. Benzathine salt of perindopril in an amorphous form.

5. Benzathine salt of fosinopril in crystal form with the following X-ray powder diffractogram:

No.	Position [2Θ/°]	Spacing [d/Å]	Rel. intensity [%]
1	5.2077	16.95574	41.12
2	12.2576	7.21499	65.38
3	16.3771	5.40822	37.00
4	16.8437	5.25944	100.00
5	17.3788	5.09870	47.64
6	18.3355	4.83474	73.92
7	19.0872	4.64601	56.65
8	19.6200	4.52103	38.92
9	20.4326	4.34303	37.21
10	20.8643	4.25413	57.53
11	21.5937	4.11204	26.29
12	22.0858	4.02152	21.83
13	22.7456	3.90634	19.16
14	23.4929	3.78374	15.57
15	24.4831	3.63291	15.47
16	24.8190	3.58449	22.19
17	25.8486	3.44601	22.72
18	27.6789	3.22028	15.09
19	28.7615	3.10148	55.69
20	29.4269	3.03285	31.20
21	30.0668	2.96975	46.72
22	32.5029	2.75251	19.68
23	33.9593	2.63772	19.01
24	35.6444	2.51679	15.83

6. Benzathine salt of enalapril in crystal form with the following X-ray powder diffractogram:

No.	Position [2Θ/°]	Spacing [*d*/Å]	Rel. intensity [%]
1	5.7194	15.43988	100.00
2	13.7934	6.41492	28.44
3	16.5103	5.36489	54.37
4	17.7514	4.99251	17.00
5	18.7449	4.73007	60.88
6	19.0720	4.64968	10.32
7	19.4392	4.56266	13.07
8	20.5924	4.30967	14.80
9	21.1680	4.19377	33.97
10	23.3380	3.80850	26.51
11	24.9277	3.56911	10.42
12	25.2710	3.52141	23.54
13	27.9803	3.18628	29.46
14	35.2158	2.54643	11.94

7. Benzathine salt of ramipril in crystal form with the following X-ray powder diffractogram:

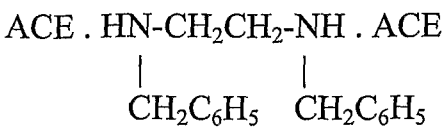
No.	Position [2Θ/°]	Spacing [*d*/Å]	Rel. intensity [%]
1	5.6472	15.63699	100.00
2	11.2714	7.84394	41.27
3	13.9095	6.36162	14.47
4	15.0119	5.89683	10.67
5	16.5107	5.36477	49.26
6	17.0071	5.20928	37.15
7	17.6850	5.01109	14.42

8	19.8578	4.46743	10.16
9	20.4361	4.34229	39.35
10	20.7197	4.28348	36.94
11	22.5331	3.94442	89.77
12	24.2194	3.67187	10.98
13	25.6742	3.46701	18.31
14	27.5848	3.23106	26.25
15	33.3840	2.68185	14.44
16	34.1824	2.62102	12.71
17	35.7393	2.51032	10.31

8. Benzathine salt of cilazapril in crystal form with the following X-ray powder diffractogram:

No.	Position [2Θ/°]	Spacing [*d*/Å]	Rel. intensity [%]
1	5.4139	16.31028	41.24
2	11.7645	7.51623	12.54
3	13.2925	6.65550	26.78
4	14.2868	6.19446	50.55
5	17.2822	5.12697	100.00
6	21.3132	4.16553	11.51
7	23.2854	3.81700	8.00
8	24.8299	3.58295	10.59

9. A process for the preparation of benzathine salts of ACE inhibitors of a general formula:



by the reaction of two moles of ACE inhibitors with one mole of N,N'-dibenzylethylenediamine.

10. A process for the preparation of benzathine salts in crystal form according to claim 9, characterized in that at crystallization water or an organic solvent from the group of esters, lower alcohols, ketones, nitriles or ethers, preferably ethyl acetate, acetone, ethanol, acetonitrile and methyl tert-butyl ether is used as a solvent.

11. A process for the preparation of benzathine salts of ACE inhibitors in an amorphous form according to claim 9, characterized in that the solution of benzathine salt in water is prepared, which is frozen and lyophilized or transformed to a dry state in another manner so that no crystallization occurs.

12. A process for the preparation of a granulate containing benzathine salts of ACE inhibitors according to claims 1 to 8, characterized in that an aqueous or alcohol/ aqueous solution of benzathine salt of ACE inhibitor is sprayed onto a mixture of inert ingredients for the preparation of a granulate and simultaneously dried in a counterflow of warm air with a temperature of not more than 60 °C.

13. A pharmaceutical formulation containing benzathine salts of ACE inhibitors according to claims 1 to 8.

14. A pharmaceutical formulation containing benzathine salts of ACE inhibitors according to claims 1 to 8, characterized in that it additionally contains one or more compounds from the group of diuretics, antitrombolitics, calcium ion influx inhibitors, anti-hyperlipoproteinemics or antioxidants.

15. Pharmaceutical formulation according to claims 13 and 14 for the treatment of cardiovascular diseases associated with hypertension, ischemia and heart muscle weakness.

Fig. 1.

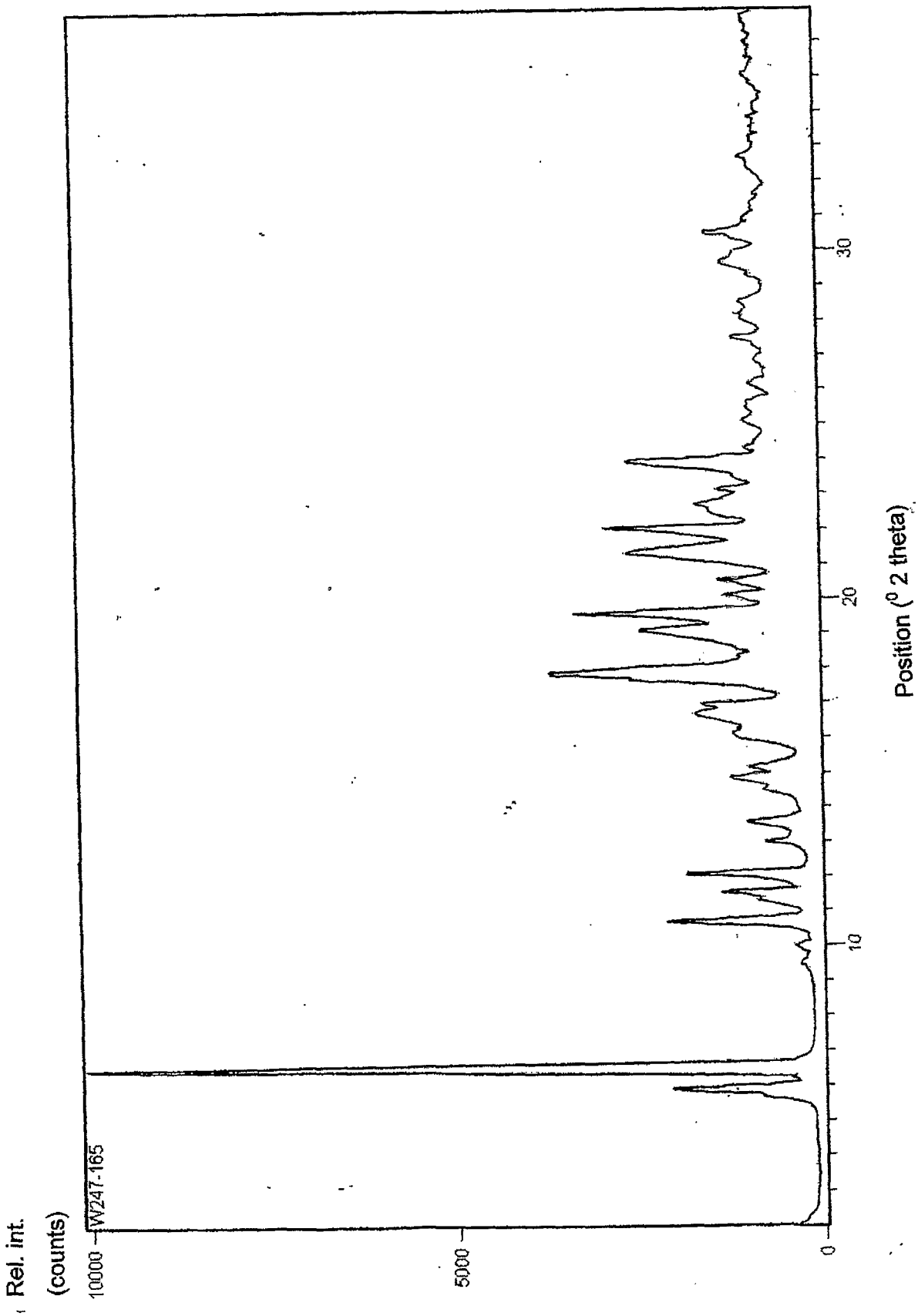


Fig. 2.

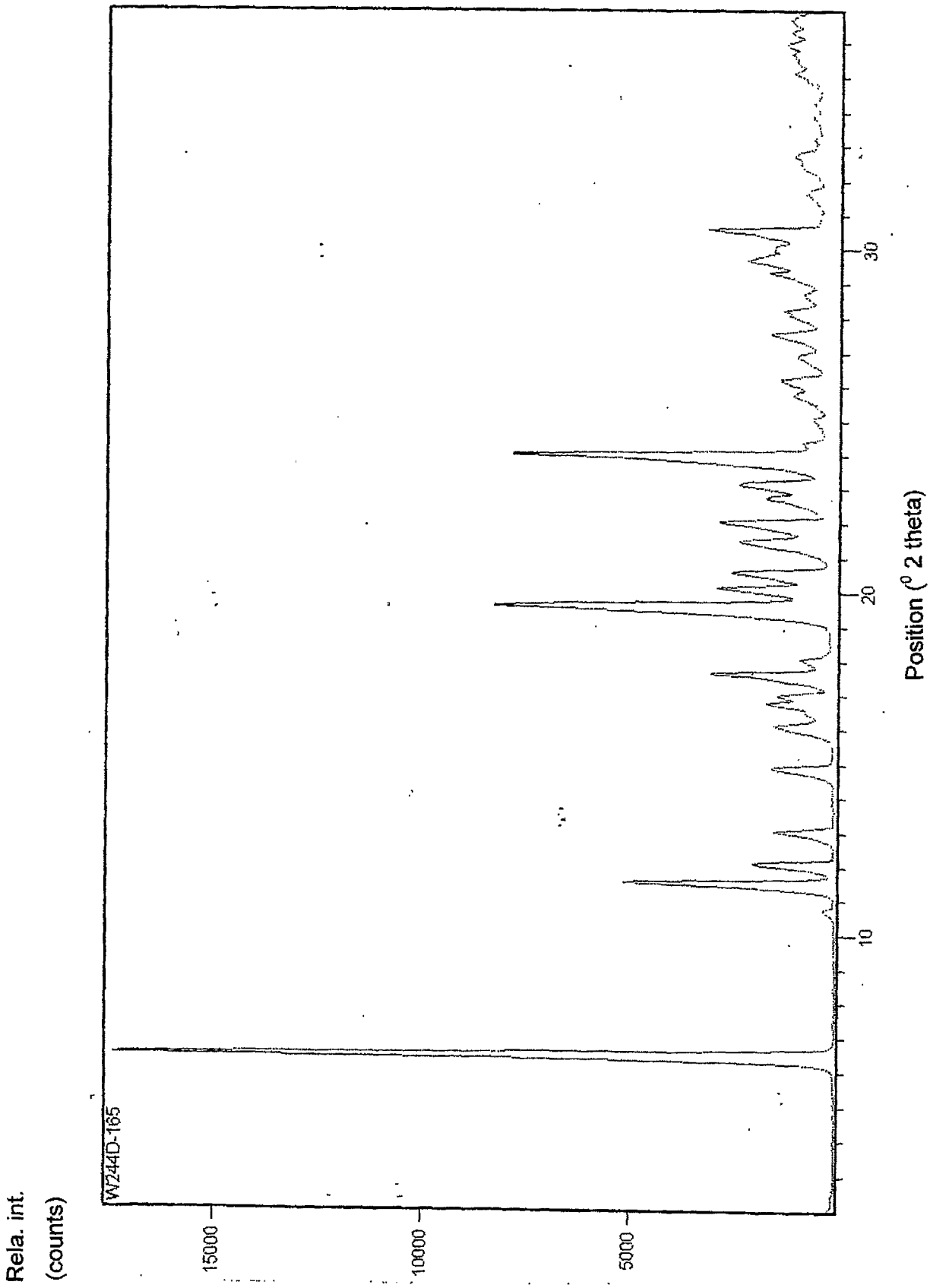

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Fig. 3.

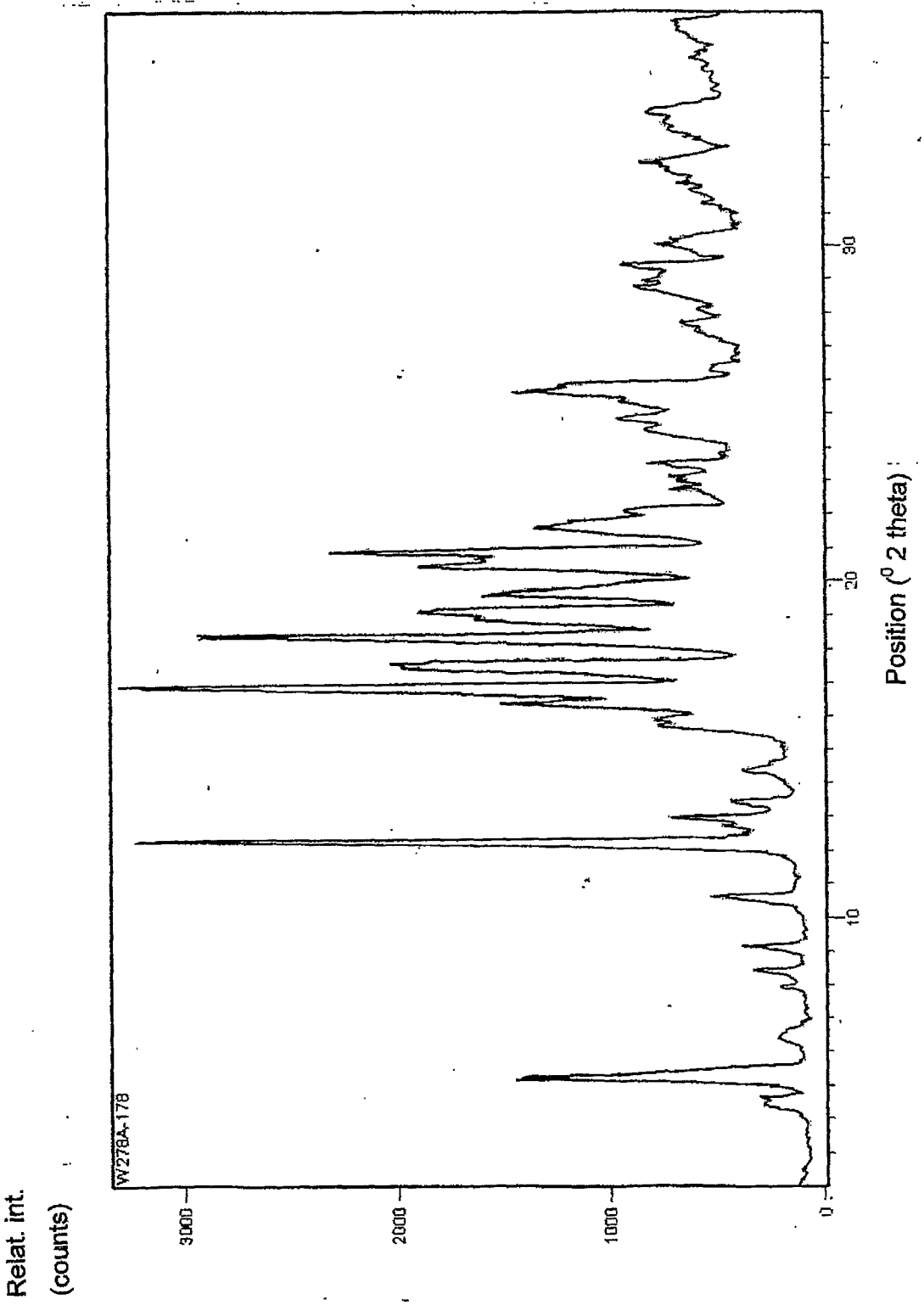
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Fig. 4.

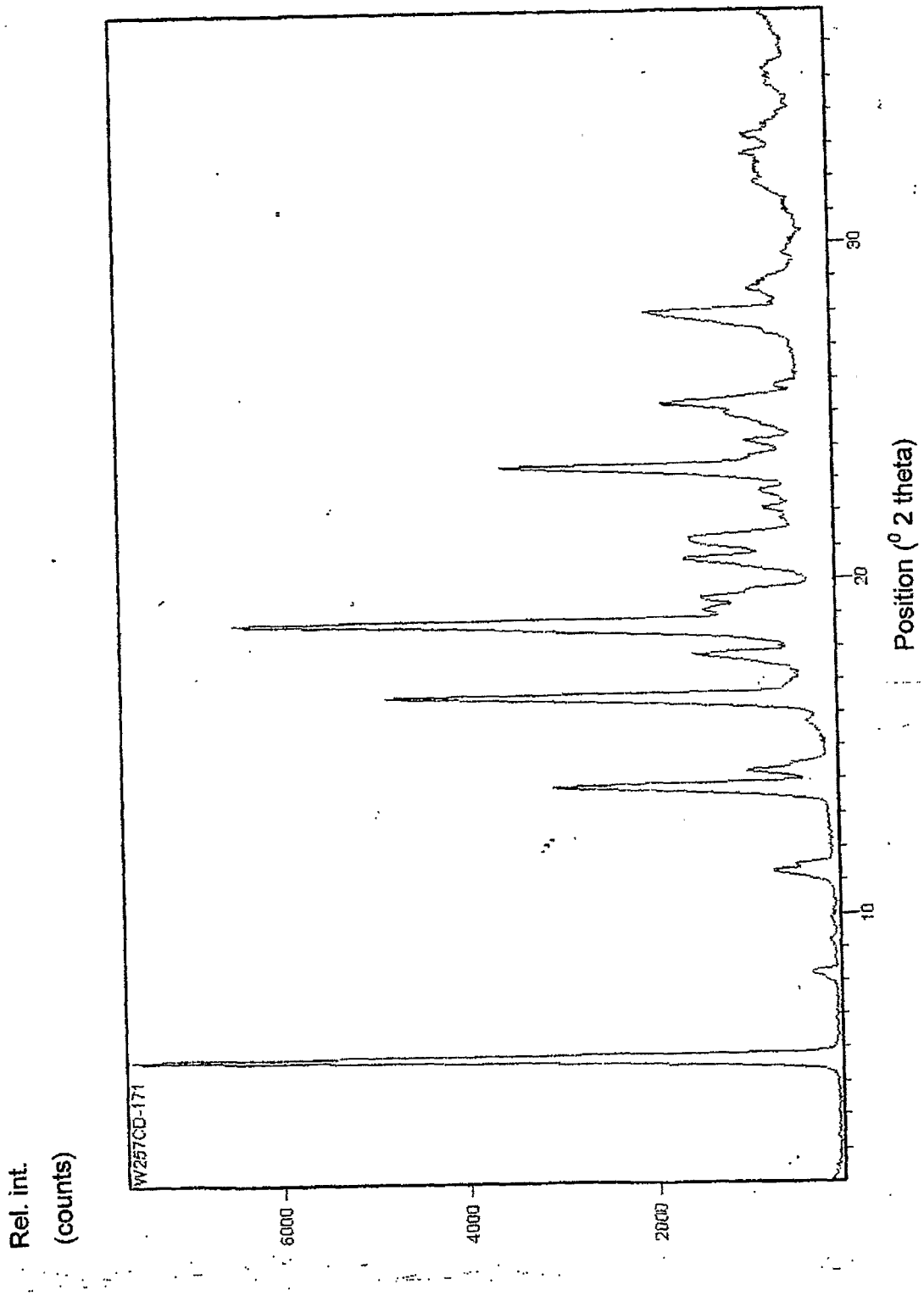
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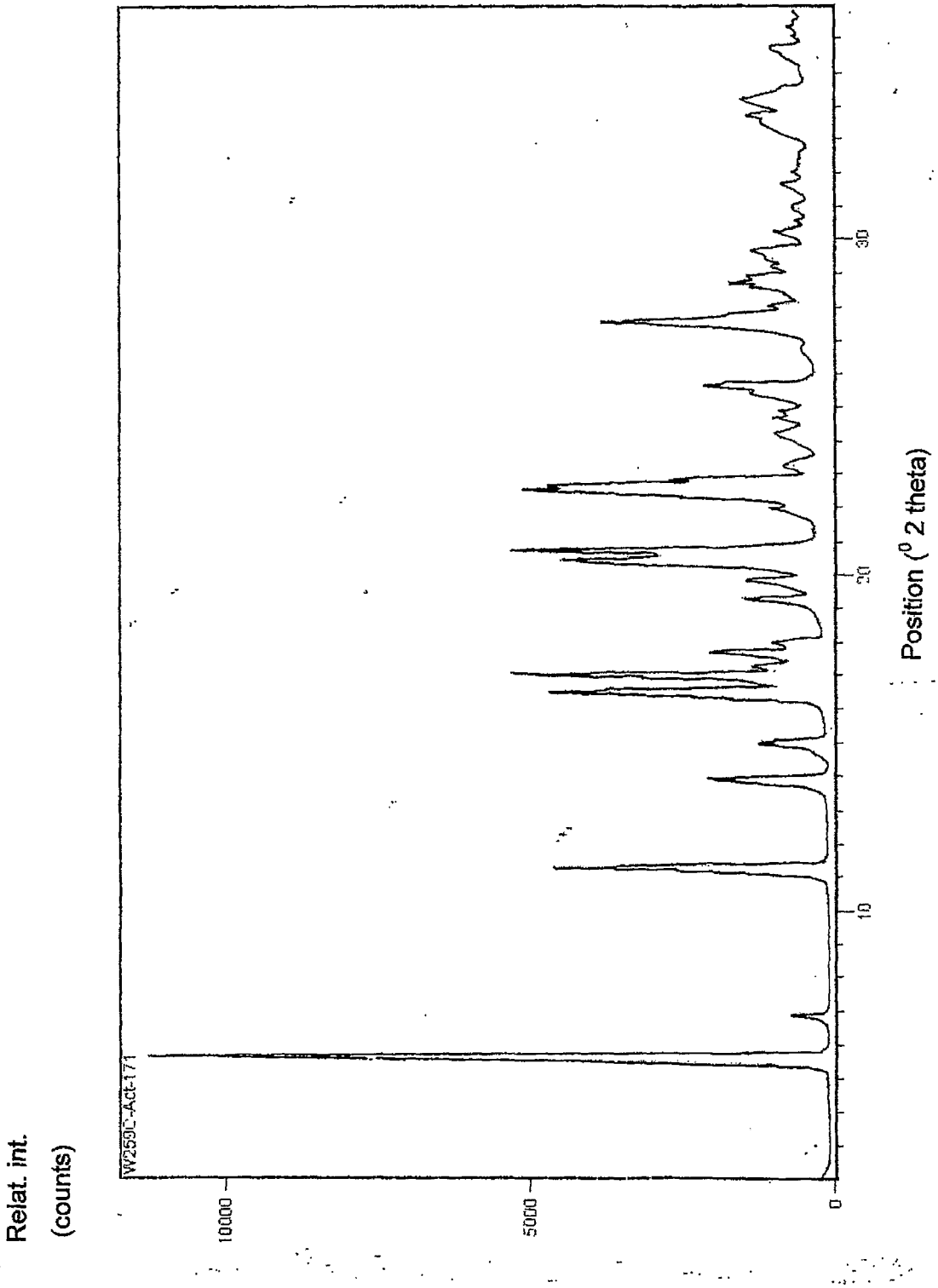
Fig. 5.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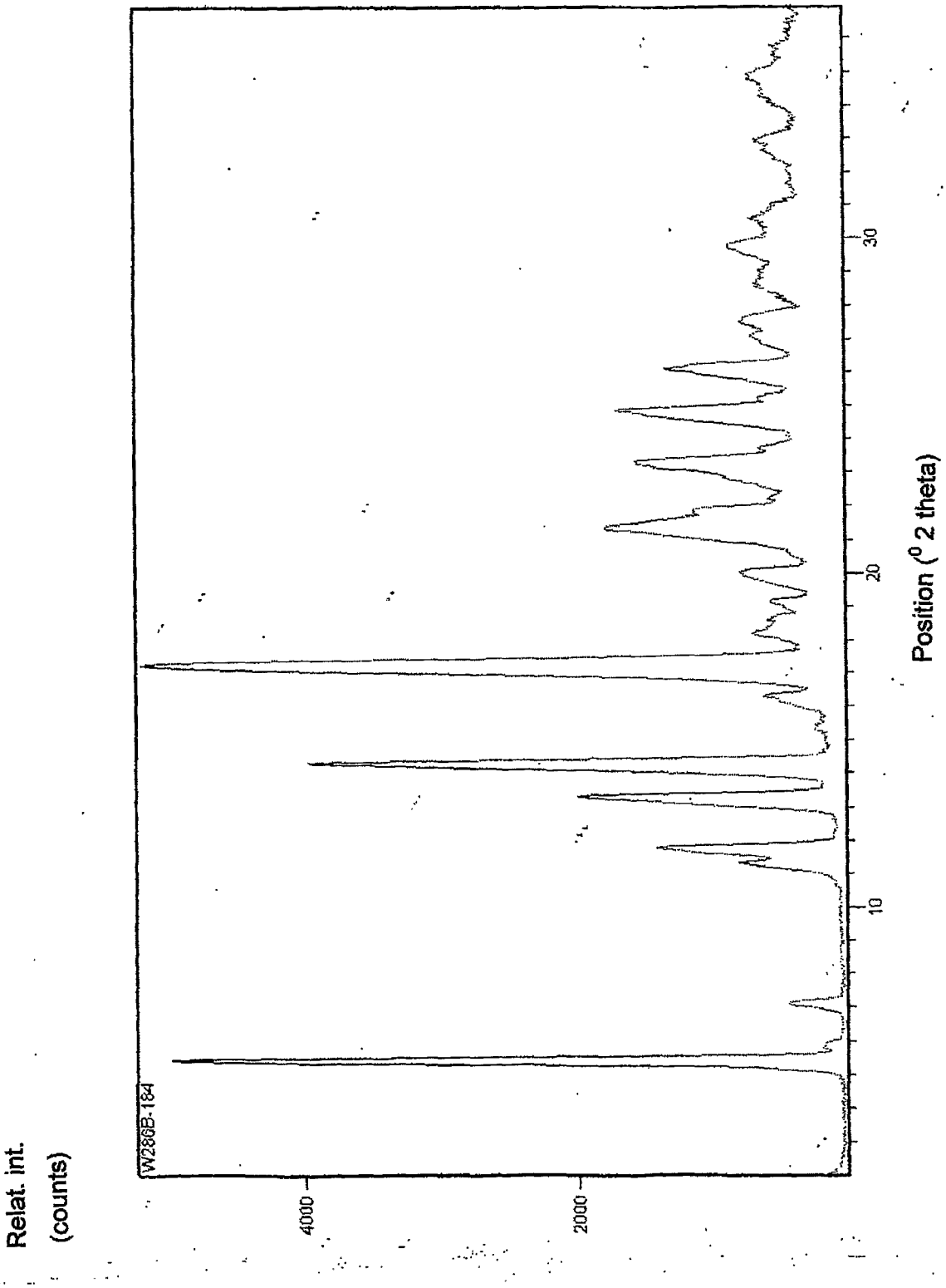
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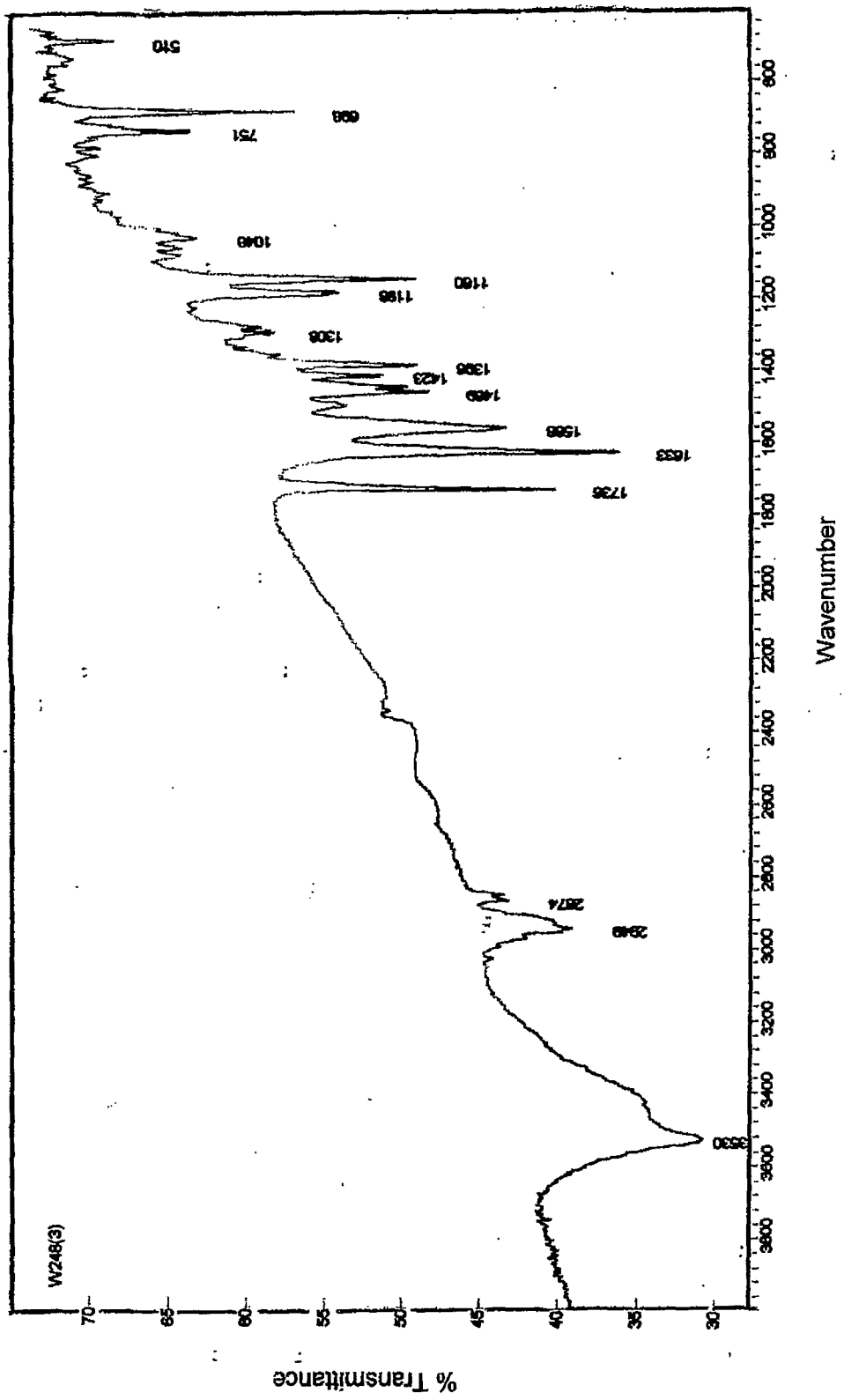
Fig. 7.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2400
2600
2800
3000
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3400
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3800
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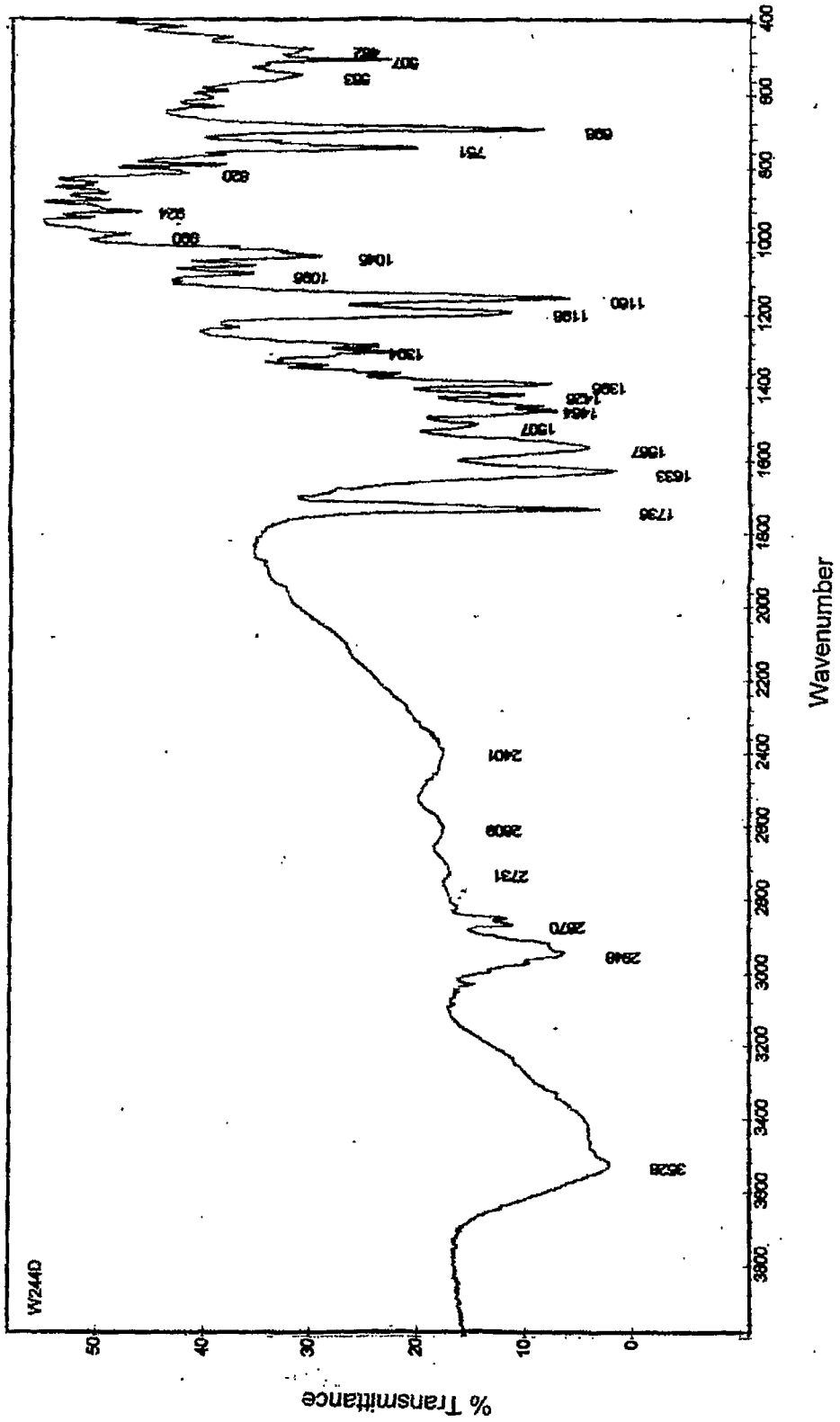
Fig. 8.


W244D
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Wavenumber
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Fig. 9.

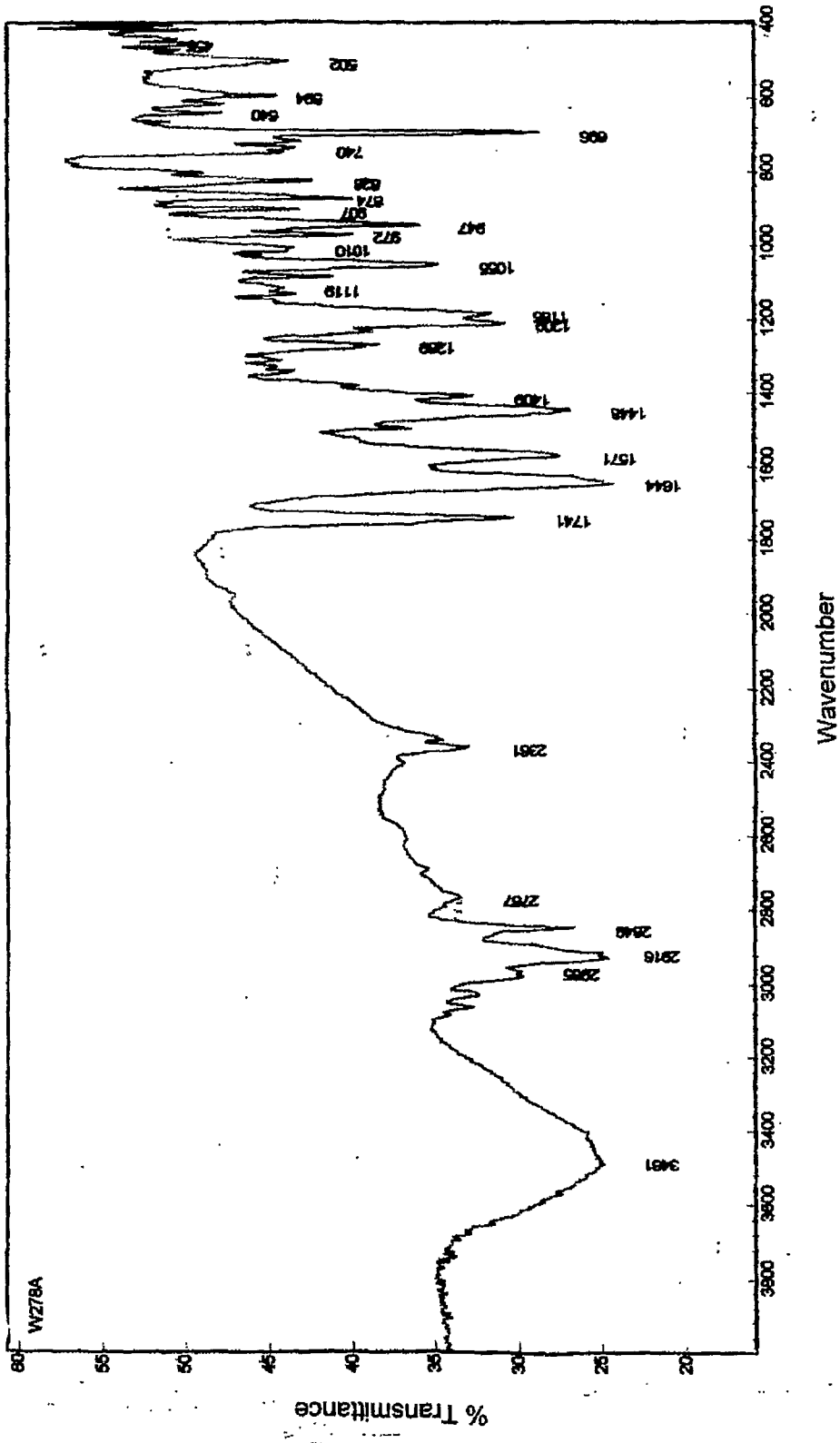
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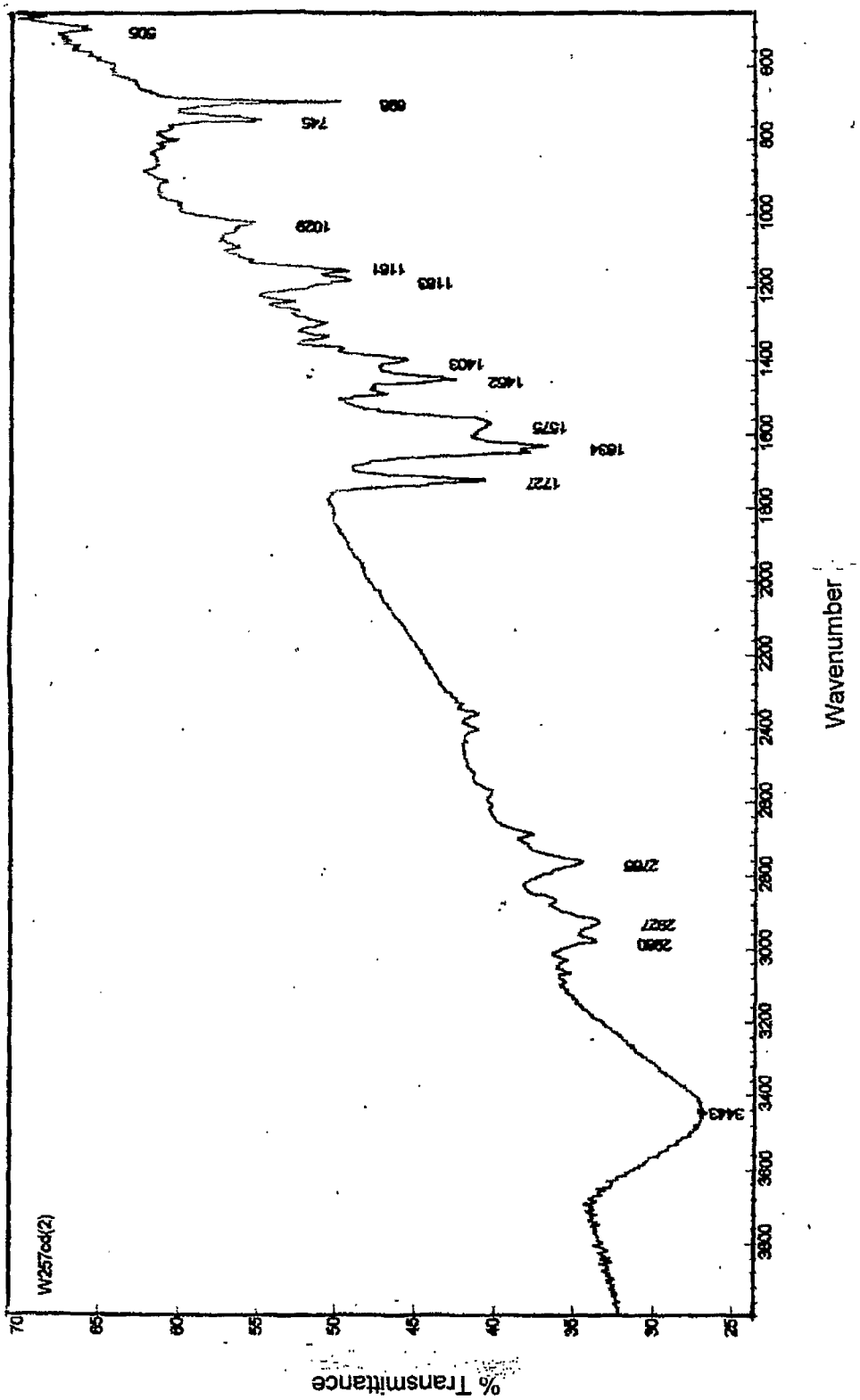
Fig. 10.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2860
3443

Fig. 11.

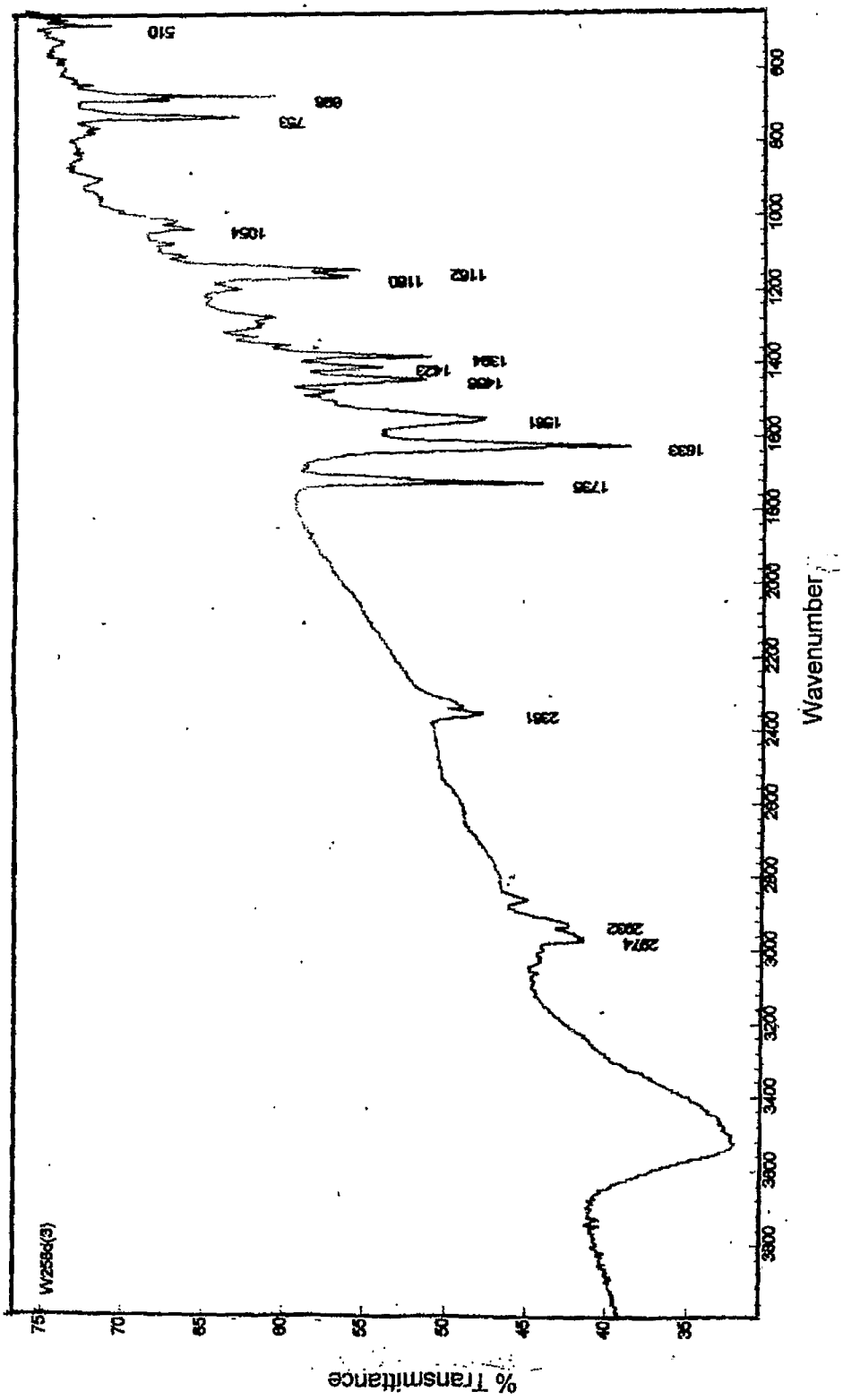
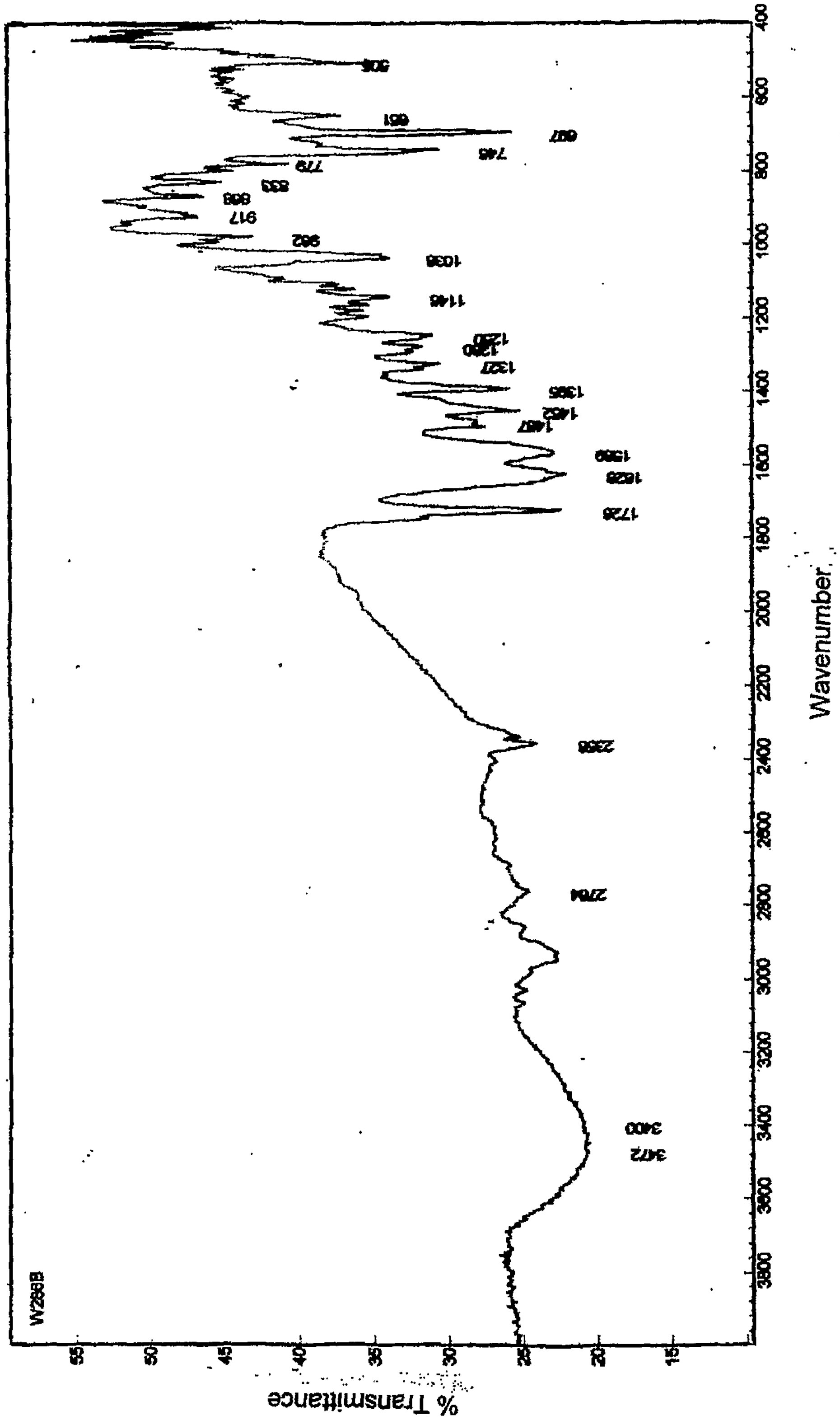

W2584(3)
% Transmittance
Wavenumber
510
656
753
1054
1162
1180
1354
1423
1456
1561
1633
1735
2351
2874
2932

Fig. 12.


W288B
% Transmittance
Wavenumber
506
651
697
745
779
833
868
917
982
1036
1146
1250
1280
1327
1395
1452
1487
1589
1628
1726
2358
2764
3400
3472