

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
3 March 2011 (03.03.2011)

(10) International Publication Number  
**WO 2011/023954 A2**

(51) International Patent Classification:  
**C07D 211/90** (2006.01)

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(21) International Application Number:  
**PCT/GB2010/001615**

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date:  
26 August 2010 (26.08.2010)

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English  
(26) Publication Language: English  
(30) Priority Data:  
1970/MUM/2009 27 August 2009 (27.08.2009) IN

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

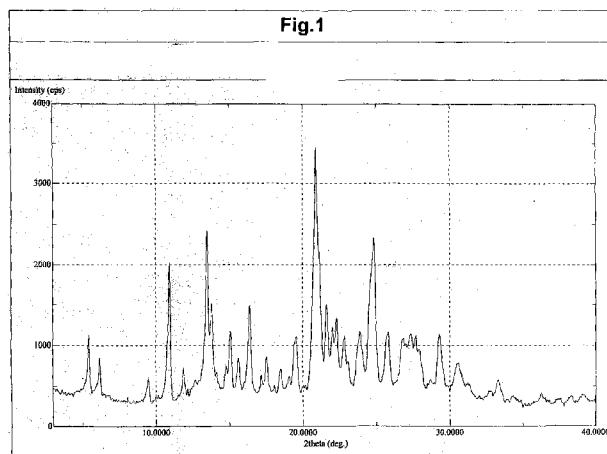
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(54) Title: POLYMORPHIC FORMS OF MANIDIPINE



(57) Abstract: The invention relates to various new polymorphic forms of manidipine and pharmaceutically acceptable salts thereof. The invention also relates to processes for the preparation of the polymorphic forms of manidipine and pharmaceutically acceptable salts thereof.

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## POLYMORPHIC FORMS OF MANIDIPINE

### **Field of the Invention**

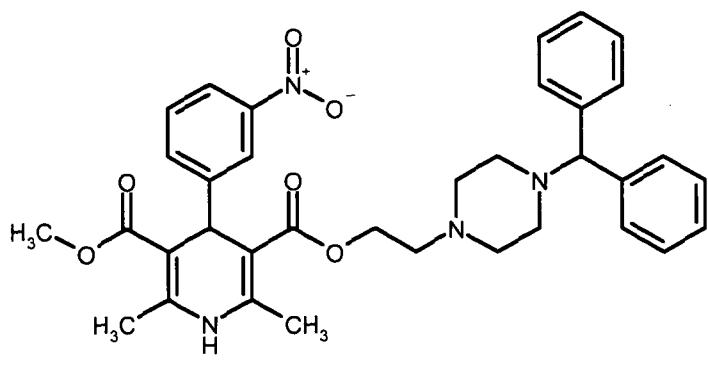
The present invention relates to novel polymorphic forms of a calcium channel blocker 5 and processes for their preparation.

In particular the present invention relates to novel polymorphic forms of manidipine and pharmaceutically acceptable salts thereof. The invention also relates to processes for preparation of said novel polymorphs.

10

### **Background**

Manidipine, chemically described as 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-[4-(diphenylmethyl)-1-piperazinyl]ethyl methyl ester is a dihydropyridine calcium channel blocker. It is also known as franidipine and 15 represented by the structure (I) shown below.



(I)

Manidipine is a lipophilic and highly vasoselective agent and has long-lasting activity for the treatment of hypertension. Manidipine is a dihydropyridine (DHP) calcium channel antagonist, which effectively reduces blood pressure in patients with mild-to-moderate 20 hypertension and effectively maintains reduced blood pressure levels throughout the dosing period of 24-hours. It is effective in the long term with no evidence of intolerance. Manidipine provides a first-line option for lowering blood pressure in patients with mild-to-moderate hypertension.

25 The preparation of manidipine and its existence in polymorphic forms is described in EP0094159B1 and its equivalent US4892875. Also, Chem. Pharm. Bull., 1989, 37, (8),

2225-8 describes the synthesis of enantiomeric (+)- and (-)-manidipine dihydrochlorides by esterification of optically active monocarboxylic acids.

Chem. Pharm. Bull., 1985, 33, (9), 3787-3797 discloses two crystalline forms of 5 manidipine dihydrochloride: the  $\alpha$  form and the  $\beta$  form, characterized by melting points.

Further, the literature data also shows that manidipine can exist in crystalline base as well as manidipine dihydrochloride monohydrate forms.

10 Eur J. Med. Chem., 33, 1998, 399-420 discloses manidipine, but gives no characterisation data.

FR 2924223 discloses a method of determine polymorphic purity of manidipine dihydrochloride using Raman spectra. This can be used to prepare manidipine 15 dihydrochloride having predetermined polymorphic purity.

Consequently, it would be a significant contribution to the art to provide a crystalline form of manidipine and pharmaceutically acceptable salts thereof; having increased solubility, and methods of preparation, pharmaceutical formulations, and methods of 20 use thereof.

### Objects of the invention

An object of the present invention is to provide various polymorphic forms of manidipine 25 and pharmaceutically acceptable salts thereof.

Another object of the present invention is to provide processes for the preparation of novel polymorphic forms of manidipine and pharmaceutically acceptable salts thereof.

30 Yet another object of the invention is to provide an industrially advantageous, cost effective and environmentally friendly process for preparing highly pure manidipine in high yields.

**Brief Description of Drawings**

Figure 1 shows an X-ray diffraction spectrum of form I of manidipine dihydrochloride.

Figure 2 shows an X-ray diffraction spectrum of form II of manidipine dihydrochloride.

5 Figure 3 shows an X-ray diffraction spectrum of form III of manidipine dihydrochloride.

Figure 4 shows an X-ray diffraction spectrum of form IV of manidipine dihydrochloride.

Figure 5 shows an X-ray diffraction spectrum of amorphous form V of manidipine dihydrochloride.

Figure 6 shows an X-ray diffraction spectrum of form VI of manidipine base.

10 Figure 7 shows an X-ray diffraction spectrum of amorphous form VII of manidipine base.

**Summary of the Invention**

15 The present invention provides novel polymorphic forms of manidipine dihydrochloride and base, referred to as Form I, Form II, Form III, Form IV, Form V, Form VI and Form VII.

Accordingly, the invention also provides methods for preparing these novel forms in  
20 high purity and high yield.

Each of the new forms is differentiated by a unique powder X-ray diffraction pattern.

The present invention further provides pharmaceutical compositions comprising novel  
25 manidipine forms I to VII together with one or more pharmaceutically acceptable excipients.

The invention also provides methods for preparing pharmaceutical composition comprising novel manidipine forms I to VII.

30

The present invention further provides method of treatment of diseases or symptoms wherein manidipine and pharmaceutically acceptable salts thereof, are useful.

The advantages of the process include simplicity, eco-friendliness and suitability for commercial use.

### **Detailed description of the Invention**

5

The present invention provides novel crystalline forms of manidipine and pharmaceutically acceptable salts thereof, methods of preparing the novel forms of manidipine and pharmaceutically acceptable salts thereof in high purity and high yield and pharmaceutical compositions comprising them. The advantages of the process 10 include simplicity, eco-friendliness and suitability for commercial use.

As polymorphic forms are most reliably characterized primarily by peak positions in the X-ray diffractogram, the polymorphs of the present invention have been characterized by powder X-ray diffraction spectroscopy which produces a fingerprint of the particular 15 crystalline form. Measurements of  $2\theta$  values typically are accurate to within  $\pm 0.2$  degrees. All the powder diffraction patterns were measured on a Rigaku Dmax 2200 advanced X-ray powder diffractometer with a copper-K- $\alpha$  radiation source. The XRD pattern is expressed in terms of 2 theta values ( $2\theta$ ) and percentage intensity (%).

20 All the polymorphs obtained in the present invention are stable, highly pure and with low amounts of residual solvents.

The invention further provides processes for the preparation of polymorphs.

25 Thus, in one aspect the present invention provides a novel polymorphic form of manidipine dihydrochloride which is hereinafter designated as 'Form I' which is substantially non-hygroscopic and has good flow characteristics.

In another aspect, the present invention provides a process for preparing the novel 30 form I of manidipine dihydrochloride in high yield and purity. The present invention also provides pharmaceutical compositions comprising Form I of manidipine dihydrochloride.

In an embodiment, the process involves isolation of the Form I of manidipine dihydrochloride in a solvent-free media, thus producing manidipine dihydrochloride free of solvents or having a negligible solvent content.

- 5 In an embodiment, the crystalline polymorph Form I of manidipine dihydrochloride has an XRD pattern with peaks at 10.94, 13.50, 20.90, 21.14 and  $24.86 \pm 0.2^\circ 2\theta$ . The XRD pattern may comprise further peaks at 13.82, 16.40, 20.72, 24.50 and  $24.58^\circ 2\theta \pm 0.2^\circ 2\theta$ .
- 10 In an embodiment, the crystalline polymorph Form I of manidipine dihydrochloride has an XRD pattern with peaks at 2θ-values as shown in Table 1.

Diffraction angle (2θ-values)	Intensity (%)
5.44	27
6.18	17
9.48	12
10.94	61
11.88	14
13.50	68
13.82	35
14.8	11
15.08	26
16.40	38
17.52	16
19.42	21
19.56	25
20.72	49
20.90	100
21.14	51
21.62	27
22.00	17

22.30	22
22.82	18
23.86	22
24.50	32
24.58	42
24.86	61
25.70	21
25.80	23
26.76	16
26.86	16
27.30	17
27.68	17
29.26	24
29.38	21

Table 1

In another embodiment, the X-ray powder diffraction spectrum of crystalline polymorphic Form I of manidipine dihydrochloride is depicted in Figure 1.

5 According to another aspect of the present invention there is provided a process for preparation of Form I, comprising dissolving manidipine dihydrochloride in methanol at reflux, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, isolating the precipitated crystalline Form I of manidipine dihydrochloride and drying under vacuum at about 40-45°C for at least 10 hours. The crystalline Form I of  
 10 manidipine dihydrochloride prepared by the process may be in the form as described above.

In a preferred embodiment, the Form I manidipine dihydrochloride is provided in the form of a racemate.

15

Another aspect the present invention provides a novel polymorphic form of manidipine dihydrochloride which is hereinafter designated as 'Form II' which is substantially non-hygroscopic and has good flow characteristics.

In another aspect, the present invention provides a process for preparing the novel form II of manidipine dihydrochloride in high yield and purity. The present invention also provides pharmaceutical compositions comprising Form II of manidipine dihydrochloride.

5

In an embodiment, the process involves isolation of the Form II of manidipine dihydrochloride in a solvent-free media, thus producing manidipine dihydrochloride free of solvents or having a negligible solvent content.

10 In an embodiment, Form II of the present invention is characterized by X-ray powder diffraction spectrum comprising peaks at 10.94, 22.02, 22.74 and  $22.84 \pm 0.2^\circ 2\theta$ . The XRD pattern may comprise further peaks at 13.5, 17.52 and  $21.02 \pm 0.2^\circ 2\theta$ .

15 In an embodiment, the crystalline polymorph 'Form II' of manidipine dihydrochloride has an XRD pattern with peaks at  $2\theta$ -values as shown in Table 2.

Diffraction angle ( $2\theta$ -values)	Intensity (%)
5.46	26
8.06	8
10.12	10
10.94	81
11.88	8
12.66	7
13.50	37
13.98	10
14.78	23
16.20	17
17.52	46
18.06	12
19.06	14
20.16	15
20.64	9

21.02	49
22.02	53
22.50	18
22.74	69
22.84	100
23.72	11
24.08	12
24.44	9
24.86	18
25.56	17
26.40	15
27.72	19
28.10	16
30.60	10

Table 2

In another embodiment, the X-ray powder diffraction spectrum of crystalline polymorphic Form II of manidipine dihydrochloride is depicted in Figure 2.

5 According to another aspect of the present invention there is provided a process for preparation of Form II, comprising dissolving manidipine dihydrochloride in a mixture of methanol and denatured ethanol (1:1) at reflux, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, stirring for 12-14 hours, isolating the precipitated crystalline Form II of manidipine dihydrochloride and drying under vacuum

10 at about 40-45°C for at least 10 hours. The crystalline Form II of manidipine dihydrochloride prepared by the process may be in the form as described above.

In a preferred embodiment, the Form II manidipine dihydrochloride is provided in the form of a racemate.

15

Yet another aspect the present invention provides a novel polymorphic form of manidipine dihydrochloride which is hereinafter designated as 'Form III' which is substantially non-hygroscopic and has good flow characteristics.

In another aspect, the present invention provides a process for preparing the novel Form III of manidipine dihydrochloride in high yield and purity. The present invention also provides pharmaceutical compositions comprising Form III of manidipine dihydrochloride.

5

In an embodiment, the process involves isolation of the Form III of manidipine dihydrochloride in a solvent-free media, thus producing manidipine dihydrochloride free of solvents or having a negligible solvent content.

10 In an embodiment, Form III of the present invention is characterized by X-ray powder diffraction spectrum comprising peaks at 9.06, 13.44, 20.98, 21.70, 21.80, 21.92, 22.80 and  $24.42 \pm 0.2^\circ 2\theta$ . The XRD pattern may comprise further peaks at 10.90, 14.28, 15.80, 18.28, 27.60 and  $27.70 \pm 0.2^\circ 2\theta$ .

15 In an embodiment, the crystalline polymorph Form III of manidipine dihydrochloride has an XRD pattern with peaks at  $2\theta$ -values as shown in Table 3.

Diffraction angle ( $2\theta$ -values)	Intensity (%)
5.80	25
6.70	19
9.06	72
10.90	30
11.84	18
13.44	51
14.28	36
15.80	36
16.14	19
17.50	23
18.00	20
18.28	31
20.98	100
21.70	55
21.80	65

21.92	67
22.80	57
24.02	29
24.42	57
24.80	25
25.76	28
26.34	24
27.60	37
27.70	41
28.10	28
28.24	22

Table 3

In another embodiment, the X-ray powder diffraction spectrum of crystalline polymorphic Form III of manidipine dihydrochloride is depicted in Figure 3.

5 According to another aspect of the present invention there is provided a process for preparation of Form III, comprising dissolving manidipine dihydrochloride in a mixture of methanol and toluene (1:1) at 75-80°C, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, stirring for 12-14 hours, isolating the precipitated crystalline Form III of manidipine dihydrochloride and drying under vacuum at about 10 40-45°C for at least 10 hours. The crystalline Form III of manidipine dihydrochloride prepared by the process may be in the form as described above.

In a preferred embodiment, the Form III manidipine dihydrochloride is provided in the form of a racemate.

15

Yet another aspect the present invention provides a novel polymorphic form of manidipine dihydrochloride which is hereinafter designated as 'Form IV' which is substantially non-hygroscopic and has good flow characteristics.

20 In another aspect, the present invention provides a process for preparing the novel form IV of manidipine dihydrochloride in high yield and purity. The present invention

also provides pharmaceutical compositions comprising Form IV of manidipine dihydrochloride.

In an embodiment, the process involves isolation of the Form IV of manidipine dihydrochloride in a solvent-free media, thus producing manidipine dihydrochloride free of solvents or having a negligible solvent content.

In an embodiment, Form IV of the present invention is characterized by X-ray powder diffraction spectrum comprising peaks at 12.58, 20.34 and  $23.36 \pm 0.2^\circ 2\theta$ . The XRD 10 pattern may comprise further peaks at 7.90, 10.10, 18.98, 22.28, 26.62 and  $28.32 \pm 0.2^\circ 2\theta$ .

In an embodiment, the crystalline polymorph Form IV of manidipine dihydrochloride has an XRD pattern with peaks at  $2\theta$ -values as shown in Table 4.

15

Diffraction angle ( $2\theta$ -values)	Intensity (%)
5.60	16
6.22	29
7.90	32
10.10	39
11.14	21
12.58	87
14.60	19
14.92	13
15.20	14
15.90	14
16.58	13
16.66	16
18.02	21
18.86	24
18.98	32
20.34	100

20.98	21
22.00	24
22.28	41
23.36	61
23.92	18
25.10	18
25.34	29
26.62	34
27.64	13
28.32	46
30.14	18
30.74	13
33.24	13

Table 4

In another embodiment, the X-ray powder diffraction spectrum of crystalline polymorphic Form IV of manidipine dihydrochloride is depicted in Figure 4.

5

According to another aspect of the present invention there is provided a process for preparation of Form IV, comprising dissolving manidipine dihydrochloride in a mixture of toluene and denatured ethanol (1:1) at 75-80°C, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, stirring for 12-14 hours, isolating the 10 precipitated crystalline Form IV of manidipine dihydrochloride and drying under vacuum at about 40-45°C for at least 10 hours. The crystalline Form IV of manidipine dihydrochloride prepared by the process may be in the form as described above.

In a preferred embodiment, the Form IV manidipine dihydrochloride is provided in the 15 form of a racemate.

In still another aspect the present invention there is provided an amorphous form of manidipine dihydrochloride which is hereinafter designated as 'Form V' which is substantially non-hygroscopic and has good flow characteristics.

In another aspect, the present invention provides a process for preparing the novel form V of manidipine dihydrochloride in high yield and purity. The present invention also provides pharmaceutical compositions comprising Form V of manidipine dihydrochloride.

5

In an embodiment, the process involves isolation of the Form V of manidipine dihydrochloride in a solvent-free media, thus producing manidipine dihydrochloride free of solvents or having a negligible solvent content.

10 In an embodiment, Form V of the present invention is characterized by X-ray powder diffraction spectrum.

In another embodiment, an amorphous Form V of manidipine dihydrochloride is characterized by having an XRD pattern as shown in Figure 5.

15

According to another aspect of the present invention there is provided a process for preparation of Form V, comprising dissolving manidipine dihydrochloride in methanol at reflux, concentrating under vacuum to dryness, isolating the precipitated amorphous Form V of manidipine dihydrochloride and drying under vacuum at about 40-45°C for 20 at least 10 hours. The amorphous Form V of manidipine dihydrochloride prepared by the process may be in the form as described above.

In a preferred embodiment, the Form V manidipine dihydrochloride is provided in the form of a racemate.

25

The manidipine dihydrochloride used in the preparation of the Forms I, II, III, IV or V, may be in any polymorphic form or in a mixture of any polymorphic forms.

30 In yet another aspect the present invention provides a crystalline form of manidipine base which is hereinafter designated as 'Form VI' which is substantially non-hygroscopic and has good flow characteristics.

In another aspect, the present invention provides a process for preparing the novel form VI of manidipine base in high yield and purity. The present invention also provides pharmaceutical compositions comprising Form VI of manidipine base.

5 In an embodiment, the process involves isolation of the Form VI of manidipine base in a solvent-free media, thus producing manidipine base free of solvents or having a negligible solvent content.

In an embodiment, Form VI of the present invention is characterized by X-ray powder 10 diffraction spectrum comprising peaks at 5.08, 14.04, 15.40, 20.60 and  $21.94 \pm 0.2^\circ 2\theta$ . The XRD pattern may comprise further peaks at 15.08, 18.96, 19.44 and  $22.26 \pm 0.2^\circ 2\theta$ .

In an embodiment, the crystalline polymorph Form VI of manidipine base has an XRD 15 pattern with peaks at 2θ-values as shown in Table 5.

Diffraction angle (2θ-values)	Intensity (%)
5.08	51
10.94	25
12.36	15
13.52	21
13.78	27
14.04	59
14.28	13
15.08	42
15.40	58
15.80	19
16.04	16
17.88	12
18.42	18
18.62	21
18.96	44

19.44	34
20.24	21
20.60	56
21.94	100
22.26	42
22.82	7
23.84	7
24.16	11
24.82	20
25.90	11
26.30	9
27.24	8
28.92	11
30.34	13
31.86	7
37.32	7

Table 5

In another embodiment, crystalline Form VI of manidipine base is characterized by having an XRD pattern as shown in Figure 6.

5

According to another aspect of the present invention there is provided a process for preparation of Form VI, comprising dissolving manidipine base in methanol at reflux, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, adding n-Heptane under stirring, stirring for 10-12 hours, isolating the precipitated crystalline 10 Form VI of manidipine base and drying under vacuum at about 40-45°C for at least 10 hours. The crystalline Form VI of manidipine base prepared by the process may be in the form as described above.

In a preferred embodiment, the Form VI manidipine base is provided in the form of a 15 racemate.

In still another aspect the present invention provides an amorphous form of manidipine base which is hereinafter designated as 'Form VII' which is substantially non-hygroscopic and has good flow characteristics.

5 In another aspect, the present invention provides a process for preparing the novel Form VII of manidipine base in high yield and purity. The present invention also provides pharmaceutical compositions comprising Form VII of manidipine base.

In an embodiment, the process involves isolation of the Form VII of manidipine base in 10 a solvent-free media, thus producing manidipine base free of solvents or having a negligible solvent content.

In an embodiment, Form VII of the present invention is characterized by X-ray powder diffraction spectrum.

15

In another embodiment, amorphous Form VII of manidipine base is characterized by having an XRD pattern as shown in Figure 7.

According to another aspect of the present invention there is provided a process for 20 preparation of Form VII, comprising dissolving manidipine base in methylene dichloride at about 40°C, concentrating under vacuum to dryness, isolating the precipitated Amorphous Form VII of manidipine base and drying under vacuum at about 40-45°C for at least 10 hours. The amorphous Form VII of manidipine base prepared by the process may be in the form as described above.

25

In a preferred embodiment, the Form VII manidipine base is provided in the form of a racemate.

The manidipine base used in the preparation of the Forms VI or VII may be in any 30 polymorphic form or in a mixture of any polymorphic forms.

The novel polymorphs of manidipine obtained according to the present invention is substantially free from other forms of manidipine. "Substantially free" from other forms

of manidipine shall be understood to mean that the polymorphs of manidipine contain less than 10%, preferably less than 5%, of any other forms of manidipine and less than 1% of other impurities, water or solvates.

5 The process of invention may be used as a method for purifying any form of manidipine, as well as for the preparation of the new polymorphic forms.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising polymorphic Forms of manidipine or 10 pharmaceutically acceptable salts thereof as described above, together with one or more pharmaceutically acceptable excipients. The manidipine dihydrochloride used in the preparation of pharmaceutical compositions may substantially consist of one of forms I, II, III, IV or V described above, or may substantially consist of a combination of two or more of said forms. The manidipine based used in the preparation of 15 pharmaceutical compositions may substantially consist of one of forms V or VI described above, or may substantially consist of a combination of both of said forms.

Manidipine or its salts have been found to be effective for the control of elevated blood pressure (hypertension). Pharmaceutical compositions according to the present 20 invention comprise novel polymorphs I, II, III, IV, V, VI or VII of manidipine as an active ingredient together with one or more pharmaceutically acceptable carriers, excipients or diluents. Any conventional technique may be used for the preparation of pharmaceutical compositions and dosage forms according to the invention.

25 Manidipine polymorphs I, II, III, IV, V, VI and VII are useful for treating a variety of diseases and disorders, including: ankle edema. The drug also significantly lowers blood pressure in patients with hypertension and concomitant Type 2 diabetes mellitus or renal impairment,

30 Accordingly, the present invention provides a method for treating a human suffering from a disease or a disorder known to be responsive to the administration of manidipine, by administering to said human, an effective amount of manidipine forms.

Various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but should be considered as exemplification of mere embodiments.

5 The present invention will now be further illustrated by the following examples, which do not limit the scope of the invention in any way.

## EXAMPLES

### Example 1

10 **Preparation of Manidipine base**

To a solution of benzhydryl piperazine (7.28 gm) in toluene (35 ml) at room temperature, dimethyl formamide (70 ml), 2-chloroethanol (5 ml) and potassium carbonate (5 gm) were added. The reaction mass was heated to reflux with constant stirring for 14-16 hours. Reaction mass was cooled, filtered, and concentrated under 15 vacuum to get 2-(4-benzhydryl piperazine-1-yl) ethanol (yield: 7.5 gm).

To a suspension of 2,6-dimethyl-4-(3-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid monomethyl ester (5 gm), dicyclohexyl carbodiimide (3.08 gm) and dimethylamino pyridine (0.25gm) in toluene (30ml) at room temperature was added 2-(4-benzhydryl 20 piperazine-1-yl)ethanol (7.5 gm). Reaction mass was then heated to 70-75°C for 2 hours. Reaction mass was then cooled to room temperature and filtered. Toluene layer was concentrated under vacuum to get manidipine base (5 gm).

### Example 2

25 **Preparation of Manidipine Dihydrochloride**

Manidipine base was dissolved in acetone (15 ml). The pH of the solution was adjusted to 1-1.5 with IPA-HCl solution with constant stirring to get manidipine Dihydrochloride. The reaction mass was filtered and dried for 2 hours (yield: 3 gm).

30 **EXAMPLE 3**

### Preparation of crystalline Form I of Manidipine dihydrochloride

Manidipine Dihydrochloride (16 g) was dissolved in methanol (320 ml) at 65°C. The solution was cooled to room temperature with constant stirring for 4 hours. The solid

obtained was filtered, washed with methanol and dried under vacuum at about 40-45°C for 10-12 hours to yield crystals of Form I (Yield: 14.6 gm) (Purity: 99.81%)

The polymorph was characterized by XRD.

## 5 EXAMPLE 4

### **Preparation of crystalline Form II of Manidipine dihydrochloride**

Manidipine dihydrochloride (0.5 g) was dissolved in (1:1) mixture of methanol and denatured ethanol (8 ml) at 65°C. The clear solution was cooled slowly and stirred at room temperature for 12-14 hours. The solid obtained was filtered, washed with 10 methanol and dried under vacuum at about 40-45°C for 10-12 hours to yield crystals of form II. (Yield: 0.4gm) (Purity: 99.89%)

The polymorph was characterized by XRD.

## EXAMPLE 5

### **15 Preparation of crystalline Form III of Manidipine dihydrochloride**

Manidipine dihydrochloride (0.5 g) was dissolved in (1:1) mixture of methanol and toluene (4.5 ml) at 75°C. The clear solution was cooled slowly and stirred at room temperature for 12-14 hours. The solid thus obtained was filtered, washed with methanol and dried under vacuum at about 45°C for 10-12 hours to yield crystals of 20 form III. (Yield: 0.4 gm) (Purity: 99.81%)

The polymorph was characterized by XRD.

## EXAMPLE 6

### **Preparation of crystalline Form IV of Manidipine dihydrochloride**

25 Manidipine dihydrochloride (0.5 g) was dissolved in toluene: denatured ethanol (1:1) mixture (9.5 ml) at 75-80°C. The clear solution was cooled slowly and stirred at room temperature for 12-14 hours. The solid obtained was filtered, washed with denatured ethanol and dried under vacuum at 45°C for 10-12 hours to yield crystals of form IV. (Yield: 0.35 gm) (Purity: 99.87%)

30 The polymorph was characterized by XRD.

## EXAMPLE 7

### **Preparation of amorphous Form V of Manidipine dihydrochloride**

20

Manidipine dihydrochloride (1 g) was dissolved in methanol (20 ml) at 65°C. The solvent was distilled off completely under vacuum below 50°C. Solid obtained was dried under vacuum at 40-45°C for at least 10 hours to yield amorphous form V. (Yield: 0.9gm) (Purity: 99.80%)

5 The amorphous form was characterized by XRD.

### **EXAMPLE 8**

#### **Preparation of crystalline Form VI of Manidipine base**

Manidipine base (1 g) was dissolved in methanol (2 ml) at 45°C. The solution was 10 cooled to room temperature. N-heptane (20 ml) was added to the clear solution. Stirring was continued for 10-12 hours and precipitate was filtered and washed by n-heptane. Isolated compound was dried under vacuum at 45-50°C for 10-12 hours. (Yield: 0.8 gm) (Purity: 99.79%)

The polymorphic form VI was characterized by XRD.

15

### **EXAMPLE 9**

#### **Preparation of amorphous Form VII of Manidipine base**

Manidipine base (1 g) was dissolved in methylene dichloride (5 ml) at 60°C. The solvent was distilled off completely. The compound thus obtained was isolated and 20 dried under vacuum at 45-50°C for 10-12 hours. (Yield: 0.9 gm) (Purity: 99.77%)

The amorphous form VII was characterized by XRD.

**CLAIMS**

1. Crystalline Form I of manidipine dihydrochloride, characterized by having an XRD pattern comprising peaks at 10.94, 13.50, 20.90, 21.14 and  $24.86 \pm 0.2^\circ 2\theta$ .  
5
2. Crystalline polymorph Form I of manidipine dihydrochloride according to claim 1, characterized by having an XRD pattern comprising further peaks at 13.82, 16.40, 20.72, 24.50 and  $24.58^\circ 2\theta \pm 0.2^\circ 2\theta$ .
- 10 3. Crystalline Form I of manidipine dihydrochloride, characterized by having an XRD pattern as shown in Figure 1.
4. A process for preparing crystalline Form I of manidipine dihydrochloride according to any preceding claim, the process comprising dissolving manidipine dihydrochloride in methanol at reflux, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, isolating the precipitated crystalline Form I of manidipine dihydrochloride and drying under vacuum at about 40-45°C for at least 10 hours.  
15
- 20 5. A process according to claim 4, wherein the manidipine dihydrochloride used to prepare the Form I manidipine dihydrochloride is in any polymorphic form or in a mixture of any polymorphic forms.
6. Crystalline Form I of manidipine dihydrochloride, prepared by a process  
25 according to claim 4 or 5.
7. Crystalline Form II of manidipine dihydrochloride, characterized by having an XRD pattern comprising peaks at 10.94, 22.02, 22.74 and  $22.84 \pm 0.2^\circ 2\theta$ .
- 30 8. Crystalline polymorph Form II of manidipine dihydrochloride according to claim 7, characterized by having an XRD pattern comprising further peaks at 13.5, 17.52 and  $21.02 \pm 0.2^\circ 2\theta$ .

9. Crystalline Form II of manidipine dihydrochloride, characterized by having an XRD pattern as shown in Figure 2.

10. A process for preparing crystalline Form II of manidipine dihydrochloride  
5 according to any one of claims 7 to 9, the process comprising dissolving manidipine dihydrochloride in a mixture of methanol and denatured ethanol (1:1) at reflux, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, stirring for 12-14 hours, isolating the precipitated crystalline Form II of manidipine dihydrochloride and drying under vacuum at about 40-45°C for at least 10 hours.

10

11. A process according to claim 10, wherein the manidipine dihydrochloride used to prepare the Form II manidipine dihydrochloride is in any polymorphic form or in a mixture of any polymorphic forms.

15

12. Crystalline Form II of manidipine dihydrochloride, prepared by a process according to claims 10 or 11.

15

13. Crystalline Form III of manidipine dihydrochloride, characterized by having an XRD pattern comprising peaks at 9.06, 13.44, 20.98, 21.70, 21.80, 21.92, 22.80 and  
20 24.42 ± 0.2 °2θ.

25

14. Crystalline polymorph Form III of manidipine dihydrochloride according to claim 13, characterized by having an XRD pattern comprising further peaks at 10.90, 14.28, 15.80, 18.28, 27.60 and 27.70 ± 0.2 °2θ.

15.

Crystalline Form III of manidipine dihydrochloride, characterized by having an XRD pattern as shown in Figure 3.

16.

A process for preparing crystalline Form III of manidipine dihydrochloride  
30 according to any one of claims 13 to 15, the process comprising dissolving manidipine dihydrochloride in a mixture of methanol and toluene (1:1) at 75-80°C, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, stirring for 12-14

hours, isolating the precipitated crystalline Form III of manidipine dihydrochloride and drying under vacuum at about 40-45°C for at least 10 hours.

17. A process according to claim 16, wherein the manidipine dihydrochloride used to 5 prepare the Form III manidipine dihydrochloride is in any polymorphic form or in a mixture of any polymorphic forms.

18. Crystalline Form III of manidipine dihydrochloride, prepared by a process according to claim 16 or 17.

10

19. Crystalline Form IV of manidipine dihydrochloride, characterized by having an XRD pattern comprising peaks at 12.58, 20.34 and  $23.36 \pm 0.2$  °2θ.

15

20. Crystalline polymorph Form IV of manidipine dihydrochloride, according to claim 19, characterized by having an XRD pattern comprising further peaks at 7.90, 10.10, 18.98, 22.28, 26.62 and  $28.32 \pm 0.2$  °2θ.

21. Crystalline Form IV of manidipine dihydrochloride, characterized by having an XRD pattern as shown in Figure 4.

20

22.

A process for preparing crystalline Form IV of manidipine dihydrochloride according to one one of claims 19 to 21, the process comprising dissolving manidipine dihydrochloride in a mixture of toluene and denatured ethanol (1:1) at 75-80°C, cooling the reaction mass to a temperature ranging from about 25°C to 30°C, stirring for 12-14 25 hours, isolating the precipitated crystalline Form IV of manidipine dihydrochloride and drying under vacuum at about 40-45°C for at least 10 hours.

30

23. A process according to claim 22, wherein the manidipine dihydrochloride used to prepare the Form IV manidipine dihydrochloride is in any polymorphic form or in a mixture of any polymorphic forms.

24. Crystalline Form IV of manidipine dihydrochloride, prepared by a process according to claim 22 or 23.

25. Amorphous manidipine dihydrochloride (Form V).

26. Amorphous manidipine dihydrochloride, characterized by having an XRD pattern  
5 as shown in Figure 5.

27. A process for preparing amorphous manidipine dihydrochloride according to  
claim 25 or 26, the process comprising dissolving manidipine dihydrochloride in  
methanol at reflux, concentrating under vacuum to dryness, isolating the precipitated  
10 amorphous manidipine dihydrochloride and drying under vacuum at about 40-45°C for  
at least 10 hours.

28. A process according to claim 27, wherein the manidipine dihydrochloride used to  
prepare the amorphous manidipine dihydrochloride is in any polymorphic form or in a  
15 mixture of any polymorphic forms.

29. Amorphous manidipine dihydrochloride, prepared by a process according to  
claim 27 or 28.

20 30. Crystalline Form VI of manidipine base, characterized by having an XRD pattern  
comprising peaks at 5.08, 14.04, 15.40, 20.60 and  $21.94 \pm 0.2$  °2θ.

31. Crystalline Form VI of manidipine base according to claim 30, characterized by  
having an XRD pattern comprising further peaks at 15.08, 18.96, 19.44 and  $22.26 \pm 0.2$   
25 °2θ.

32. Crystalline Form VI of manidipine base, characterized by having an XRD pattern  
as shown in Figure 6.

30 33. A process for preparing crystalline Form VI of manidipine base according to any  
on of claims 30 to 32, the process comprising dissolving manidipine base in methanol  
at reflux, cooling the reaction mass to a temperature ranging from about 25°C to 30°C,  
adding n-Heptane under stirring, stirring for 10-12 hours, isolating the precipitated

crystalline Form VI of manidipine base and drying under vacuum at about 40-45°C for at least 10 hours.

34. A process according to claim 33, wherein the manidipine base used to prepare 5 the Form VI manidipine base is in any polymorphic form or in a mixture of any polymorphic forms.

35. Crystalline Form VI of manidipine base, prepared by a process according to claim 33 or 34.

10

36. Amorphous manidipine base (Form VII).

37. Amorphous manidipine base, characterized by having an XRD pattern as shown in Figure 7.

15

38. A process for preparing amorphous manidipine base according to claim 36 or 37, the process comprising dissolving methylene dichloride at about 40°C, concentrating under vacuum to dryness, isolating the precipitated amorphous manidipine base and drying under vacuum at about 40-45°C for at least 10 hours.

20

39. A process according to claim 38, wherein the manidipine base used to prepare the amorphous manidipine base is in any polymorphic form or in a mixture of any polymorphic forms.

25 40. Amorphous manidipine base, prepared by a process according to claim 38 or 39.

41. A pharmaceutical composition comprising a polymorphic form of manidipine dihydrochloride according to any one of claims 1 to 3 or 6, optionally in combination with one or more pharmaceutical acceptable excipients.

30

42. A pharmaceutical composition comprising a polymorphic form of manidipine dihydrochloride according to any one of claims 7 to 9 or 12, optionally in combination with one or more pharmaceutical acceptable excipients.

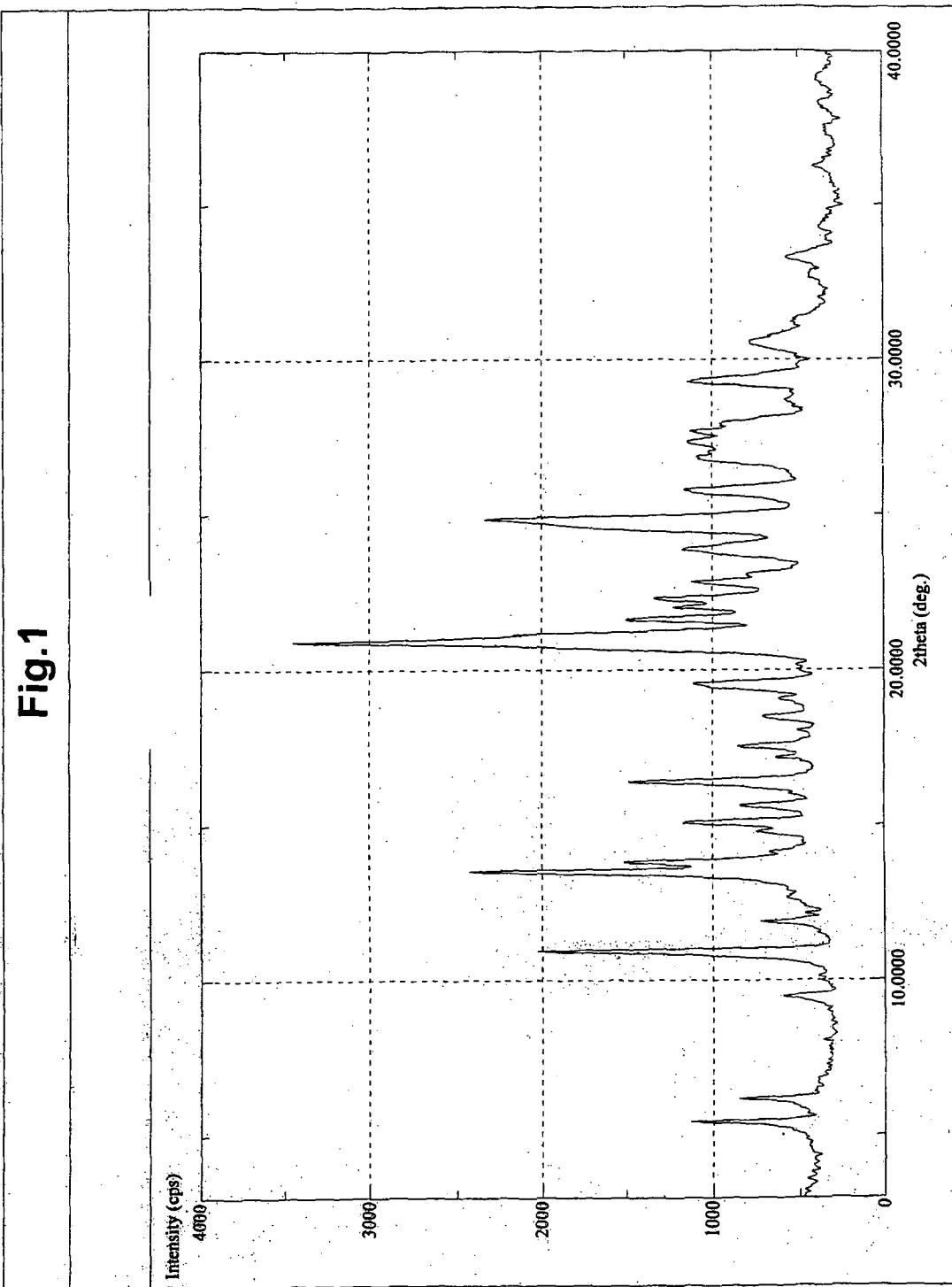
43. A pharmaceutical composition comprising a polymorphic form of manidipine dihydrochloride according to any one of claims 13 to 15 or 18, optionally in combination with one or more pharmaceutical acceptable excipients.

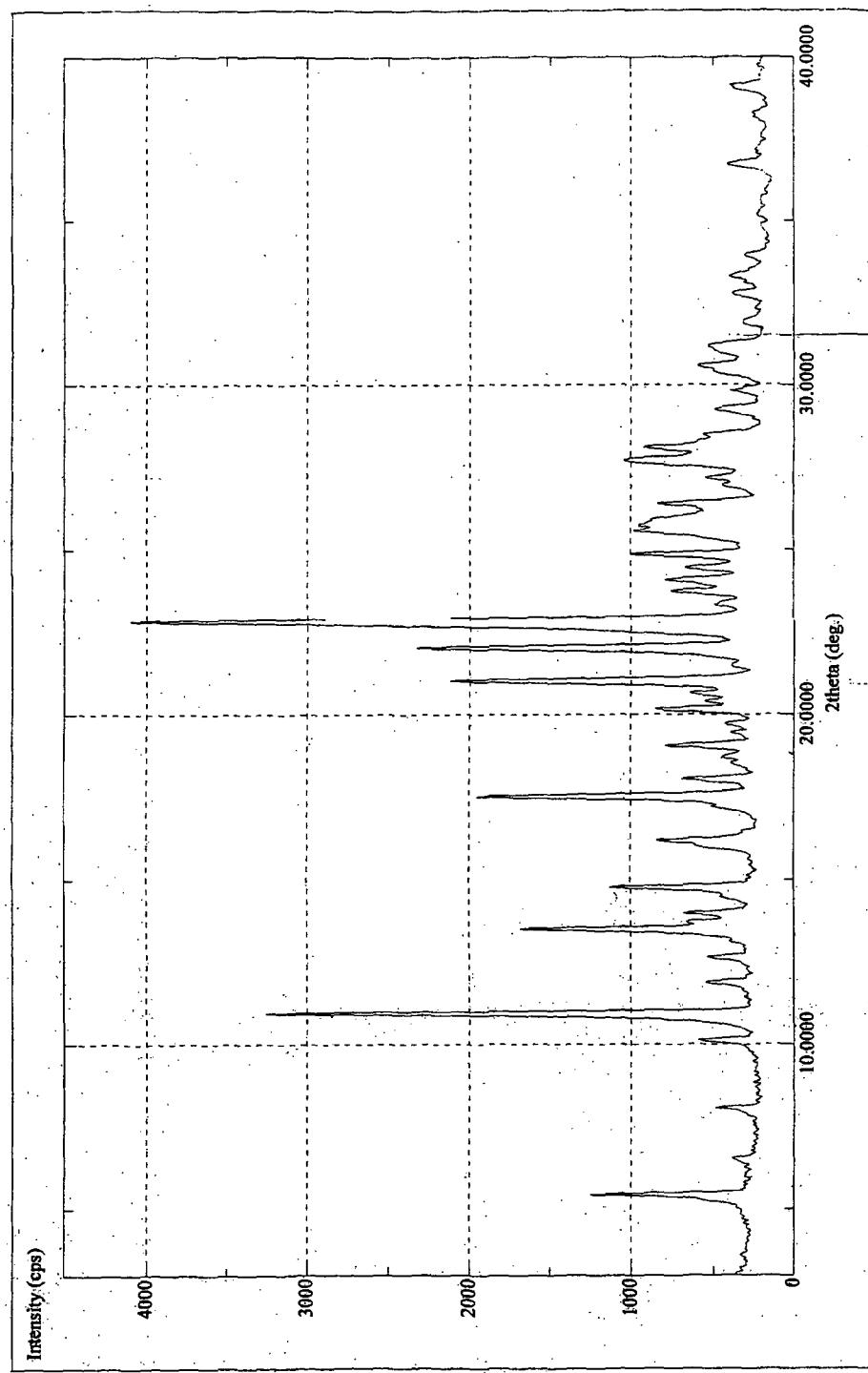
5 44. A pharmaceutical composition comprising a polymorphic form of manidipine dihydrochloride according to any one of claims 19 to 21 or 24, optionally in combination with one or more pharmaceutical acceptable excipients.

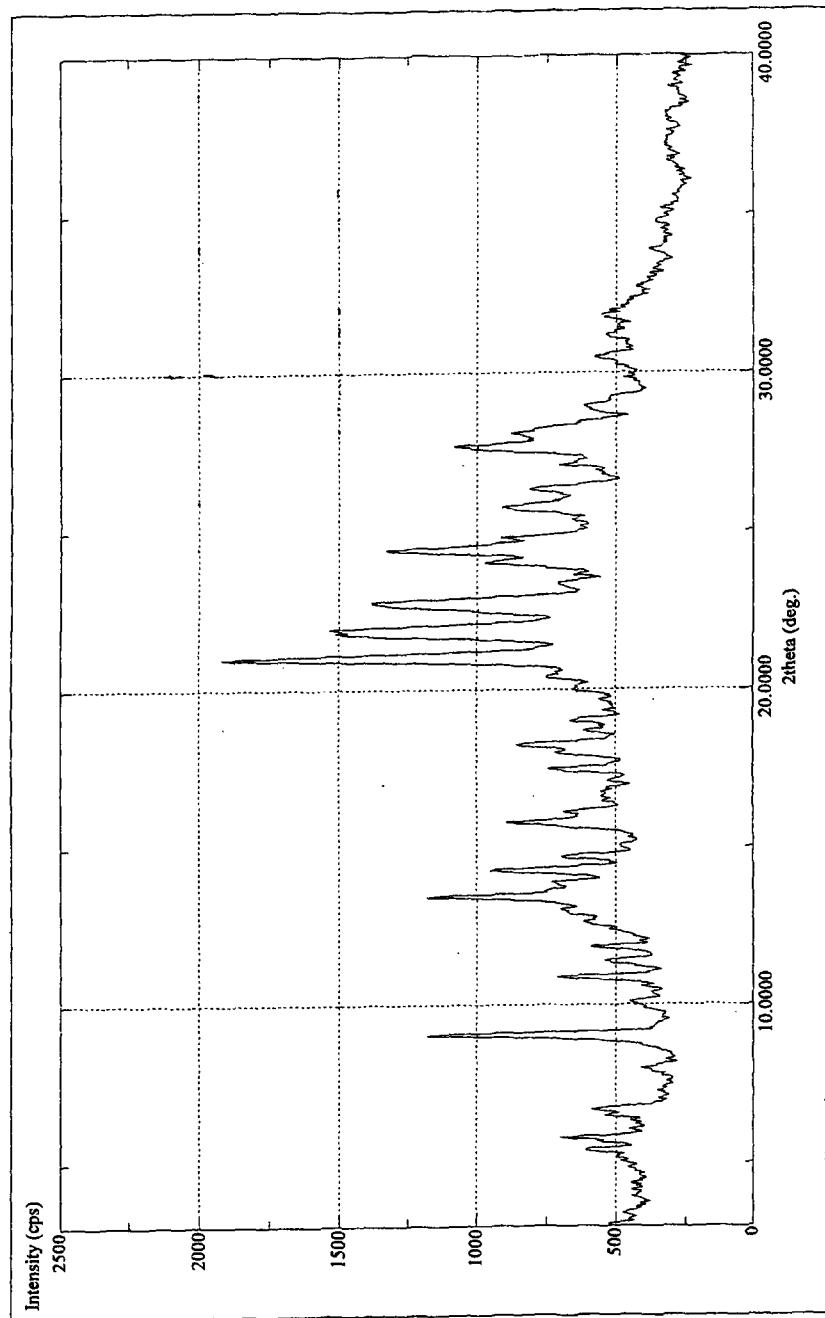
10 45. A pharmaceutical composition comprising a polymorphic form of manidipine dihydrochloride according to any one of claim 25, 26 or 29, optionally in combination with one or more pharmaceutical acceptable excipients.

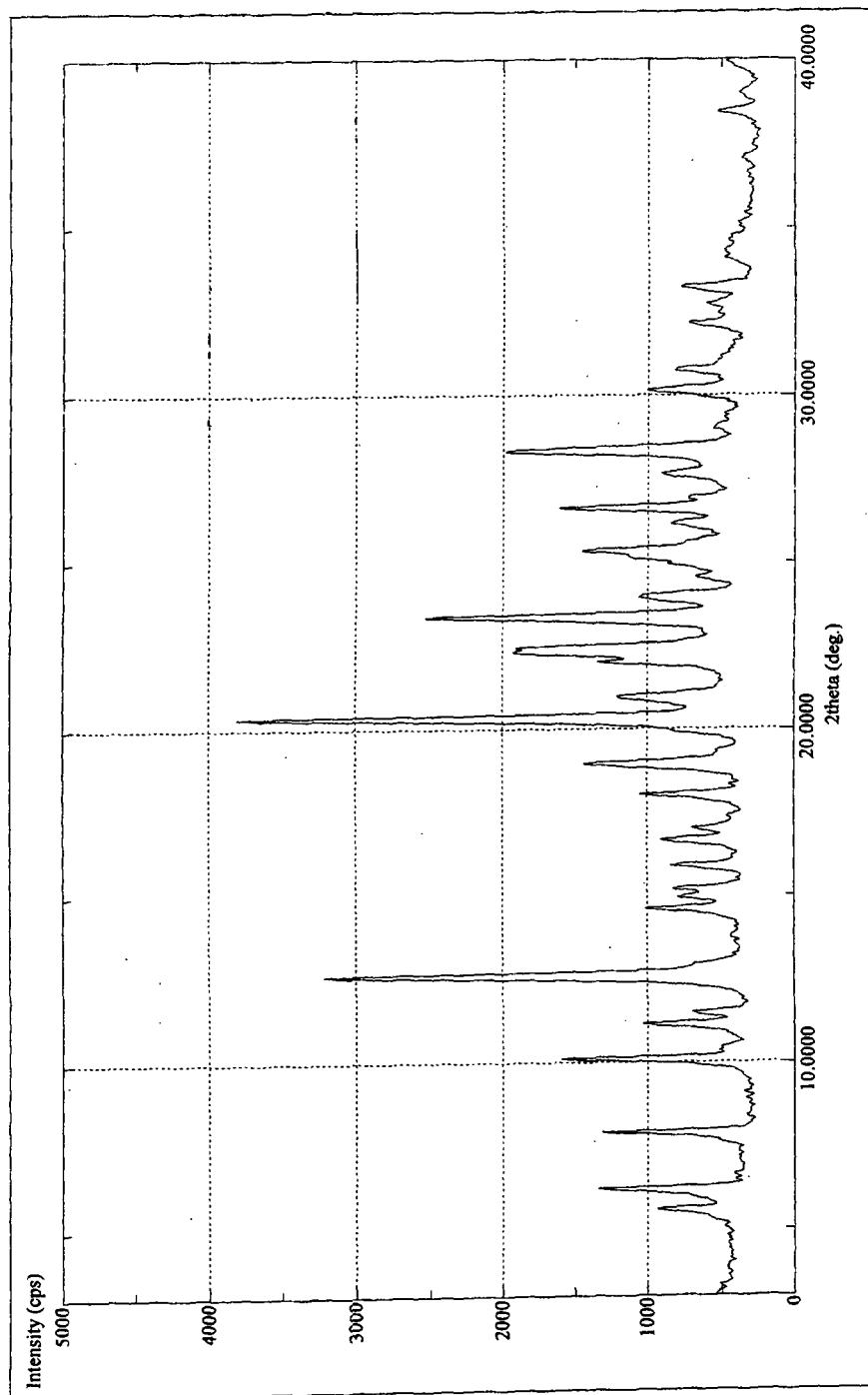
15 46. A pharmaceutical composition comprising a polymorphic form of manidipine base according to any one of claims 30 to 32 or 35, optionally in combination with one or more pharmaceutical acceptable excipients.

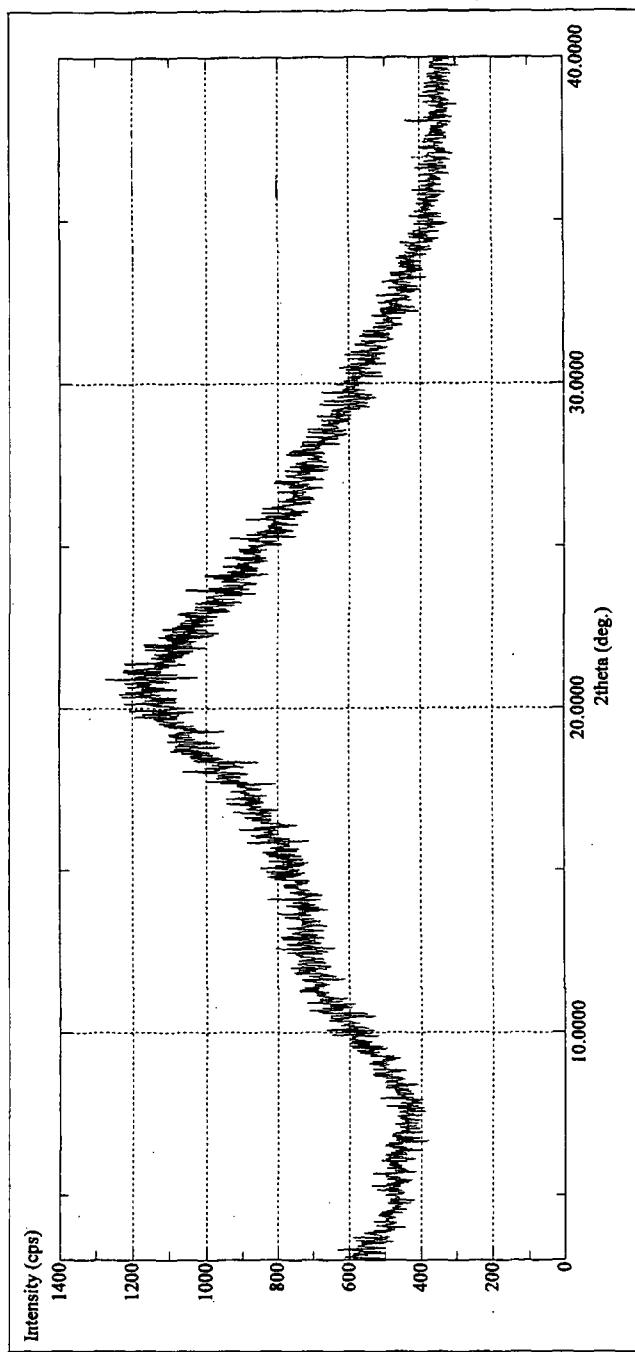
47. A pharmaceutical composition comprising a polymorphic form of manidipine base according to any one of claims 36, 37 or 40, optionally in combination with one or more pharmaceutical acceptable excipients.

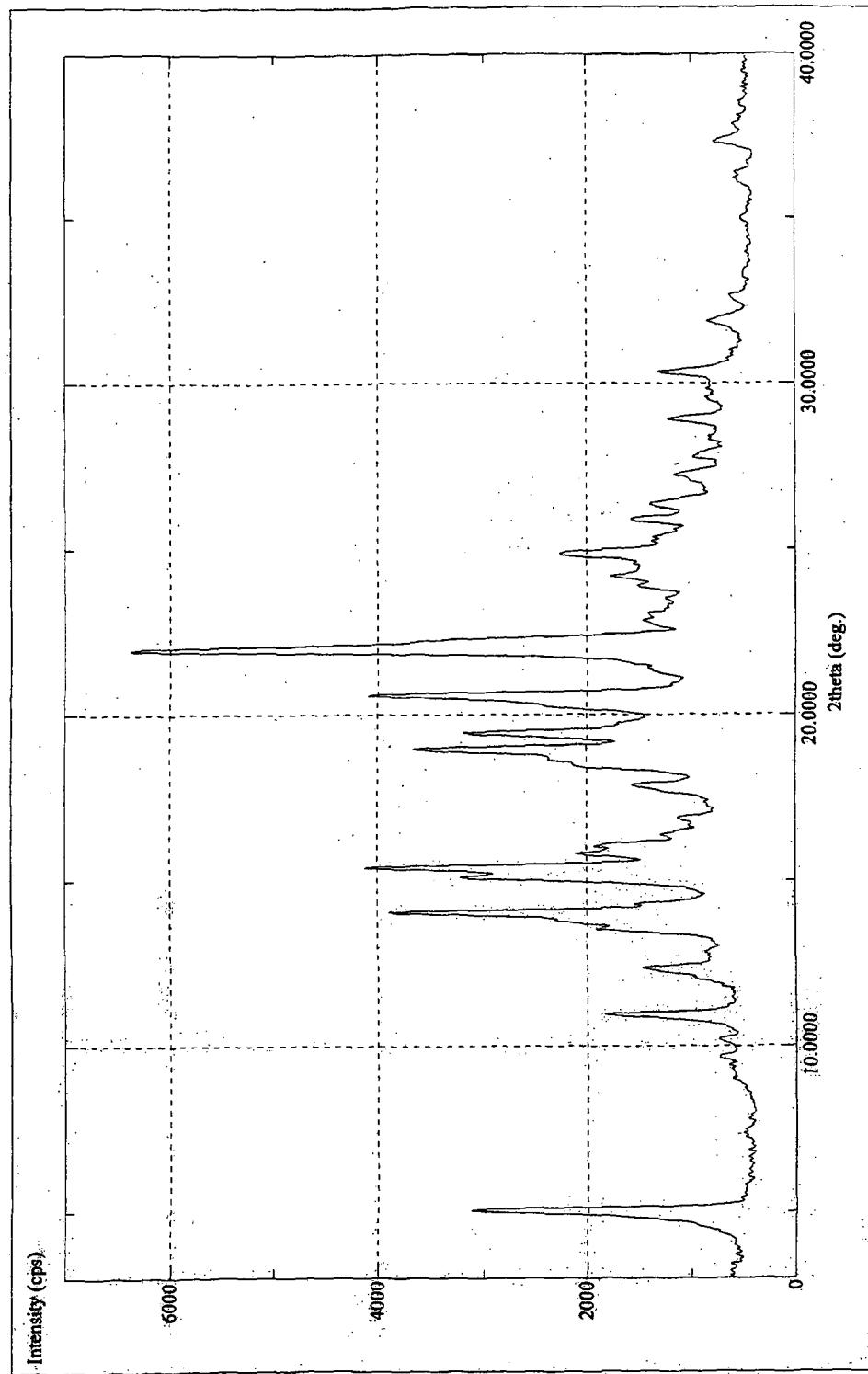


**Fig.2**

**Fig.3**

**Fig.4**

**Fig.5**

**Fig.6**

**Fig.7**