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(54) Title: PREPARATION OF TELMISARTAN SALTS

(57) Abstract: New salts of telmisartan, in amorphous and crystalline forms, together with two new polymorphic forms of telmisartan potassium, have been prepared by crystallization, evaporation of solvent, spray-drying or lyophilization and were included into a pharmaceutical formulation.

Preparation of Telmisartan Salts

Description

FIELD OF THE INVENTION

The present invention relates to novel telmisartan salts, and/or novel polymorphs of telmisartan salts, together with processes for their preparation and pharmaceutical formulations containing them.

BACKGROUND OF THE INVENTION

Telmisartan with its chemical name 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimid-azol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid is a non-peptide angiotensin II receptor type AT_1 antagonist used for the treatment of hypertension. It might be used alone or in combination with another pharmaceutically active compound, e.g. hydrochlorothiazide.

It is disclosed in **EP 502314** as well as in J. Med. Chem. 36 (25), 4040-4051 (1993), and its polymorphs are known from **EP 1144386**, and J. Pharm. Sci., 89 (11), 1465-1479 (2000).

The object of the present invention is to provide salts of telmisartan and/or its polymorphs, which are to be used for the preparation of solid pharmaceutical oral dosage forms on industrial scale thus overcoming the problem of the poor solubility of telmisartan under physiological conditions.

WO 2004/028505 discloses a solid oral dosage form consisting of telmisartan, a basic agent, a surfactant, and a water-soluble diluent and **WO 03/059327** describes a tablet matrix

with substantially amorphous telmisartan wherein the ratio of alkali versus telmisartan is above one.

WO 2003/037876 provides telmisartan sodium salt and describes its preparation from acid addition salts, prepared with hydrochloride, hydrobromide, toluene sulphonic and methane sulphonic acid.

US 2003/0130331 and **WO 2006/050509** disclose polymorphic forms of telmisartan sodium. **WO 2004/096215** also provides telmisartan sodium in crystalline form, as well as the hydrochloride addition salt of telmisartan.

WO 2006/050921 describes alkali and earth alkali salts of telmisartan, together with their crystalline and amorphous forms.

In **WO 2006/044754** the bisulphate and potassium salt of telmisartan are prepared.

CN 1548421 discloses the preparation of alkali, earth alkali, arginine and lysine salts of telmisartan including the reaction of telmisartan with organic and inorganic alkali, arginine and lysine in an organic solvent or water, at 20°c to 150°C, although only the preparation of alkali salts is described in the examples.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an X-ray powder diffraction spectrum of amorphous telmisartan ammonium salt.

Figure 2 is an X-ray powder diffraction spectrum of amorphous telmisartan choline salt.

Figure 3 are X-ray powder diffraction spectra of amorphous telmisartan choline salt with different levels of hydratation.

Figure 4 is an X-ray powder diffraction spectrum of telmisartan *tert*-butylamine salt, polymorphic form I.

Figure 5 is an X-ray powder diffraction spectrum of telmisartan *tert*-butylamine salt, polymorphic form II.

Figure 6 is an X-ray powder diffraction spectrum of telmisartan meglumine salt.

Figure 7 is telmisartan meglumine as seen through a microscope.

Figure 8 is an X-ray powder diffraction spectrum of amorphous telmisartan meglumine salt.

Figure 9 is an X-ray powder diffraction spectrum of amorphous telmisartan ethanolamine salt.

Figure 10 is an X-ray powder diffraction spectrum of amorphous telmisartan piperazine salt.

Figure 11 is an X-ray powder diffraction spectrum of telmisartan diethylamine salt.

Figure 12 is an X-ray powder diffraction spectrum of telmisartan tris-(hydroxymethyl)amine salt.

Figure 13 is an X-ray powder diffraction spectrum of telmisartan sulphate salt.

Figure 14 is an X-ray powder diffraction spectrum of amorphous telmisartan L-arginine salt.

Figure 15 is an X-ray powder diffraction spectrum of telmisartan potassium salt, polymorph A.

Figure 16 is an X-ray powder diffraction spectrum of telmisartan potassium salt, polymorph B.

Figure 17 is an X-ray powder diffraction spectrum of telmisartan maleate.

Figure 18 is an X-ray powder diffraction spectrum of telmisartan tartrate.

Figure 19 is an X-ray powder diffraction spectrum of telmisartan citrate

Figure 20 is an X-ray powder diffraction spectrum of telmisartan fumarate.

Figure 21 is an X-ray powder diffraction spectrum of telmisartan 2-naphthalenesulphonate.

Figure 22 is an X-ray powder diffraction spectrum of telmisartan oxalate.

Figure 23 is an X-ray powder diffraction spectrum of telmisartan benzenesulfonate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel telmisartan salts and polymorphs thereof suitable for pharmaceutical use. It is known from US 6,358,986 that crystals of telmisartan polymorph form A are in the shape of long needles with an electrostatic charge that could cause many problems in large scale production of the substance and in the production of pharmaceutical compositions containing such substance as for example difficulties during filtration, washing up, isolation, drying. The need to further re-crystallization leads to higher content of residual solvents and lower yield. Therefore there exists a constant need for a preparation method for telmisartan and/or salts thereof having such physical properties that enable easy handling during the preparation of pharmaceutical compositions as for example having particles without an electrostatic charge and being not in the shape of long needles in high yield. This goal is achieved by the preparation of novel telmisartan salts according to the present invention.

We have now surprisingly and unexpectedly prepared novel salt forms of telmisartan including salts with ammonium, choline (trimethyl-ethanolamine), *tert*-butyl amine (erbumine), arginine, meglumine (N-methylglucamine), ethanolamine, piperazine, diethylamine, sulfuric acid, maleic acid, tartaric acid, citric acid, fumaric acid, oxalic acid, benzenesulfonic acid, naphthalene-2-sulphonic acid, tris-(hydroxymethyl)amine, as well as new polymorphic forms of telmisartan potassium, which have desirable properties and can be prepared in high yield. The obtained telmisartan salts according to the present invention are characterized by having a different crystal shape than needles. As such, these salt forms are pharmaceutically acceptable and can be readily

used in the preparation of pharmaceutical formulations especially because the basic and acid salts of telmisartan have a much higher solubility than telmisartan itself.

Thus, the present invention provides basic and acid addition salts of telmisartan that are pure, have good stability, and have advantageous formulation properties compared to the free acid form of telmisartan.

Melting points were taken on a Koffler melting point apparatus and IR spectra were taken on a Paragon 100 Perkin-Elmer FT-IR spectrometer.

X-ray powder diffraction patterns were obtained by a Phillips PW3040/60 X'Pert PRO diffractometer using CuK_α radiation of 1,541874 Å.

Telmisartan salts according to the present invention may be prepared by crystallization: a telmisartan salt, or a mixture of telmisartan or a telmisartan salt with an organic or inorganic base is dissolved in a polar solvent, such as: N,N,-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), alcohols such as for example methanol, ethanol and isopropanol, acetone, acetonitrile or water, or any mixtures thereof, at a temperature ranging from room temperature to reflux temperature of the solvent applied. The solution can be filtered and then cooled to a temperature between about -10 and about 30°C, preferably to room temperature. Optionally, active charcoal may be applied in order to purify the active ingredient or the mixture containing the active ingredient and an organic or inorganic base. The precipitate is filtered and the product is dried at a temperature between about 10°C and about 60°C, preferably between about 40 °C and about 50°C. As used herein, the term

"drying" generally refers to a removal of solvent until the telmisartan salt prepared contains less than about 5000 ppm residual solvents. Drying may be achieved e.g. via application of heat, preferably carried out under ambient or reduced pressure or via contacting a telmisartan salt with humid air in a fluidized bed drier, wherein the atmosphere in the fluidized bed drier has at least 15% humidity. Preferably, vacuum drying in a commercially available vacuum dryer is applied. As bases organic amines, ammonium, and alkali and earth alkali hydroxides may be used.

In one aspect of the present invention acid addition salts of telmisartan according to the present invention are prepared by suspending a mixture of a telmisartan salt, or a mixture of telmisartan or a telmisartan salt with an organic or inorganic acid, in a polar solvent such as: N,N,-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), alcohols such as for example methanol, ethanol, and isopropanol, acetone, acetonitrile and water, or any mixtures thereof, at a temperature ranging from room temperature to the reflux temperature of the solvent. The suspension may be cooled to a temperature between about -10 and about 30°C, preferably to room temperature. The suspension is filtered and the product is dried at a temperature between about 10°C and about 60°C, preferably between about 40 °C and about 50°C, preferably in a vacuum drier, but also other means of drying as described above may be used.

Telmisartan salts according to the present invention may also be prepared by lyophilization or by spray-drying of a solution of telmisartan, or a telmisartan salt, and an organic or inorganic base, in a polar solvent such as: N,N,-dimethylformamide (DMF), N,N-dimethylacetamide (DMA),

dimethyl sulfoxide (DMSO), alcohols such as for example methanol, ethanol and isopropanol, acetone, acetonitrile and water, or any mixtures of them, at a temperature ranging from room temperature to reflux temperature of the solvent. Optionally, active charcoal may be applied in order to purify the active ingredient or the mixture containing the active ingredient and an organic or inorganic base applied. The solution is spray-dried or freezed with liquid nitrogen and then lyophilized. The obtained solid product is collected and if necessary additionally dried as described above. The isolated products are telmisartan salts. In case of spray-drying, the solution is spray-dried at a temperature between about 20°C and about 100 °C. The spray-drying of the solution as described in the examples was performed with a Büchi Mini-Spray Drier 190. Also, similar equipment can be used. As organic or inorganic base organic amines, ammonium, and alkali and earth alkali hydroxides can be used.

In another aspect of the present invention telmisartan salts according to the present invention are prepared by evaporation of the solvent and the trituration of the residue. A telmisartan salt, or a mixture of telmisartan or a telmisartan salt with an organic or inorganic base, is dissolved in a polar solvent such as: N,N,-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), alcohols such as for example methanol, ethanol and isopropanol, acetone, acetonitrile and water, or mixtures of them, at a temperature ranging from room temperature to the reflux temperature of the solvent. Optionally, active charcoal may be applied in order to purify the active ingredient or the mixture containing the active ingredient and an organic or inorganic base applied. The solution is optionally filtered and the solvent is evaporated, preferably at a temperature between about 20 and about 100°C, under

reduced pressure. The residue is suspended in an organic solvent such as alcohols such as for example methanol, ethanol and isopropanol, esters such as for example methyl acetate, ethyl acetate, isopropyl acetate, propyl acetate, butyl acetate, isobutyl acetate and *tert*-butyl acetate, ethers such as for example diethyl ether, diisopropyl ether and *tert*-butyl methyl ether, acetone or any mixtures thereof. The product is filtered, dried at a temperature between about 10°C and about 60°C, preferably between about 40 °C and about 50°C, preferably in a vacuum drier. As bases organic amines and hydroxides can be used.

In case telmisartan is used in the above mentioned preparations of telmisartan salts according to the present invention, it can be prepared by any method known from the prior art.

In another aspect of the present invention telmisartan is obtained from 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile by hydrolysis of the cyano group in a solvent. The hydrolysis could be carried out by the addition of strong bases such as for example NaOH, KOH, LiOH, $Ca(OH)_2$, and similar compounds. According to another aspect of the present invention the hydrolysis could be carried out by the addition of strong acids such as for example H_2SO_4, HCl, HBr, H_3PO_4, HNO_3, $HClO_4$, p-toluene sulphonic acid, methane sulphonic acid, benzene sulphonic acid, and similar. The isolation of telmisartan is performed by optional addition of water and adjustment of pH to about 5 to about 7. The obtained telmisartan can be in any polymorph form.

Accordingly, a first aspect of the present invention is directed towards amorphous telmisartan ammonium salt

characterized by the X-ray powder diffraction pattern as shown in Figure 1, and a melting interval of 150-158°C.

In a second aspect, the invention is directed to amorphous telmisartan choline salt, or solvates or hydrates thereof, characterized by a melting interval of 65-110°C and by the X-ray powder diffraction pattern as shown in Figure 2. Also the hydrated forms of amorphous telmisartan choline salt, characterized by a melting interval of 65-80°C and by the X-ray powder diffraction patterns as shown in Figure 3, were prepared.

In a third aspect, the present invention is directed to the telmisartan *tert*-butylamine salt, and the polymorphs I and II thereof characterized by a melting interval of 264-268 °C and 168-175 °C, respectively, and by the X-ray powder diffraction patterns as shown in Figures 4 and 5, respectively.

A typical X-ray diffraction pattern of polymorphic form I of telmisartan *tert*-butylamine salt is given in the following Table 1 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 1:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	5.7	15.59	4
2	6.6	13.44	100
3	9.0	9.81	5
4	10.7	8.26	7
5	13.2	6.71	93
6	13.8	6.40	16

7	14.1	6.30	27
8	14.7	6.02	8
9	15.2	5.84	9
10	16.1	5.50	7
11	16.5	5.37	8
12	17.0	5.22	21
13	17.5	5.08	19
14	17.8	4.98	14
15	18.1	4.90	12
16	19.5	4.55	34
17	19.9	4.46	10
18	20.3	4.38	8
19	20.9	4.25	16
20	21.5	4.13	17
21	22.1	4.02	17
22	22.8	3.90	6
23	23.5	3.78	17
24	23.8	3.74	10
25	24.6	3.61	7
26	25.6	3.48	6
27	26.1	3.41	7
28	26.6	3.36	12
29	27.4	3.26	9
30	28.4	3.14	5
31	30.0	2.98	7

Polymorphic form I of telmisartan *tert*-butylamine salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 6.6, 13.2, 14.1, 17.0and 19.5 ± 0.2 degrees 2-theta.

A typical X-ray diffraction pattern of polymorphic form II of telmisartan *tert*-butylamine salt is given in the following

Table 2 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 2:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	4.5	19.71	20
2	6.8	13.09	6
3	7.1	12.47	4
4	8.4	10.54	3
5	9.1	9.71	10
6	9.4	9.38	4
7	11.8	7.53	3
8	13.3	6.65	55
9	13.7	6.49	100
10	14.3	6.17	10
11	14.9	5.96	14
12	15.8	5.62	7
13	16.1	5.52	8
14	16.9	5.26	9
15	17.2	5.15	8
16	18.3	4.85	15
17	19.1	4.65	45
18	20.0	4.44	15
19	21.1	4.22	30
20	21.5	4.14	15
21	22.1	4.02	13
22	22.9	3.88	8
23	23.4	3.81	8
24	25.4	3.51	14

25	26.0	3.42	10
26	27.5	3.24	9
27	28.0	3.18	11
28	29.1	3.07	8
29	30.0	2.98	8

Polymorphic form II of telmisartan *tert*-butylamine salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 4.5, 13.3, 13.7, 19.1, 21.1 ± 0.2 degrees 2-theta.

In a fourth aspect, the present invention is directed to telmisartan meglumine salt (telmisartan N-methylglucamine salt) characterized by a melting interval of 198-205 °C, and by the X-ray powder diffraction pattern as shown in Figure 6.

A typical X-ray diffraction pattern of telmisartan meglumine salt is given in the following Table 3 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 3:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	5.3	16.55	9
2	6.9	12.85	84
3	9.7	9.11	8
4	10.7	8.24	31

5	12.5	7.07	28
6	13.3	6.68	37
7	14.3	6.18	41
8	14.9	5.93	20
9	15.5	5.71	100
10	16.7	5.30	55
11	17.3	5.13	29
12	17.9	4.95	95
13	19.0	4.67	40
14	19.4	4.58	41
15	20.4	4.36	34
16	21.2	4.19	17
17	22.1	4.03	73
18	22.5	3.94	53
19	22.8	3.91	52
20	23.4	3.80	81
21	23.8	3.74	40
22	24.1	3.70	27
23	24.9	3.58	36
24	26.0	3.43	22
25	27.4	3.26	33
26	27.5	3.24	28
27	29.5	3.03	14
28	30.0	2.97	17

Telmisartan meglumine salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 6.9, 15.5, 17.9, 22.1, 23.4 ± 0.2 degrees 2-theta.

In a fifth aspect the present invention is directed to amorphous telmisartan meglumine salt (telmisartan N-methylglucamine salt) characterized by a melting interval of

86-91 °C, and by the X-ray powder diffraction pattern as shown in Figure 8.

In a sixth aspect, the present invention is directed to the amorphous ethanolamine salt of telmisartan characterized by a melting interval of 265-268 °C and by the X-ray powder diffraction pattern as shown in Figure 9.

In a seventh aspect, the present invention is directed to the amorphous piperazine salt of telmisartan characterized by a melting interval of 155-160 °C and by the X-ray powder diffraction pattern as shown in Figure 10.

In an eigth aspect, the present invention is directed to telmisartan diethylamine salt characterized by a melting interval of 120-135 °C, and by the X-ray powder diffraction pattern as shown in Figure 11.

A typical X-ray diffraction pattern of telmisartan diethylamine salt is given in the following Table 4 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 4:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	6.0	14.64	100
2	7.0	12.71	23
3	8.3	10.70	7
4	9.8	9.03	9
5	10.6	8.34	8

6	11.5	7.68	28
7	12.1	7.34	19
8	12.3	7.17	16
9	13.0	6.82	15
10	13.9	6.36	27
11	14.5	6.09	16
12	15.1	5.87	16
13	15.6	5.69	18
14	15.9	5.56	14
15	17.0	5.20	11
16	18.1	4.90	16
17	18.6	4.78	13
18	19.7	4.51	8
19	20.9	4.25	13
20	21.6	4.12	17
21	22.5	3.95	16
22	22.9	3.89	18
23	23.5	3.78	17
24	24.8	3.59	14
25	25.4	3.51	11
26	25.9	3.44	11
27	26.7	3.34	10
28	27.1	3.29	8
29	28.7	3.11	9

Telmisartan diethylamine salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 6.0, 7.0, 11.5, 12.1, 13.9 ± 0.2 degrees 2-theta.

In a nineth aspect, the present invention is directed to telmisartan tris-(hydroxymethyl)amine salt characterized by a melting interval of 189-198 °C, and by the X-ray powder diffraction pattern as shown in Figure 12.

A typical X-ray diffraction pattern of telmisartan tris-(hydroxymethyl)amine salt is given in the following Table 5 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 5:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	5.1	17.37	15
2	7.2	12.19	32
3	10.3	8.58	21
4	12.0	7.38	32
5	12.5	7.10	26
6	13.1	6.77	55
7	13.5	6.57	43
8	14.0	6.31	78
9	14.3	6.19	89
10	15.6	5.69	94
11	16.5	5.37	33
12	16.9	5.24	60
13	17.5	5.07	40
14	19.4	4.58	40
15	20.2	4.41	76
16	20.5	4.33	77
17	22.3	3.99	41
18	23.4	3.81	44
19	24.1	3.70	100
20	24.6	3.62	78
21	25.7	3.47	42
22	26.2	3.40	49

23	27.1	3.29	37
24	29.0	3.08	48

Telmisartan tris-(hydroxymethyl)amine salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 14.0, 14.3, 15.6, 20.2, 20.5, 24.1 ± 0.2 degrees 2-theta.

In an tenth aspect, the present invention is directed to telmisartan sulphate salt characterized by a melting interval of 218-227°C and by the X-ray powder diffraction pattern as shown in Figure 13.

A typical X-ray diffraction pattern of telmisartan sulphate salt is given in the following Table 6 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 6:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	5.9	14.91	19
2	7.2	12.34	31
3	7.6	11.59	26
4	8.2	10.74	10
5	9.4	9.37	13
6	11.7	7.55	45
7	12.3	7.19	41
8	12.8	6.90	76
9	13.6	6.52	72
10	14.3	6.18	21

11	14.9	5.95	39
12	15.1	5.88	43
13	15.8	5.62	49
14	15.9	5.56	57
15	16.5	5.36	93
16	16.9	5.26	53
17	17.1	5.17	38
18	17.8	4.97	76
19	18.4	4.83	36
20	18.7	4.74	44
21	19.1	4.65	24
22	19.7	4.51	34
23	20.4	4.36	27
24	20.9	4.25	52
25	21.4	4.15	100
26	21.8	4.07	66
27	22.5	3.95	71
28	23.4	3.80	69
29	23.8	3.74	44
30	24.6	3.62	81
31	25.4	3.50	44
32	26.8	3.33	49
33	28.0	3.19	32
34	29.1	3.06	40
35	30.0	2.98	21

Telmisartan sulphate salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 12.8, 13.6, 16.5, 17.8, 21.4 ± 0.2 degrees 2-theta.

In an eleventh aspect, the present invention is directed to the amorphous telmisartan *L*- arginine salt characterized by a

melting interval of about 160-175°C and by the X-ray powder diffraction pattern as shown in Figure 14.

In a twelth aspect, the present invention is directed to the novel polymorphic forms of telmisartan potassium salt characterized by a melting interval of 182 - 194°C (form A), and 205-225 °C (form B), respectively, and by the X-ray powder diffraction patterns as shown in Figures 15 (form A) and 16 (form B).

A typical X-ray diffraction pattern of polymorphic form A of telmisartan potassium salt is given in the following Table 7 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 7:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	3.40	26.00	5
2	5.76	15.33	100
3	10.34	8.56	7
4	11.57	7.65	28
5	12.51	7.08	12
6	13.55	6.53	35
7	13.73	6.45	28
8	15.77	5.62	14
9	17.41	5.09	9
10	17.97	4.94	16
11	21.05	4.22	8
12	22.67	3.92	11
13	23.26	3.82	11

14	24.29	3.66	31
15	25.11	3.55	14
16	25.49	3.50	13
17	26.03	3.42	13
18	26.79	3.33	11
19	27.63	3.23	17
20	28.21	3.16	17
21	29.26	3.05	9

Polymorphic form A of telmisartan potassium salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 5.8, 11.6, 13.6, 13.7, 24.3 ± 0.2 degrees 2-theta.

A typical X-ray diffraction pattern of polymorphic form B of telmisartan potassium salt is given in the following Table 8 by listing 2-theta degrees (± 0.2 degrees 2-theta) together with the corresponding intensities.

Table 8:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	3.8	23.02	8
2	5.4	16.23	88
3	5.9	14.85	100
4	7.3	12.10	8
5	10.4	8.52	19

6	10.8	8.20	31
7	11.6	7.60	25
8	12.0	7.38	16
9	13.6	6.51	10
10	15.6	5.69	15
11	17.6	5.04	20
12	20.1	4.41	13
13	22.6	3.93	17
14	24.3	3.67	13
15	25.1	3.55	13
16	27.6	3.24	13

Polymorphic form B of telmisartan potassium salt is preferably characterized by an X-ray powder diffraction pattern having peaks at: 5.4, 5.9, 10.4, 11.6, 17.6 ± 0.2 degrees 2-theta.

In a thirteenth aspect, the present invention is directed to the telmisartan maleate salt characterized by a melting interval of about 265-270°C and by the X-ray powder diffraction pattern as shown in Figure 17 and in Table 9.

Table 9:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	11.6	7.61	29
2	12.6	7.03	42
3	16.1	5.50	50
4	17.3	5.13	100
5	20.7	4.29	60

6	22.8	3.90	44

In a fourteenth aspect, the present invention is directed to the telmisartan tartrate salt characterized by a melting interval of about 230-235°C and by the X-ray powder diffraction pattern as shown in Figure 18 and in Table 10.

Table 10:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	6.5	13.61	100
2	8.1	10.87	8
3	9.9	8.91	8
4	13.0	6.80	10
5	16.0	5.53	9
6	20.0	4.44	12
7	21.9	4.05	25

In a fifteenth aspect, the present invention is directed to the telmisartan citrate salt characterized by a melting interval of about 267-271°C and by the X-ray powder diffraction pattern as shown in Figure 19 and in Table 11.

Table 11:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	6.1	14.45	100
2	7.9	11.17	69

3	11.9	7.44	77
4	14.2	6.22	64
5	16.2	5.49	55
6	22.1	4.03	57

In a sixteenth aspect, the present invention is directed to the telmisartan fumarate salt characterized by a melting interval of about 121-130°C and by the X-ray powder diffraction pattern as shown in Figure 20 and in Table 12.

Table 12:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	3.7	23.77	10
2	6.2	14.36	100
3	15.7	5.64	43
4	27.1	3.29	26

In a seventeenth aspect, the present invention is directed to the telmisartan 2-naphthalenesulphonate salt characterized by a melting interval of about 258-264°C and by the X-ray powder diffraction pattern as shown in Figure 21 and in Table 13.

Table 13:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	4.5	19.68	100
2	9.0	9.87	5
3	13.4	6.59	16
4	27.0	3.30	5

In a eighteenth aspect, the present invention is directed to the telmisartan oxalate salt characterized by a melting interval of about 223-225°C and by the X-ray powder diffraction pattern as shown in Figure 22 and in Table 14.

Table 14:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	13.1	6.77	47
2	16.6	5.36	71
3	18.5	4.81	100
4	21.7	4.09	57
5	23.1	3.85	53
6	23.8	3.74	93
7	25.2	3.54	86
8	27.3	3.27	44

In a nineteenth aspect, the present invention is directed to the telmisartan benzenesulfonate salt characterized by a melting interval of about 220-225°C and by the X-ray powder diffraction pattern as shown in Figure 23 and in Table 15.

Table 15:

No.	Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
1	7.3	12.17	56
2	8.5	10.36	12
3	13.4	6.63	81

4	14.5	6.09	100
5	21.2	4.20	18
6	23.4	3.81	36
7	24.4	3.65	26
8	24.9	3.58	26

Another aspect of the present invention are telmisartan salts according to the present invention prepared in high purity in a stoichiometric ratio of 1:1 which means the molar ratio of telmisartan in salt is from about 0.35 to about 0.65, preferably from about 0.40 to about 0.50 and more preferably from about 0.45 to about 0.55

Yet another aspect of the present invention are the telmisartan salts according to the present invention characterized by having water content less than 2%, preferably less than 1%, more preferably less than 0.5%.

A further aspect of the present invention are telmisartan salts according to the present invention characterized by having a different shape than needles as for example telmisartan meglumine salt according to the present invention has a crystal shape in the form of a round shape.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a telmisartan salt according to the present invention in a unit dosage form, alone or in combination with another active ingredient such as hydrochlorothiazide and pharmaceutically acceptable carriers comprising inactive ingredients such as fillers (diluents), binders, disintegrants, glidants, lubricants, and other excipients. Any manufacturing process for the solid oral dosage form

preparation may be applied, including the wet granulation process (with water or any other suitable and pharmaceutically acceptable organic solvent), the dry granulation process, and the direct compression method, or any other method known in the art. Such pharmaceutical compositions may be administered to a patient in any dosage form, such as for example tablet, pill, troche, lozenge, capsule, powder, liquid, suppository, sachet, elixir, solution, syrup, suspension etc. Dosage forms may be adapted for administration to the patient by for example oral, buccal, parenteral, ophthalmic, rectal and transdermal route.

A telmisartan salt according to the present invention can be included in the pharmaceutical composition or it can be formed in-situ during the preparation of the pharmaceutical composition. In the latter case telmisartan is placed in a solvent together with a corresponding basic agent and mixed together. A dissolved salt form of telmisartan is obtained. The telmisartan salt can be used directly either in a spray-drying or in a fluid-bed process.

Surprisingly, it was found that when a telmisartan salt according to the present invention is used in a pharmaceutical composition according to the present invention, no surfactant is needed for the preparation of the final composition of telmisartan.

If telmisartan is prepared by a spray-drying method, either the salt form of telmisartan or telmisartan together with a basic agent and optionally a crystallization retarder is dissolved in an appropriate solvent (water or organic solvent) and spray-dried. The spray-dried granulate is mixed further with other excipients to form the final composition ready for tabletting. In case of fluid-bed granulation,

either a salt form of telmisartan or telmisartan together with a basic agent and optionally a crystallization retarder as for example Povidone, Copovidone is dissolved in an appropriate solvent (water or organic solvent) to form a granulation liquid. Other excipients are placed in the fluid-bed granulating machine and sprayed together with the granulation liquid. When granulation is completed the granulate is dried and optionally mixed with additional excipients like flow control agent and/or lubricant to form the final composition ready for tabletting. The lubricant and flow control agent may be selected from, but not restricted to hydrophobic lubricants like magnesium stearate, calcium stearate, stearic acid and hydrogenated vegetable oil or hydrophilic lubricants like sodium stearyl fumarate and glyceryl.

To prepare final compositions in the form of tablet or capsules, various types of binders and fillers can be used. The binder may be selected from, but not restricted to starch paste, pregelatinized starch, gum acacia, gelatin, alginates, cellulose derivatives like methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone and copovidone etc.; and any mixtures thereof. The filler may be selected from water-soluble or water-insoluble fillers. Examples of such fillers are, but are not restricted to sucrose, dextrose, dextrates, fructose, sorbitol, xylitol, maltodextrin, lactose, mannitol, copovidone, calcium phosphates, calcium sulphates, starch, cellulose and its derivatives like microcrystalline cellulose etc. and mixtures of these. Surprisingly, it was found that similar dissolution profiles can be obtained with both, water-soluble and water-insoluble fillers. The amount of water soluble or water insoluble fillers can be between about 20 to about 95 wt%, preferably between about 50 to 95 wt%,

more preferably between about 70 to about 95wt% and most preferably between about 70 to 80 wt %.

In case that a water-insoluble filler is used, also a disintegrant is needed. The disintegrant may be selected from, but not restricted to traditional products like starch and pregelatinized starch, alginic acid and amberlite resins as well as super disintegrants like sodium starch glycolate, croscarmellose sodium, crospovidone and soy polysaccharide etc.; and mixtures of these.

Finally, the present invention provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist to a patient in need of such treatment.

The invention is further described by the following non-limiting examples.

EXAMPLES:

Preparation of telmisartan

Example 1

The mixture of 1.0 g (2.0 mmol) of 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile, 5 ml of ethylene glycol, 0.1 ml of water and 1.03 g (18.4 mmol) of KOH is heated to 140 -150°C for 21 h. Then the solution is cooled to room temperature and 10 ml of water are added. The mixture is neutralized by the addition of 3M HCl to adjust the pH to about 7. The product telmisartan is filtered, washed and dried (1.02 g, 98 %).

Example 2

The mixture of 1.0 g (2.0 mmol) of 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile, 4 ml of water and 4 ml of conc. HCl is heated at reflux temperature for 136 h. Then the mixture is cooled to room temperature and 1M NaOH is added to adjust the pH to about 5 to 7. The product is filtered, washed and dried. 0.65 g (63%) of telmisartan is isolated.

Example 3

The mixture of 1.0 g (2.0 mmol) of 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile, 4 ml of ethylene glycol, 0.1 ml of water and 1.03 g (18.4 mmol) of KOH is heated to 155 -170°C for 18 h. Then the mixture is cooled to room temperature and 20 ml of water are added. To the mixture H_2SO_4 (1:1) is added to

adjust the pH to about 7. The product is filtered, washed, dried and isolated.

Preparation of telmisartan sulphate from 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile

Example 4

The mixture of 1.0 g (2.0 mmol) of 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile, 5 ml of water and 2 ml of conc. H_2SO_4 is heated at reflux temperature for 46 h. Then the mixture is cooled to room temperature and 5 ml of water are added and stirred at room temperature for 18 h. The product is filtered, washed and dried. 0.90 g (73%) of telmisartan sulphate salt is isolated.

I.) Preparation of telmisartan salts by crystallization

Example 5: Telmisartan *tert*-butylamine salt, polymorph I

1 g (2 mmol) of telmisartan is added to 13 mL of DMF and 0.21 mL (2 mmol) *tert*-butylamine, and the mixture is heated until all telmisartan is dissolved. The solution is cooled to room temperature. The precipitate formed is filtered, washed with water and dried. 0.65 g of telmisartan *tert*-butylamine salt is isolated.

T 264-268 °C
IR: 2629, 1640, 1540, 1389, 1221, 1006, 851, 745, 658
XRD: crystalline, figure 4

Example 6: Telmisartan *tert*-butylamine salt, polymorph II

1 g (2 mmol) of telmisartan is added to 10 mL of isopropanol and 0.3 mL (2.9 mmol) *tert*-butylamine, and the mixture is heated under reflux for 3 h. The solution is cooled to room temperature. The precipitate formed is filtered, washed with water and dried. 1 g of telmisartan *tert*-butylamine salt is isolated.

T 168-175 °C
IR: 2627, 1635, 1558, 1534, 1387, 1225, 1006, 843, 743
XRD: crystalline, figure 5

II.) Preparation of telmisartan acid salts by suspending

Example 7: Telmisartan sulphate salt

1 g (2 mmol) of telmisartan is added to 10 mL of water and 0.2 mL (3.6 mmol) concentrated sulfuric acid, and the suspension is mixed at room temperature for 1 h. The suspension is filtered, washed with water and dried at 45°C in a vacuum drier. 1.16 g of sesquihydrate telmisartan sulphate salt is isolated.

T: 218-227°C
IR: 1696, 1566, 1472, 864, 762, 577
XRD: crystalline, figure 13

Example 8: Telmisartan maleate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.23 g (2 mmol) of maleic acid is added. The suspension is heated under reflux temperature for 3 h and then cooled to room temperature, filtered, washed with water

and dried at 35°C in a vacuum drier. 0.9 g telmisartan maleate is isolated.

T: 265-270°C
IR: 1696, 1566, 1472, 864, 762, 577
XRD: crystalline, figure 17

Example 9: Telmisartan tartrate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.30 g (2 mmol) of tartaric acid is added. The suspension is heated under reflux temperature for 3 h and then cooled to room temperature, filtered, washed with water and dried at 35°C in a vacuum drier. 1.2 g telmisartan tartrate is isolated.

T: 230-235°C
IR: 1697, 1446, 1266, 1130, 758, 740
XRD: crystalline, figure 18

Example 10: Telmisartan citrate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.38 g (2 mmol) of citric acid is added. The suspension is heated under reflux temperature for 3 h and then cooled to room temperature, filtered, washed with water and dried at 35°C in a vacuum drier. 1.17 g telmisartan citrate is isolated.

T: 267-271°C
IR: 1748, 1701, 1466, 1446, 1265, 759, 742
XRD: crystalline, figure 19

Example 11: Telmisartan fumarate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.232 g (2 mmol) of fumaric acid is added. The suspension is heated under reflux temperature for 0.5 h and then cooled to room temperature, filtered, washed with water and dried at 35°C in a vacuum drier. 1.08 g telmisartan fumarate is isolated.

T: 121-130°C
IR: 1693, 1465, 1266, 864, 759, 741
XRD: crystalline, figure 20

Example 12: Telmisartan 2-naphthalenesulphonate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.46 g (2 mmol) of naphthalene-2-sulphonic acid is added. The suspension is heated under reflux temperature for 0.5 h and then cooled to room temperature, filtered, washed with water and dried at 35°C in a vacuum drier. 1.39 g telmisartan 2-naphthalenesulphonate is isolated.

T: 258-264°C
IR: 1697, 1461, 1269, 1264, 1189, 863, 758, 741
XRD: crystalline, figure 21

Example 13: Telmisartan oxalate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.18 g (2 mmol) of oxalic acid is added. The suspension is heated under reflux temperature for 0.5 h and then cooled to room temperature, filtered, washed with water and dried at 35°C in a vacuum drier. 1.14 g telmisartan oxalate is isolated.

T: 223-229°C
IR: 1700, 1472, 1263, 1235, 1130, 830, 763
XRD: crystalline, figure 22

Example 14: Telmisartan benzenesulfonate

1 g (2 mmol) of telmisartan is suspended in 10 mL of methanol and then 0.32 g (2 mmol) of benzenesulfonic acid is added. The suspension is heated under reflux temperature for 0.5 h and then cooled to room temperature, filtered, washed with water and dried at 35°C in a vacuum drier. 0.96 g telmisartan benzenesulfonate is isolated.

T: 220-225°C
IR: 1473, 1265, 1235, 1161, 1154, 1121, 1031, 1015, 751, 611
XRD: crystalline, figure 23

III.) Preparation of telmisartan salts by lyophilization and spray-drying

Example 15: Telmisartan choline salt

1 g (2 mmol) of telmisartan is added to 10 mL of methanol and 0.56 mL (2 mmol) of choline, and the suspension is stirred until all components are dissolved. The solution is lyophilized and 1.20 g of telmisartan choline salt is isolated.

T: 80-110°C
IR: 1583, 1450, 1380, 1280, 1088, 953, 848, 745
XRD: amorphous, figure 2

Example 16: Telmisartan choline salt

1 g (2 mmol) of telmisartan is added to 10 mL of water and 0.56 mL (2 mmol) of choline, and the suspension is stirred until all components are dissolved. The solution is lyophilized and 0.84 g of telmisartan choline salt in the hemihydrate form is isolated.

T: 65-80°C
IR: 1583, 1450, 1381, 1282, 1089, 953, 747
XRD: amorphous, figure 3

Example 17: Telmisartan L-arginine salt

1 g (2 mmol) of telmisartan is added to 10 mL of methanol and 0.35 mL (2 mmol) of L-arginine, and the suspension is heated until all components are dissolved. The solution is lyophilized and 1.07 g of telmisartan L-arginine salt in the sesquihydrate form is isolated.

T: 165-173°C
IR: 1635, 1546, 1383, 845, 744, 657
XRD: amorphous, figure 14

Example 18: Telmisartan ammonium salt

1 g (2 mmol) of telmisartan is added to 5 mL of methanol and 0.6 mL of 25% (w/w) NH_3, and the suspension is stirred until telmisartan is dissolved. 10 mL of water are added and the solution is lyophilized. 1.0 g of telmisartan ammonium salt is isolated.

T: 150-158°C
IR: 1700, 1598, 1457, 1405, 1128, 1089, 1006, 744

XRD: amorphous, figure 1

IV.) Evaporation of the solvent and trituration of the residue

Example 19: Telmisartan meglumine salt

1 g (2mmol) of telmisartan is added to 10 mL of methanol and 0.39 g (2 mmol) of meglumine, and the suspension is heated until all components are dissolved. The solution is cooled to room temperature and volatile components are evaporated. 10 mL of isopropyl acetate are added and the mixture is stirred at room temperature. The precipitate is filtered and dried for 1 h in a vacuum drier at 40 °C. 1.2 g of the product is isolated.

Elemental analysis for $C_{40}H_{47}N_5O_7$:
C: 67.43 % (67.68 %), H: 6.88 % (6.67 %), N: 9.82 % (9.87 %).
Molar ratio of telmisartan: 0.49
Water content: 0.14%

T: 198-205 °C
IR: 1603, 1557, 1456, 1384, 1079, 1031, 751
XRD: crystalline, figure 6
Crystal shape: round shape, figure 7

Example 20: Telmisartan meglumine salt

1 g (2 mmol) of telmisartan is added to 10 ml of methanol and 0.39 g (2 mmol) of meglumine, and the suspension is heated until all components are dissolved. The solution is cooled to room temperature and volatile components are evaporated to solid residue. 1.33 g of the product is isolated.

T: 86-91 °C

IR: 1560, 1557, 1457, 1388, 1283, 1079, 1033, 745

XRD: amorphous, figure 8

Example 21: Telmisartan choline salt

1 g (2 mmol) of telmisartan is added to 10 mL of methanol and 0.56 g (2 mmol) of choline, and the suspension is stirred until all components are dissolved. Volatile components are evaporated, and 10 mL of *tert*-butyl methyl ether are added, and the volatile components are evaporated again untill a solid product is obtained, which is further dried for 2 h in a vacuum drier, at a temperature of about 45°C. 1.26 g of the product is isolated.

T: 65-85 °C

IR: 1583, 1454, 1382, 1281, 1085, 952, 754

XRD: amorphous, figure 3

Example 22: Telmisartan L-arginine salt

1 g (2 mmol) of telmisartan is added to 10 mL of methanol and 0.35 g (2 mmol) of L-arginine, and the suspension is heated until all components are dissolved. Volatile components are evaporated, and 1 mL of isopropanol and 10 mL of isopropyl acetate are added. The precipitate is filtered and dried for 2 h in a vacuum drier at a temperature of about 45°C. 1.3 g of the product in form of a methanol solvate is isolated.

T: 162-172 °C

IR: 1636, 1550, 1457, 1387, 846, 746

XRD: amorphous, figure 14

Example 23: Telmisartan ethanolamine salt

1 g (2 mmol) of telmisartan is added to 8 mL of DMF and 0.12 mL (2 mmol) of ethanolamine, and the suspension is heated until all components are dissolved. Volatile components are evaporated and 5 mL of diethyl ether are added. The precipitate is filtered and dried for 2 h in a vacuum drier at a temperature of about 45°C. 0.72 g of the product is isolated.

T: 265-268 °C
IR: 1669, 1599, 1382, 1267, 1129, 863, 740
XRD: amorphous, figure 9

Example 24: Telmisartan piperazine salt

1 g (2 mmol) of telmisartan is added to 8 mL of DMF and 0.168 g (2 mmol) of piperazine, and the suspension is heated until all components are dissolved. Volatile components are evaporated untill a solid product is obtained which is further dried for 2 h in a vacuum drier at a temperature of about 45°C. 1.1 g of the product in the monohydrate form is isolated.

T: 155-160 °C
IR: 1664, 1457, 1385, 1289, 762, 656
XRD: amorphous, figure 10

Example 25: Telmisartan diethylamine salt

1 g (2 mmol) of telmisartan is added to 10 mL of methanol and 0.21 g (2 mmol) of diethylamine, and the suspension is stirred at room temperature until all components are

dissolved. Volatile components are evaporated and 5 mL of isopropyl acetate is added. The precipitate is filtered and dried for 3 h in a vacuum drier at a temperature of about 45°C. 0.83 g of the product is isolated.

T: 120-135 °C
IR: 1560, 1455, 1383, 1282, 1247, 842, 744, 660
XRD: crystalline, figure 11

Example 26: Telmisartan tris-(hydroxymethyl)amine salt

1 g (2 mmol) of telmisartan is added to 10 mL of methanol and 0.23 g (2 mmol) of tris-(hydroxymethyl)amine, and the suspension is heated until all components are dissolved. Volatile components are evaporated and 5 mL of *tert*-butyl methyl ether is added. The precipitate is filtered and dried for 2 h in a vacuum drier at a temperature of about 45°C. 1.19 g of the product is isolated.

T: 189-198 °C
IR: 1550, 1453, 1395, 1056, 863, 747, 670
XRD: crystalline, figure 12

Example 27: Telmisartan potassium salt, polymorph A

1 g (2mmol) of telmisartan is added to 10 mL of methanol and 1ml of 2M KOH, and the suspension is heated until all components are dissolved. The solution is cooled, volatile components are evaporated, and 1 mL of isopropanol and 10 ml of isopropyl acetate are added. The precipitate is filtered and dried for 1.5 h in a vacuum drier, at a temperature of about 45°C. 0.84 g of the product in the sesquihydrate form is isolated.

T: 182-194 °C

IR: 1598, 1581, 1448, 1382, 1006, 741

XRD: crystalline, figure 15

Example 28: Telmisartan potassium salt, polymorph B

1 g (2mmol) of telmisartan is added to 10 mL of methanol and 1ml of 2M KOH, and the suspension is heated until all components are dissolved. Volatile components are evaporated, and 10 mL of acetone is added. The mixture is stirred for 1h at room temperature and the precipitate is filtered and dried for 1 h in a vacuum drier, at a temperature of about 40°C. 1 g of the product as monohydrate is isolated.

T: 205-225 °C

IR: 1558, 1458, 1385, 1220, 1006, 760, 741

XRD: crystalline, figure 16

V.) Pharmaceutical formulations including telmisartan salts according to the present invention

Table 16

Formulation	**A1**	**B1**	**C1**	**D1**	**E1**	**F1**	**G1**
Telmisartan potassium salt	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg
Meglumine (1) or KOH (2) or NaOH (3)	/	/	/	10 mg (1) 4 mg (2) 3 mg (3)	10 mg (1) 4 mg (2) 3 mg (3)	10 mg (1) 4 mg (2) 3 mg (3)	10 mg (1) 4 mg (2) 3 mg (3)
Poloxamer 188	3 mg	/	/	3 mg	/	/	/

Tween 80	/	3 mg	/	/	3 mg	/	/
Sodium laurylsulphate	/	/	3 mg	/	/	3 mg	/
Lactose	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg
Microcrystalline cellulose	139 mg	139 mg	139 mg	129 mg (1) 135 mg (2) 136 mg (3)	129 mg (1) 135 mg (2) 136 mg (3)	129 mg (1) 135 mg (2) 136 mg (3)	132 mg (1) 138 mg (2) 139 mg (3)
Colloidal silica anhydrous	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
Total	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg

In formulations D1-G1, the amount of microcrystalline cellulose varies, depending on the base used in the formulation.

Table 17

Formulation	**A2**	**B2**	**C2**	**D2**	**E2**	**F2**	**G2**
Telmisartan tributylamine salt	45 mg	45 mg	45 mg	45 mg	45 mg	45 mg	45 mg
Meglumine (1) or	/	/	/	10 mg	10 mg	10 mg	10 mg

KOH (2) or NaOH (3)				(1) 4 mg (2) 3 mg (3)	(1) 4 mg (2) 3 mg (3)	(1) 4 mg (2) 3 mg (3)	(1) 4 mg (2) 3 mg (3)
Poloxamer 188	3 mg	/	/	3 mg	/	/	/
Tween 80	/	3 mg	/	/	3 mg	/	/
Sodium laurylsulphate	/	/	3 mg	/	/	3 mg	/
Lactose	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg
Microcrystalline cellulose	137 mg	137 mg	137 mg	127 mg (1) 133 mg (2) 134 mg (3)	127 mg (1) 133 mg (2) 134 mg (3)	127 mg (1) 133 mg (2) 134 mg (3)	130 mg (1) 136 mg (2) 137 mg (3)
Colloidal silica anhydrous	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
Total	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg

In formulations D2-G2, the amount of microcrystalline cellulose varies, depending on the base used in the formulation.

Table 18

Formulation	A3	B3	C3	D3	E3	F3	G3
Telmisartan meglumine salt	54 mg	54 mg	54 mg	54 mg	54 mg	54 mg	54 mg
Meglumine (1) or KOH (2) or NaOH (3)	/	/	/	10 mg (1) 4 mg (2) 3 mg (3)	10 mg (1) 4 mg (2) 3 mg (3)	10 mg (1) 4 mg (2) 3 mg (3)	10 mg (1) 4 mg (2) 3 mg (3)
Poloxamer 188	3 mg	/	/	3 mg	/	/	/
Tween 80	/	3 mg	/	/	3 mg	/	/
Sodium laurylsulphate	/	/	3 mg	/	/	3 mg	/
Lactose	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg	43 mg
Microcrystalline cellulose	128 mg	128 mg	128 mg	118 mg (1) 124 mg (2) 125 mg (3)	118 mg (1) 124 mg (2) 125 mg (3)	118 mg (1) 124 mg (2) 125 mg (3)	121 mg (1) 127 mg (2) 128 mg (3)
Colloidal silica anhydrous	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
Total	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg

In formulations D3-G3, the amount of microcrystalline cellulose varies, depending on the base used in the formulation.

Table 19

	A4	*B4*	*C4*	*D4*	*E4*
Telmisartan meglumine	55.2		55.2		
Telmisartan		40		40	40
Meglumine		15.2		15.2	15.2
Povidone	12	12	12	12	12
Sorbitol			170.4	170.4	295.2
Avicel - MCC	163.2	163.2			
Ac-Di-Sol	7.2	7.2			3.8
Mg stearate	2.4	2.4	2.4	2.4	3.8

The above mentioned compositions containing telmisartan can be prepared by various methods. Three of the appropriate methods are lyophilization, spray-drying and fluid-bed granulation. If telmisartan is prepared by the spray-drying method, telmisartan together with a basic agent and optionally a crystallization retarder is dissolved in an appropriate solvent (water or organic solvent) and spray-dried. The spray-dried granulate is mixed further with other excipients to form the final composition ready for tabletting. In case of fluid-bed granulation, telmisartan together with a basic agent and optionally a crystallization retarder is dissolved in an appropriate solvent (water or organic solvent) to form a granulation liquid. Other excipients are placed in the fluid-bed granulating machine and sprayed together with the granulation liquid. When granulation is completed the granulate is dried and optionally mixed with additional excipients like a flow

control agent and/or a lubricant to form the final composition ready for tabletting.

CLAIMS

1. A telmisartan ammonium salt or hydrate or solvate thereof.

2. The telmisartan ammonium salt or hydrate or solvate according to claim 1 characterized that the telmisartan ammonium is in amorphous form.

3. A telmisartan choline salt or hydrate or solvate thereof.

4. The telmisartan choline salt or hydrate or solvate according to claim 3 charcaterised that the telmisartan choline is in amorphous form.

5. A telmisartan *tert*-butylamine salt or hydrate or solvate thereof.

6. A polymorphic form I of telmisartan *tert*-butylamine salt or hydrate or solvate thereof according to claim 5 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 6.6, 13.2, 14.1, 17.0, 19.5 ± 0.2 degrees 2-theta.

7. A polymorphic form II of telmisartan *tert*-butylamine salt or hydrate or solvate thereof according to claim 5 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 4.5, 13.3, 13.7, 19.1, 21.1 ± 0.2 degrees 2-theta.

8. A telmisartan meglumine salt or hydrate or solvate thereof.

9. A crystalline form of telmisartan meglumine salt or hydrate or solvate thereof according to claim 8 having an X-

ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 6.9, 15.5, 17.9, 22.1, 23.4 ± 0.2 degrees 2-theta.

10. The telmisartan meglumine salt or hydrate or solvate according to claim 8 characterized in that the telmisartan meglumine is in amorphous form.

11. A telmisartan ethanolamine salt or hydrate or solvate thereof.

12. The telmisartan ethanolamine salt or hydrate or solvate according to claim 11 characterized in that the telmisartan ethanolamine is in amorphous form.

13. A telmisartan piperazine salt or hydrate or solvate thereof.

14. The telmisartan piperazine salt or hydrate or solvate according to claim 13 characterized that the telmisartan piperazine is in amorphous form.

15. A telmisartan diethylamine salt or hydrate or solvate thereof.

16. A crystalline form of telmisartan diethylamine salt or hydrate or solvate thereof according to claim 15 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 6.0, 7.0, 11.5, 12.1, 13.9 ± 0.2 degrees 2-theta.

17. A telmisartan tris-(hydroxymethyl)amine salt or hydrate or solvate thereof.

18. A crystalline form of telmisartan tris-(hydroxymethyl)amine salt or hydrate or solvate thereof according to claim 17 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 14.0, 14.3, 15.6, 20.2, 20.5, 24.1 ± 0.2 degrees 2-theta.

19. A telmisartan sulphate salt or hydrate or solvate thereof.

20. A crystalline form of telmisartan sulphate salt or hydrate or solvate thereof according to claim 19 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 12.8, 13.6, 16.5, 17.8, 21.4 ± 0.2 degrees 2-theta.

21. A telmisartan L-arginine salt or hydrate or solvate thereof.

22. The telmisartan L-arginine salt or hydrate or solvate according to claim 21 characterized in that the telmisartan L-arginine is in amorphous form.

23. A crystalline form A of telmisartan potassium salt or hydrate or solvate thereof having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 5.8, 11.6, 13.6, 13.7, 24.3 ± 0.2 degrees 2-theta.

24. A crystalline form B of telmisartan potassium salt or hydrate or solvate thereof having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 5.4, 5.9, 10.4, 11.6, 17.6 ± 0.2 degrees 2-theta.

25. A telmisartan maleate salt or hydrate or solvate thereof.

26. A crystalline form of telmisartan maleate salt or hydrate or solvate thereof according to claim 25 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 11.6, 12.6, 16.1, 17.3, 20.7, 22.8 ± 0.2 degrees 2-theta.

27. A telmisartan tartrate salt or hydrate or solvate thereof.

28. A crystalline form of telmisartan tatrate salt or hydrate or solvate thereof according to claim 27 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 6.5, 8.1, 9.9, 13.0, 16.0, 20.0, 21.9 ± 0.2 degrees 2-theta.

29. A telmisartan citrate salt or hydrate or solvate thereof.

30. A crystalline form of telmisartan citrate salt or hydrate or solvate thereof according to claim 29 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 6.1, 7.9, 11.9, 14.2, 16.2, 22.1 ± 0.2 degrees 2-theta.

31. A telmisartan fumarate salt or hydrate or solvate thereof.

32. A crystalline form of telmisartan fumarate salt or hydrate or solvate thereof according to claim 31 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 3.7, 6.2, 15.7, 27.1 ± 0.2 degrees 2-theta.

33. A telmisartan 2-naphthalenesulphonate salt or hydrate or solvate thereof.

34. A crystalline form of telmisartan 2-naphthalenesulphonate salt or hydrate or solvate thereof according to claim 33 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 4.5, 9.0, 13.4, 27.0 ± 0.2 degrees 2-theta.

35. A telmisartan oxalate salt or hydrate or solvate thereof.

36. A crystalline form of telmisartan oxalate salt or hydrate or solvate thereof according to claim 35 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 13.1, 16.6, 18.5, 21.7, 23.1, 23.8, 25.2, 27.3 ± 0.2 degrees 2-theta.

37. A telmisartan benzenesulfonate salt or hydrate or solvate thereof.

38. A crystalline form of telmisartan benzenesulfonate salt or hydrate or solvate thereof according to claim 37 having an X-ray diffraction pattern containing the following 2-theta peaks measured using CuKα radiation: 7.3, 8.5, 13.4, 14.5, 21.2, 23.4, 24.4, 24.9 ± 0.2 degrees 2-theta.

39. Process for the preparation of telmisartan salts comprising the steps:

i.) dissolving a mixture of telmisartan or telmisartan salt with an organic or inorganic base in a polar solvent at a temperature ranging from room temperature to reflux temperature of the solvent applied,

ii.) optionally applying active charcoal in order to purify the active ingredient or the mixture containing the active ingredient and an organic or inorganic base, and hot filtration,

iii.) cooling the solution to a temperature between -10 and 30°C, preferably to room temperature,

iv.) filtering the precipitate and drying the product at a temperature between 10°C and 60°C, preferably between 40 °C and 50°C.

40. Process for the preparation of of telmisartan salts according to claim 39, characterized in that the polar solvent in which telmisartan or telmisartan salt with an organic or inorganic base is dissolved, is DMF, DMA, DMSO, alcohols (such as for example methanol, ethanol, isopropanol), acetone, acetonitrile or water, or any mixtures thereof.

41. Process for the preparation of telmisartan salts comprising the steps:

i.) suspending a mixture of a telmisartan salt, or a mixture of telmisartan or a telmisartan salt with an organic or inorganic acid, in a polar solvent at a temperature ranging from room temperature to the reflux temperature of the solvent,

ii.) optionally cooling the suspension to a temperature between about -10 and about 30°C, preferably to room temperature,

iii) filtering the suspension and drying the product at a temperature between about 10°C and about 60°C, preferably between about 40 °C and about 50°C.

42. Process for the preparation of of telmisartan salts according to claim 41, characterized in that the polar solvent in which telmisartan or telmisartan salt with an organic or inorganic base is dissolved, is DMF, DMA, DMSO, alcohols (such as for example methanol, ethanol, isopropanol), acetone, acetonitrile or water, or any mixtures thereof.

43. Process for the preparation of telmisartan salts comprising the steps:

i) dissolving a telmisartan salt, or a mixture of telmisartan or telmisartan salt with an organic or inorganic base in a polar solvent, at a temperature ranging from room temperature to reflux temperature of the solvent

ii) optionally applying active charcoal in order to purify the active ingredient or the mixture containing the active ingredient and an organic or inorganic base, and hot filtration,

iii) lyophilizing or spray-drying the solution.

44. Process for the preparation of of telmisartan salts according to claim 43, characterized in that the polar solvent in which telmisartan or telmisartan salt with an organic or inorganic base is dissolved, is DMF, DMA, DMSO, alcohols (such as for example methanol, ethanol, isopropanol), acetone, acetonitrile or water, or mixtures thereof.

45. Process for the preparation of of telmisartan salts according to claim 43, characterized in that the solution is spray-dried at a temperature between about 20°C and about 100 °C.

46. Process for the preparation of telmisartan salts comprising the steps:

i.) dissolving a mixture of telmisartan or telmisartan salt with an organic or inorganic base in a polar solvent at a temperature ranging from room temperature to reflux temperature of the solvent applied,

ii.) optionally applying active charcoal in order to purify the active ingredient or the mixture containing the active ingredient and an organic or inorganic base, and hot filtration,

iii.) cooling the solution to a temperature between about -10 and about 30°C, preferably to room temperature,

iv.) evaporating the solvent, preferably at a temperature between about 20 and about 100°C, under reduced pressure,

v.) suspending the residue in an organic solvent and filtering the residue and drying the product at a temperature between about 10°C and about 60°C, preferably between about 40 °C and about 50°C.

47. Process for the preparation of of telmisartan salts according to claim 46, characterized in that the polar solvent in which telmisartan or telmisartan salt with an organic or inorganic base is dissolved, is DMF, DMA, DMSO, alcohols (such as for example methanol, ethanol, isopropanol), acetone, acetonitrile or water, or mixtures thereof.

48. Process for the preparation of of telmisartan salts according to claim 46, characterized in that the organic

solvent from step v.) is an alcohol selected from the group consisting of methanol, ethanol and isopropanol, ester selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, propyl acetate butyl acetate, isobutyl acetate and *tert*-butyl acetate, ether selected from the group consisting of diethyl ether, diisopropyl ether and *tert*-butyl methyl ether, acetone or any mixture thereof.

49. Process for the preparation of telmisartan from 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-2,5'-dibenzo[d]imidazol-3'-yl)methyl)biphenyl-2-carbonitrile comprising the steps of:
i) hydrolysis of the cyano group
ii) isolation of telmisartan, optionally by addition of water
iii) pH adjustment to pH about 5 to about 7.

50. The process for the preparation of telmisartan according to claim 49 characterized in that the hydrolysis is carried out by the addition of a strong acid or by the addition of a strong base.

51. Telmisartan salts according to claims 1 to 38 characterized by being prepared in high purity in a stoichiometric ratio of 1:1 and having the molar ratio of telmisartan in salt from about 0.35 to about 0.65, preferably from about 0.40 to about 0.50 and more preferably from about 0.45 to about 0.55

52. Telmisartan salts according to claims 1 to 38 characterized by having a water content less than 2%, preferably less than 1%, more preferably less than 0.5%.

53. Telmisartan salts according to claims 1 to 38 characterized by having a different shape than needles.

54. Telmisartan meglumine salt according to claim 53 characterized by having a crystal shape in the form of round shape.

55. A pharmaceutical composition containing a telmisartan salt according to claims 1 to 38 or a hydrate or solvate thereof and one or more water soluble or water insoluble filler in an amount of about 20 to about 95 wt% of the final composition with the proviso that said pharmaceutical composition does not contain a surfactant.

56. The pharmaceutical composition according to claim 55 characterized in that one or more water soluble or water insoluble filler is in amount of about 50 to about 95 wt%, preferably about 70 to about 95 wt%, the most preferably about 70 to about 80 wt%.

57. The pharmaceutical composition according to claims 55 and 56 characterized in that the water soluble fillers are selected from the group consisting of sucrose, dextrose, dextrates, fructose, sorbitol, xylitol, maltodextrin or any mixture thereof.

58. The pharmaceutical composition according to claim 55 characterized in that the water-insoluble fillers are selected from the group consiting of lactose, mannitol, copovidone, calcium phosphates, calcium sulphates, starch, cellulose and its derivatives like microcrystalline cellulose and any mixture thereof.

59. The pharmaceutical composition according to claim 55 further comprising binders, disintegrants, lubricants, glidants, crystallisation retarders.

60. Use of telmisatan salts according to claims 1 to 38 as a medicament.

Figure 1

Amorphous telmisartan ammonium salt

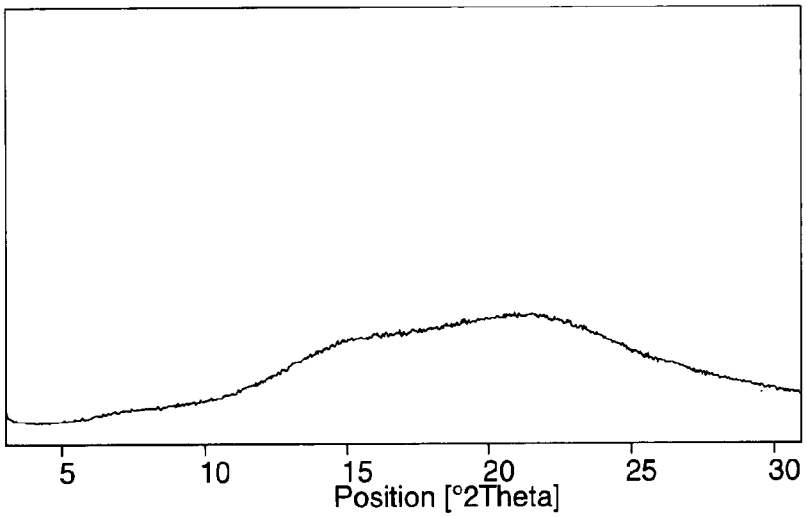

Figure 2

Amorphous telmisartan choline salt

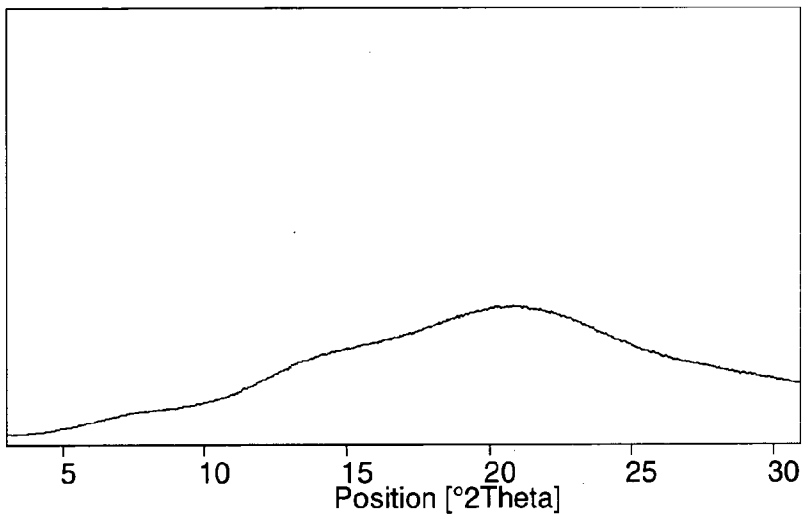

Figure 3

Amorphous telmisartan choline salt, hydrated forms

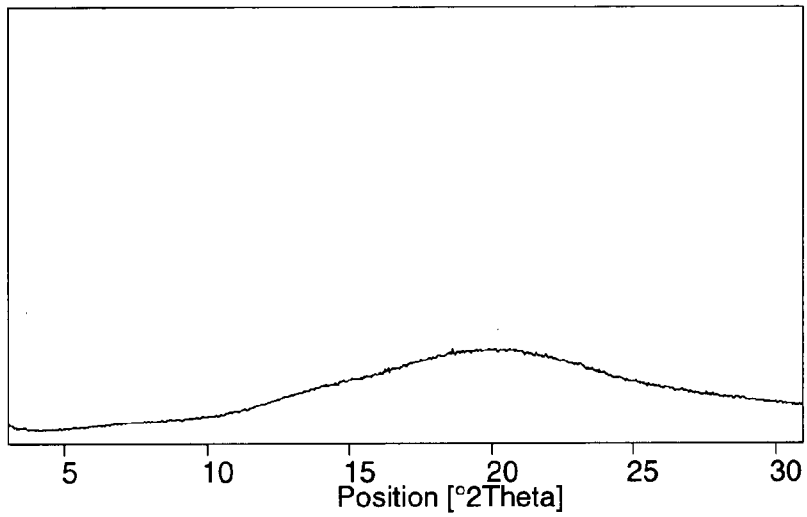

Figure 4

Telmisartan *tert*-butylamine salt, polymorphic form I

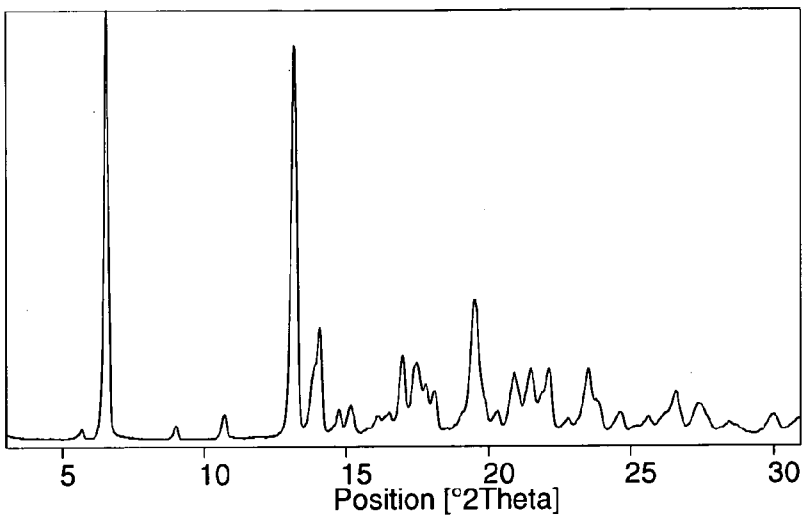

Figure 5

Telmisartan *tert*-butylamine salt, polymorphic form II

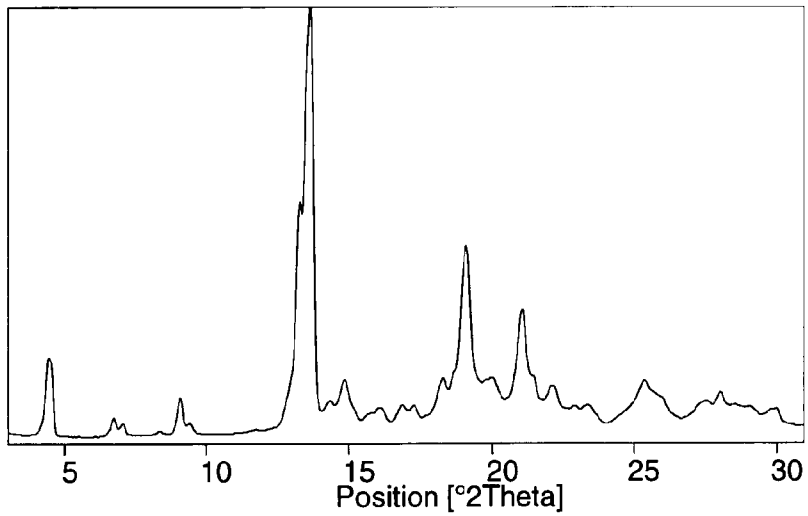

Figure 6

Telmisartan meglumine salt

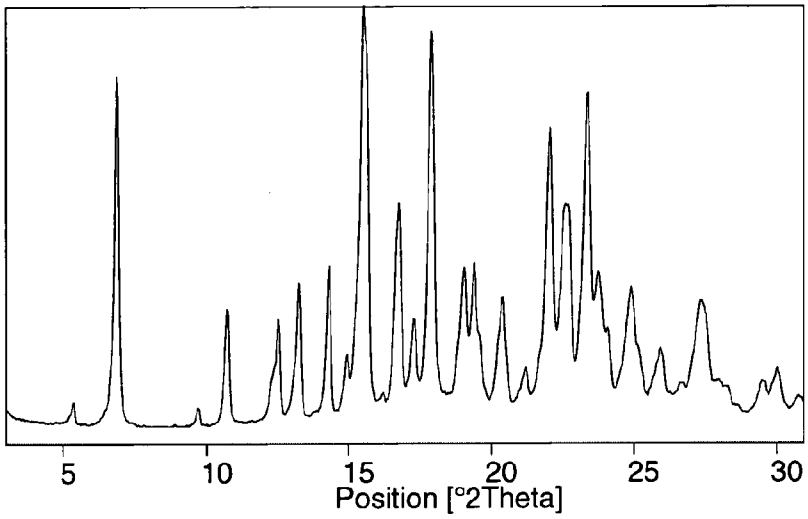

Figure 7

Telmisartan meglumine salt particles as seen through microscope

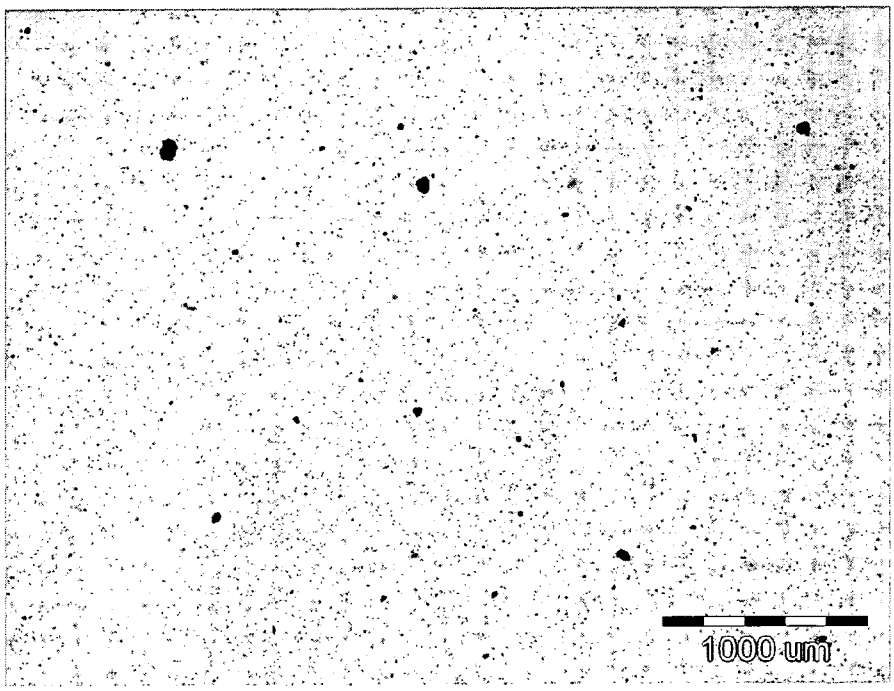

Figure 8

Amorphous telmisartan meglumine salt

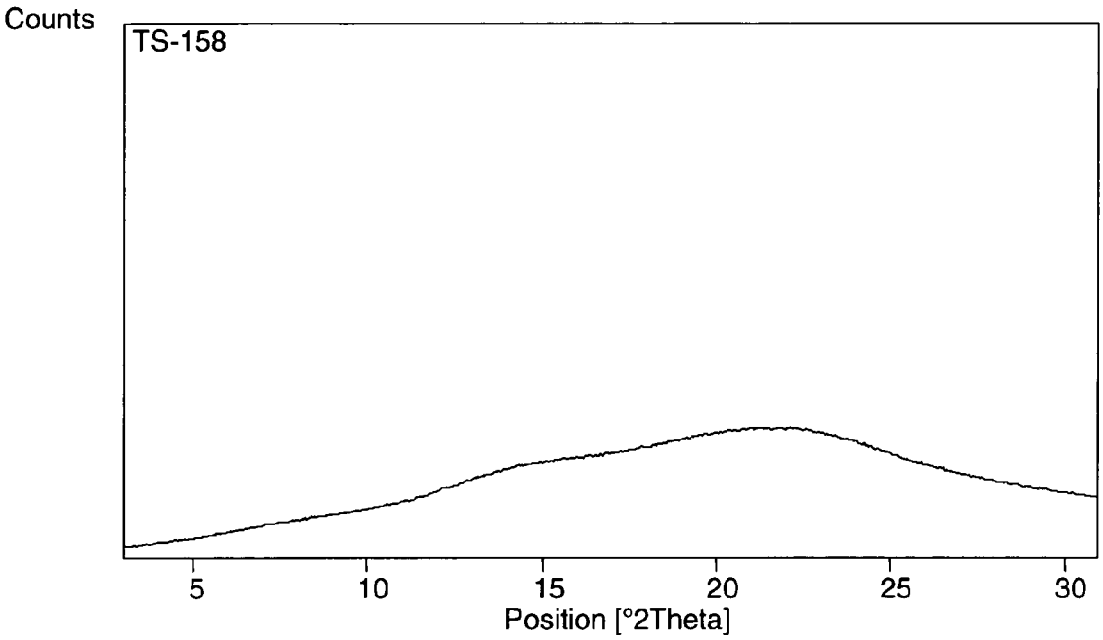

Figure 9

Amorphous telmisartan ethanolamine salt

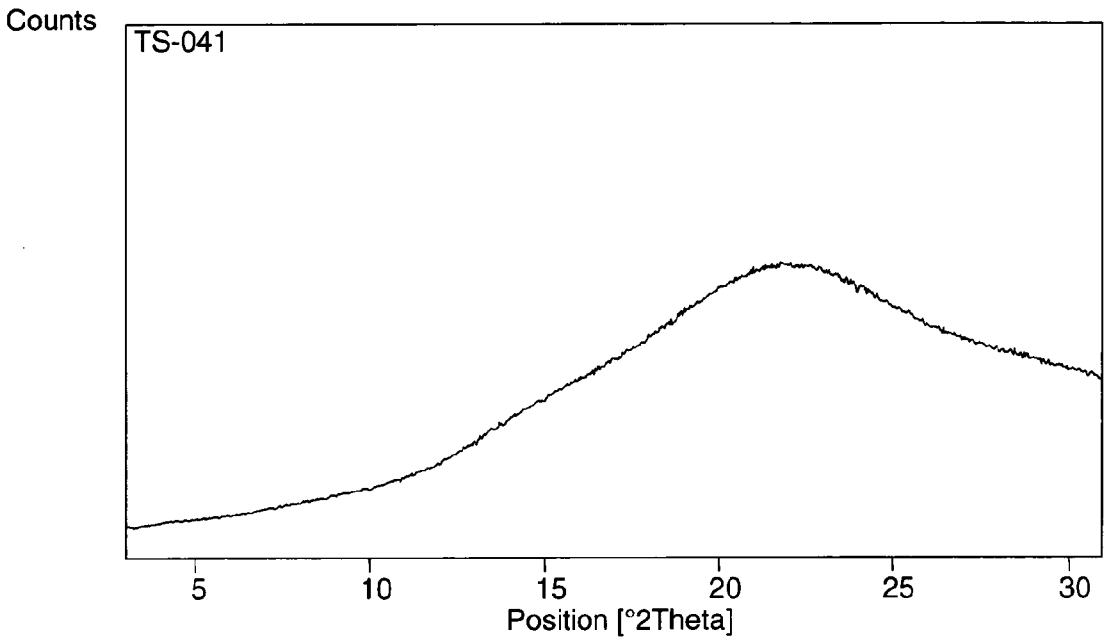

Figure 10

Amorphous telmisartan piperazine salt

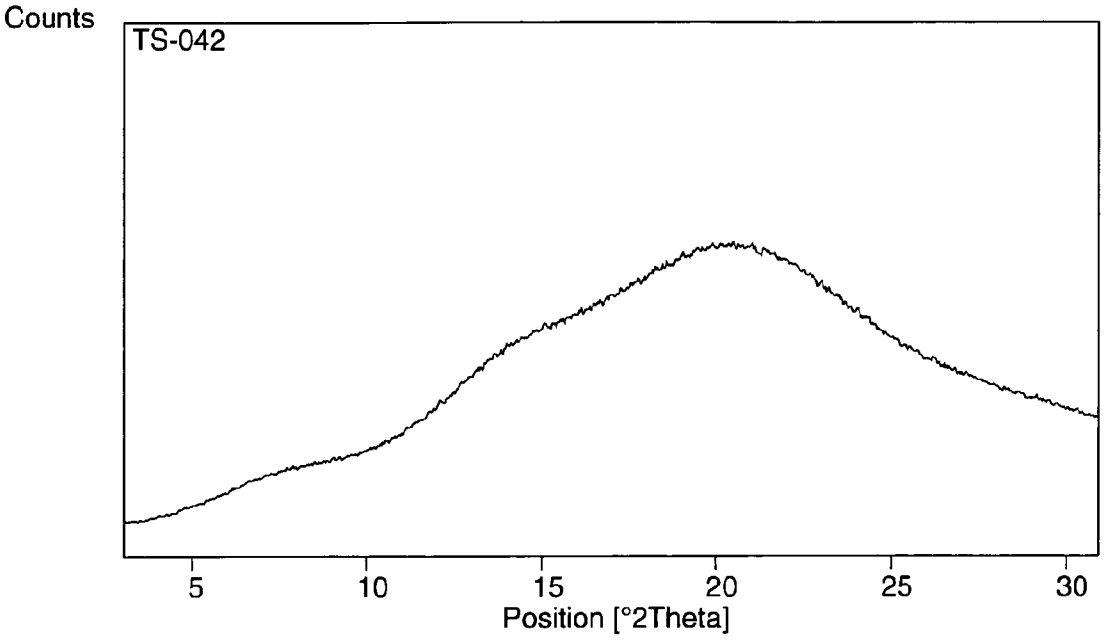

Figure 11

Telmisartan diethylamine salt

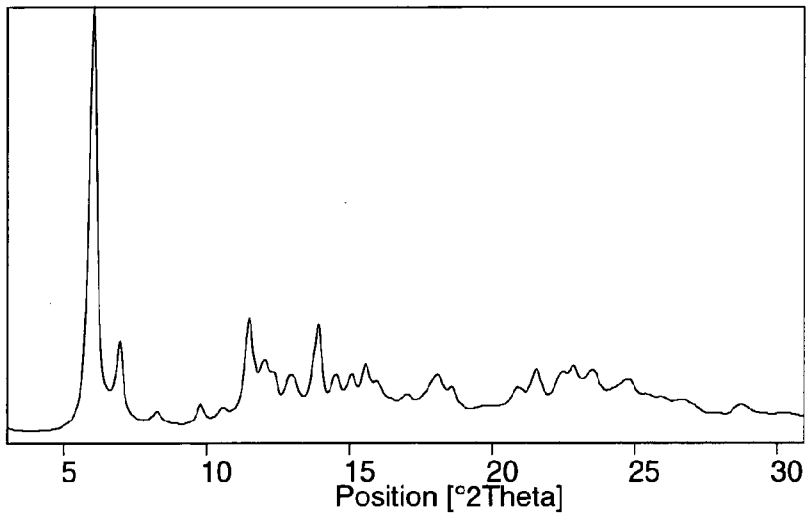

Figure 12

Telmisartan tris-(hydroxymethyl)amine salt

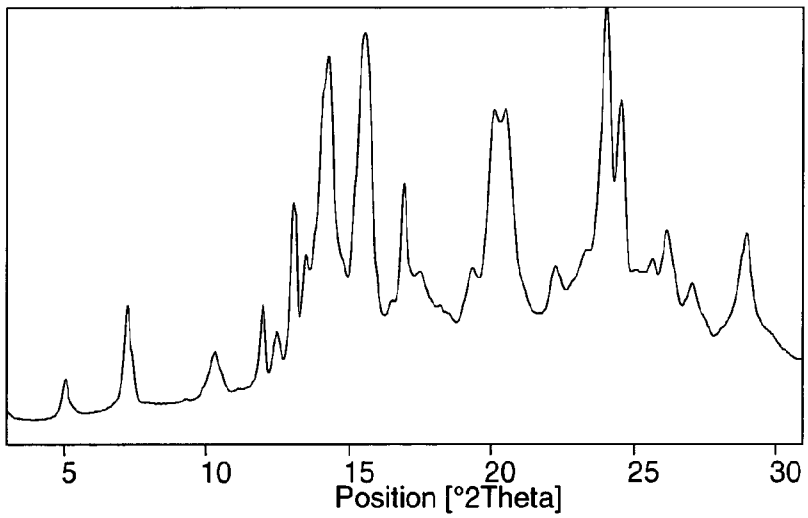

Figure 13

Telmisartan sulphate salt

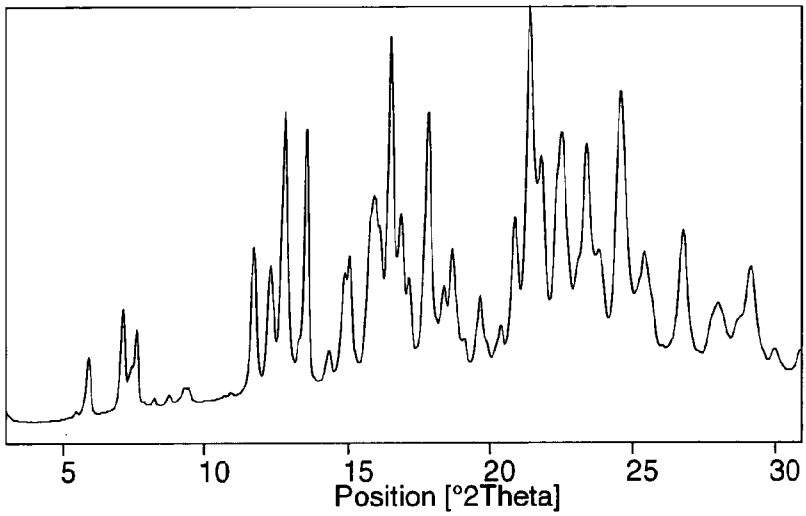

Figure 14

Amorphous telmisartan L-arginine salt

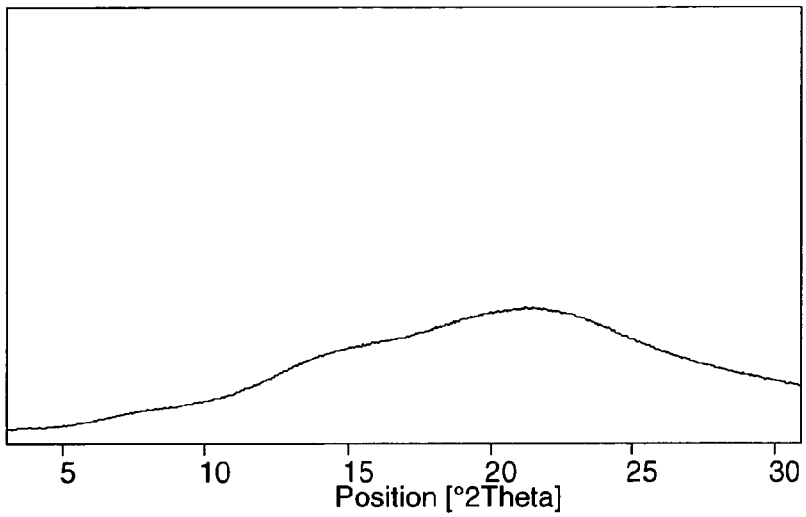

Figure 15

Telmisartan potassium salt, polymorph A

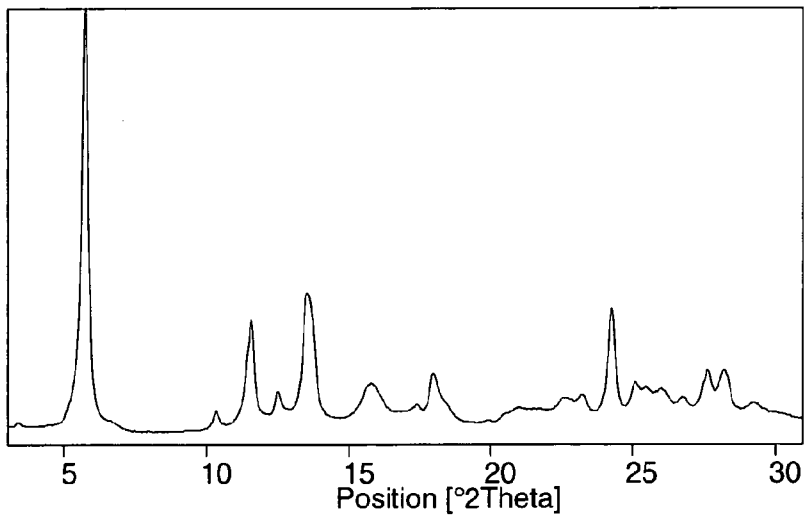

Figure 16

Telmisartan potassium salt, polymorph B

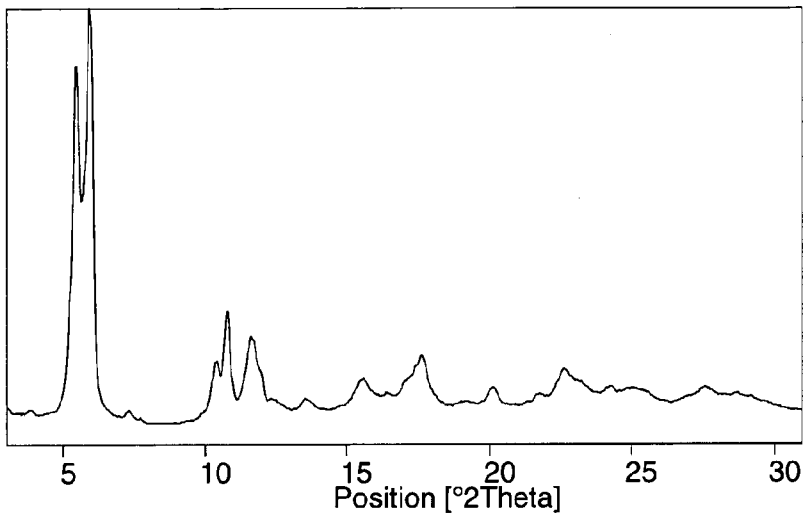

Figure 17

Telmisartan maleate

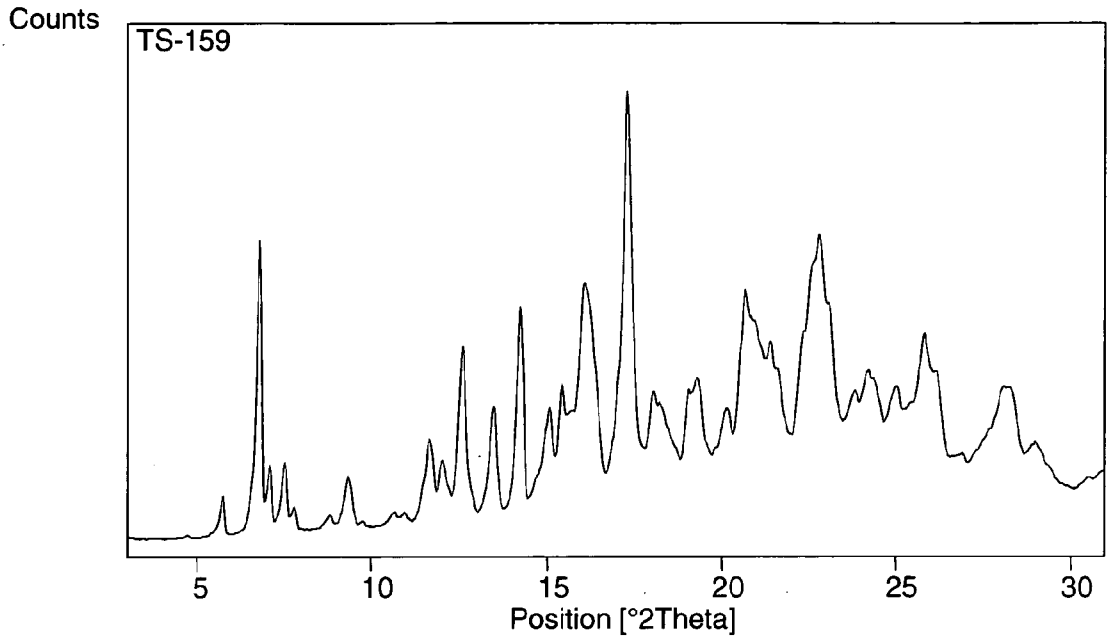

Figure 18

Telmisartan tartrate

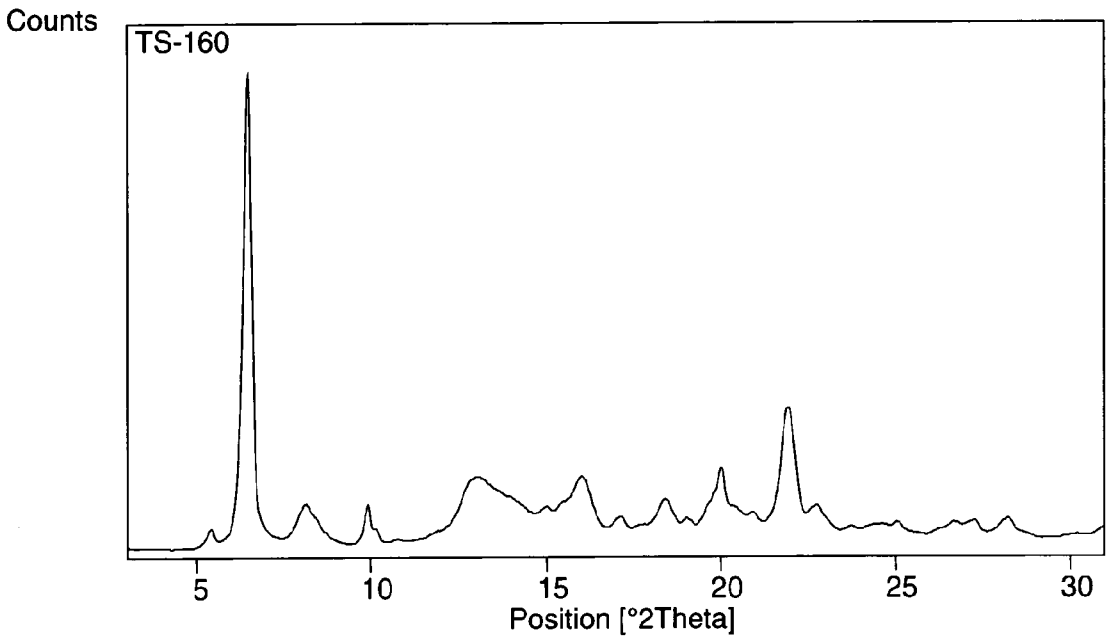

Figure 19

Telmisartan citrate

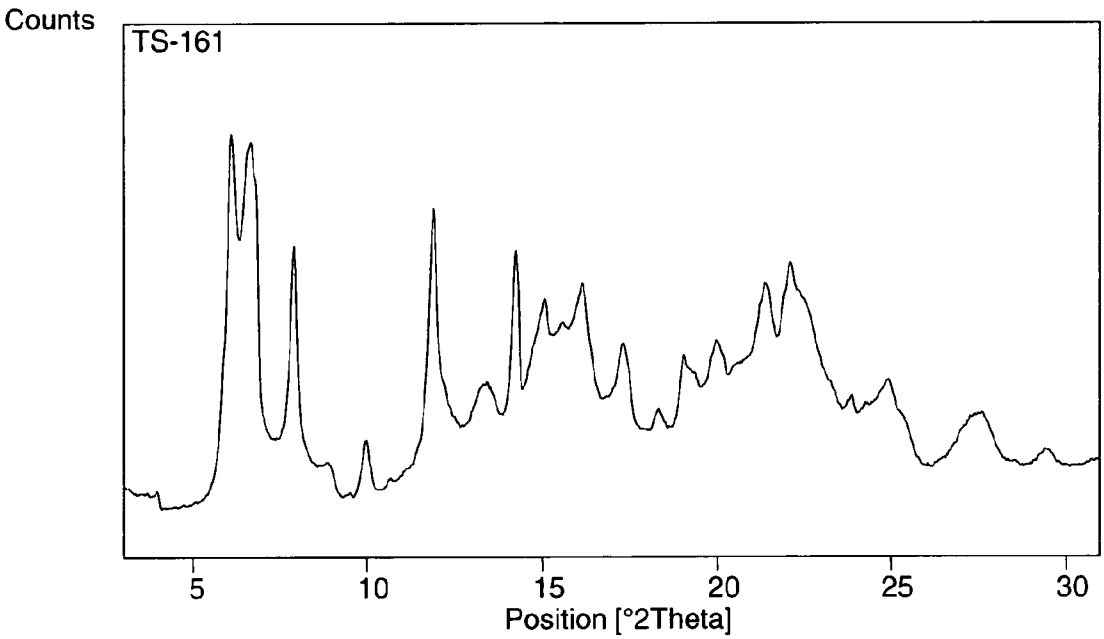

Figure 20

Telmisartan fumarate

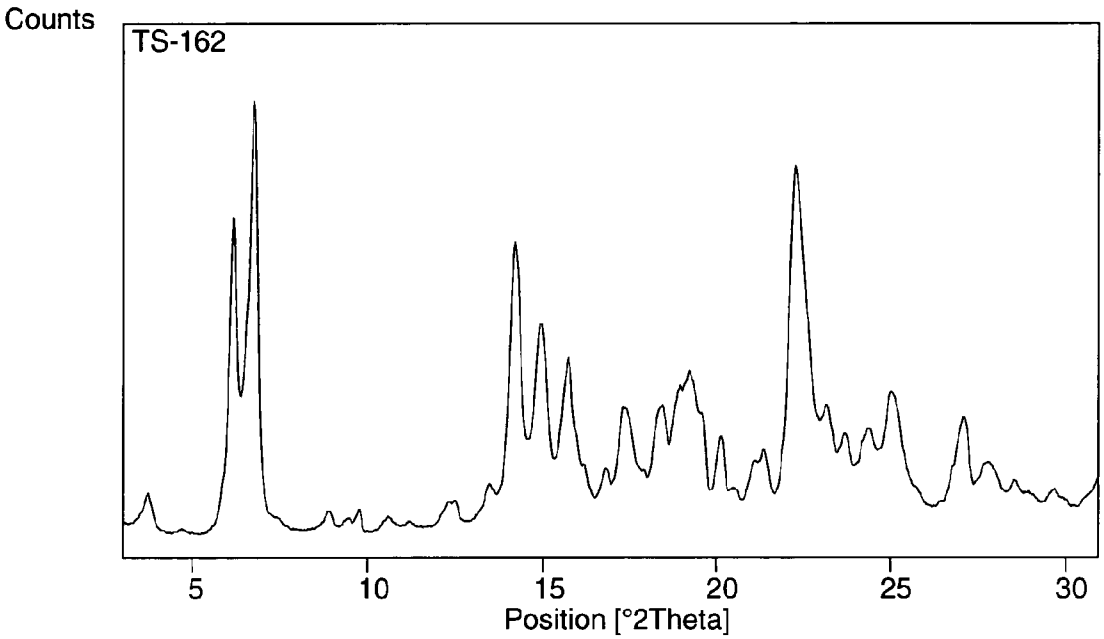

Figure 21

Telmisartan 2-naphthalenesulphonate

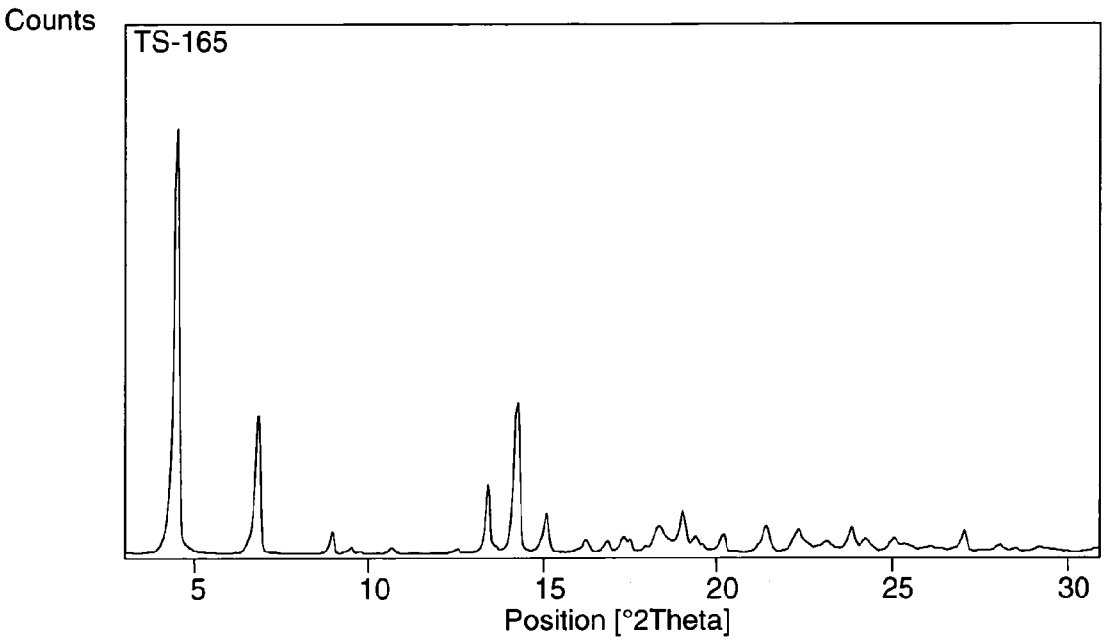

Figure 22

Telmisartan oxalate

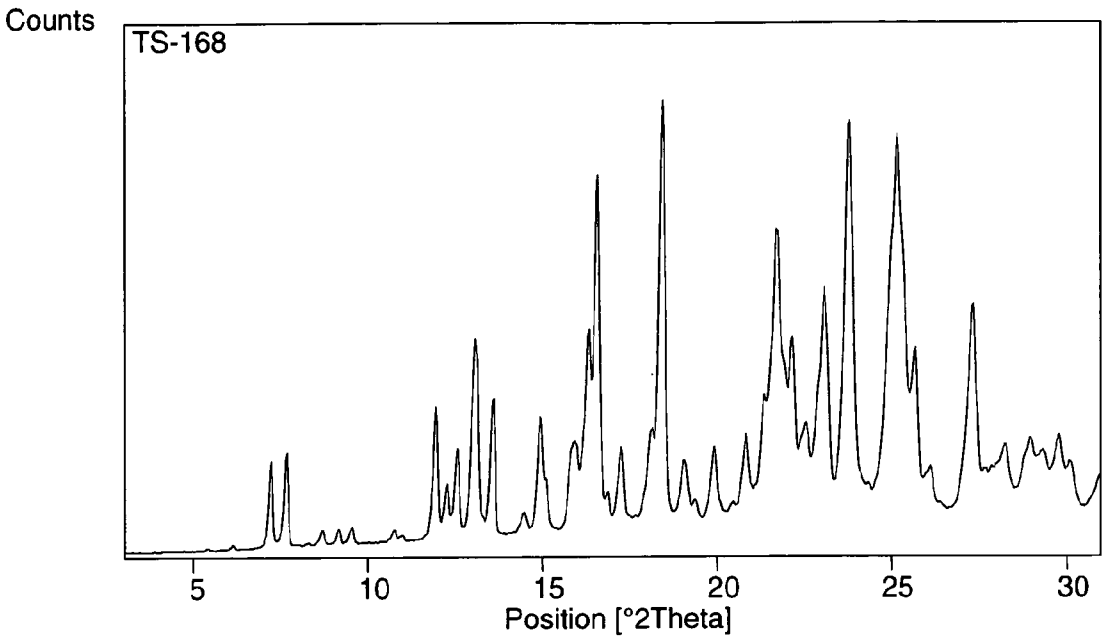

Figure 23

Telmisartan benzenesulfonate