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Polymorphism of Doxazosin Mesylate

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Nine polymorphic modifications of doxazosin mesylate have been obtained by recrystallization in organic solvents under variable conditions. Different polymorphs of doxazosin mesylate were characterized by powder X-ray crystallography diffractometry (PXRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TG). Transformation of Form 1 and Form 2 was not occurred in three relative humidities (0%, 51%, and 99%) at 20±0.5 for 30 days.

Key words: Doxazosin mesylate, Polymorphism, PXRD, DSC, TG, Transformation

INTRODUCTION

Pharmaceutical solids can exist in different crystal forms, such as crystalline, amorphous, or glass, and also in solvated or hydrated states (Haleblian *et al.*, 1969, 1975; Kühnert-Brandstaetter, 1973; Sohn, 2004). Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystal species. Polymorphism is widely observed in pharmaceutical compounds and continues to be an important issue in drug development because of its impact on the physicochemical properties of drugs (Borka, 1991). It is well recognized that polymorphism and solvate formation affect the various pharmaceutically important physicochemical properties, such as stability, solubility, dissolution rate, crystal habit (shape), tableting behavior (Gruenenberg, 1997; Kuhnert-Brandstaetter, 1973; Sohn, 2004; Sun *et al.*, 2001; Yoshinari *et al.*, 2003). Changes in certain of these physicochemical properties may ultimately affect the bioavailability of the drug (Sohn, 1995; Sohn *et al.*, 2002).

Doxazosin mesylate (Fig. 1) is a quinazoline compound (1-(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-(2, 3-dihydro-1, 4-benzodioxin-2-yl) carbonyl piperazine monomethanesulfonate, $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$), that is a selective inhibitor of the alpha1 subtype of alpha-adrenergic receptors. It was developed as an oral solid dosage form for benign prostatic hyperplasia (BPH) and antihypertensive activity.

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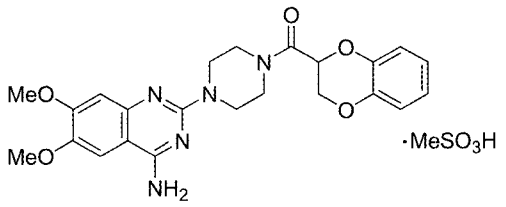

Fig. 1. Chemical structure of doxazosin mesylate

Literature data show that doxazosin mesylate can crystallize in different polymorphic forms. Giridhar *et al.* (Giridhar *et al.*, 2002) described four crystal forms, Form A, Form B, Form C, and Form D. Grcman *et al.* (Grcman *et al.*, 2002) described seven polymorphic modifications of doxazosin mesylate, designed as Form A, Form D, Form E, Form F, Form G., Form H, and Form I.

In the present study, we investigated the polymorphism of doxazosin mesylate. The polymorphs of doxazosin mesylate were characterized by determining powder X-ray diffraction, DSC and TG patterns.

MATERIALS AND METHODS

Materials

Doxazosin mesylate was donated by ChemGen Co., Ltd. (Korea). Other chemicals and solvents were of analytical reagent or special grade.

Preparation of polymorphic modifications

Form 1

Form 1 was donated and used as standard substance, which was always stored at 5-10°C.

Form 2

Form 2 was also the donated one. It was always stored at 5-10°C.

Form 3

A mixture of Form 1 and DMF was stirred and heated for 3 h at 45°C. Then the insoluble material was removed by filtration. The filtrate was cooled to room temperature. The resulting solid was filtered and dried for one week in the desiccator.

In other way, Form 3 was obtained by dissolving Form 2 in 1-propanol. After heating 210 minutes at 45°C, the insoluble material was removed by filtration. And it was dried in silica gel desiccators at room temperature.

Form 4

A suspension of Form 1 in 1-propanol was heated and stirred for 210 minutes at 45°C.

Then the insoluble material was removed by filtration. The filtrate was cooled to -4°C for 3 days. The resulting solid was filtered and dried for one week in the desiccator.

Form 5

A mixture of Form 2 and water was stirred and heated for 210 minutes at 30-45°C. Then the insoluble material was removed by filtration. The filtrate was cooled to room temperature. The resulting solid was filtered and dried for one week in the desiccator.

Form 6

A suspension of Form 2 in water was heated and stirred for 210 minutes at 45°C. Then the insoluble material was removed by filtration. The filtrate was cooled to -4 for 3 days. The resulting solid was filtered and dried for one week in the desiccators.

Form 7

Form 7 was obtained by dissolving Form 1 in DMF at 45°C and allowing the resulting solution to stand at room temperature. And it was dried in silica gel desiccator.

In another method, a suspension of Form 2 in water was heated and stirred for 210 minutes at 45°C. Then the insoluble material was removed by filtration. The filtrate was cooled to -72°C for 3 days. The resulting solid was filtered and dried for one week in the desiccator.

Form 8

A suspension of Form 2 in DMF was heated and stirred for 40 and 250 minutes at 45°C. Then the insoluble material was removed by filtration. The filtrate was cooled to room temperature, the resulting solid was dried for one week in the desiccator.

Form 9

After Form 2 was heated and stirred for 210 minutes in DMF at 45°C, the insoluble material was removed by filtration. The filtrate was cooled to -4°C. And then the resulting solid was filtered and dried at 80°C for 1 week in the desiccator.

Characterization of polymorphic modifications

Powder X-ray diffraction (PXRD)

X-ray powder diffraction (XRPD) patterns were obtained at room temperature on Rigaku DMAX-IIIA (Japan). The isothermal measurement conditions were; target, Cu; voltage, 30 kV, current, 10 mA. The XRD patterns of the samples were compared with regard to peak position and relative intensity, peak shifting, and the presence of lack of peaks in certain angular regions. The 2θ range was 5-35°, step size 0.02°, integration time 10 s/step.

Thermal analysis

Thermal analysis methods used in this study included DSC and TG (Giron, 1995). DSC patterns were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan) with the sealing pan. The temperature was usually scanned from 30 to 300°C at 5°C/min. 5 mg of sample was used for each study. TG analysis was performed on all samples indicated by DSC as being possible solvates or hydrates. TG patterns were recorded with a Shimadzu TGA-50 instrument (Shimadzu, Kyoto, Japan). The temperature was usually scanned from 30 to 200°C at 5°C/min. 5 mg of sample was used for each study.

Transformation of Form 1 and Form 2

Form 1 and Form 2 of doxazosin mesylate were stored in saturated salt solutions of three relative humidities (0%, 51%, and 99%) in desiccators at 20±0.5 for 30 days.

RESULTS AND DISCUSSION

Characterization of polymorphic modifications

X-ray powder diffraction patterns of nine doxazosin mesylate forms are presented in Fig. 2.

The characteristic diffraction peaks of nine doxazosin mesylate forms up to 35° are presented in Table I-IX.

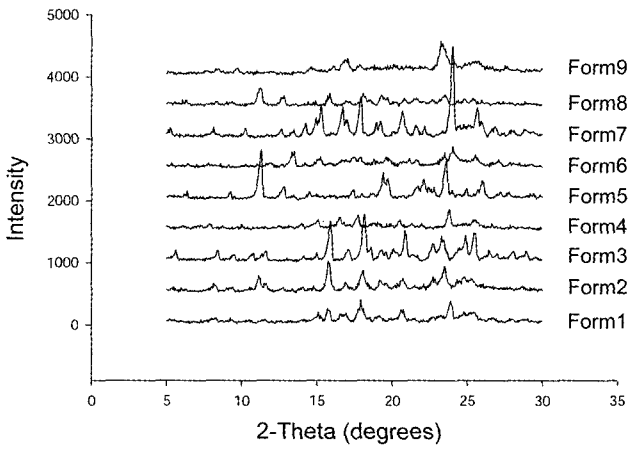

Fig. 2. X-ray powder diffraction patterns of nine doxazosin mesylate forms

Table I. X-ray crystallographic data of Form 1

Angle 2θ	Intensity	D-space
15.1	207	5.8671
15.7	272	5.6442
16.95	202	5.2307
17.9	400	4.9552
19.1	147	4.6465
20.6	255	4.3114
23.9	387	3.7231
25.25	210	3.5270

Table II. X-ray crystallographic data of Form 2

Angle 2θ	Intensity	D-space
8.15	167	10.8482
11.15	300	7.9352
15.75	530	5.6264
16.9	187	5.2461
18.1	375	4.9009
19.2	227	4.6225
20.75	260	4.2806
22.75	282	3.9086
23.5	437	3.7855
24.7	245	3.6043

Table III. X-ray crystallographic data of Form 3

Angle 2θ	Intensity	D-space
5.6	202	15.7808
8.4	200	10.5258
9.55	130	9.2607
10.75	157	8.2295
11.6	195	7.6283
14.15	120	6.2588
15.	160	5.9060
15.9	670	5.5737
17.05	220	5.2003
18.2	780	4.8742
19.3	207	4.5988
20.1	230	4.4175
20.9	525	4.2502
22.7	315	3.9171
23.3	432	3.8176
24.9	437	3.5758
25.45	482	3.4997
26.45	207	3.3696
28.1	182	3.1754
28.95	190	3.0841

Table IV. X-ray crystallographic data of Form 4

Angle 2θ	Intensity	D-space
15.1	195	5.8671
16.55	237	5.3562
17.75	265	4.9967
20.55	200	4.3218
23.85	362	3.7308
25.5	195	3.4930

Table V. X-ray crystallographic data of Form 5

Angle 2θ	Intensity	D-space
6.35	155	13.9185
9.25	142	9.5604
11.3	822	7.8302
12.8	227	6.9157
14.5	140	6.1085
19.45	462	4.5643
22.15	352	4.0131
23.65	672	3.7618
24.95	190	3.5687
26.05	327	3.4205

Table VI. X-ray crystallographic data of Form 6

Angle 2θ	Intensity	D-space
13.5	297	6.5587
15.25	207	5.8098
17.5	210	5.0675
19.6	210	4.5291
23.5	280	3.7855
24.05	380	3.7002
25.55	242	3.4862

Table VII. X-ray crystallographic data of Form 7

Angle 2θ	Intensity	D-space
5.25	175	16.8321
8.15	187	10.8481
10.25	172	8.6298
12.65	157	6.9974
14.25	250	6.2151
15.3	530	5.7909
16.75	515	5.2927
17.9	667	4.9552
19.25	287	4.6106
20.7	452	4.2908
24.05	1492	3.7002
25.7	500	3.4662

Table VIII. X-ray crystallographic data of Form 8

Angle 2θ	Intensity	D-space
11.2	315	7.8998
12.8	197	6.9157
15.85	230	5.5912
18.05	227	4.9143
19.3	202	
20.8	157	4.2704
21.6	152	4.1140
23.55	210	3.7776

Table IX. X-ray crystallographic data of Form 9

Angle 2θ	Intensity	D-space
16.95	332	5.2307
23.3	570	3.8176
25.4	267	3.5065

Table X. Thermal data (melting point) of Form 1-9

Form	Fusion E (KJ/mol)	Melting (Tpeak/°C)
1	37.06	280.22
2	41.29	260.74
3	46.37	282.17
4	30.14	272.85
5	0.09	277.58
6	10.28	238.14
7	36.08	280.61
8	0.06	262.54
9	26.65	249.66

Giridhar *et al.* (Giridhar *et al.*, 2002) described four crystal forms, Form A, Form B, Form C, and Form D. It was reported that Form A was obtained by recrystallization of doxazosin mesylate from ethanol. Form B and Form C were produced from recrystallization of doxazosin mesylate

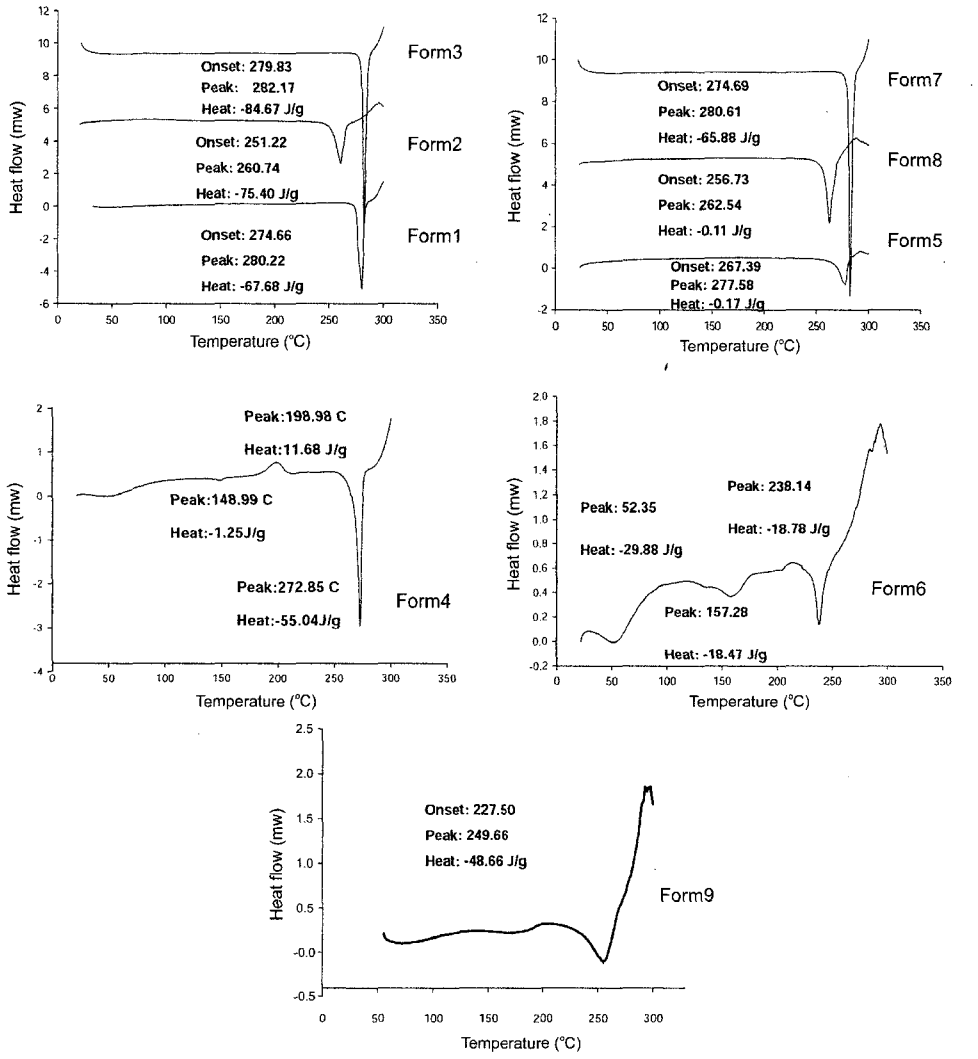

Fig. 3. DSC curves of nine doxazosin mesylate forms

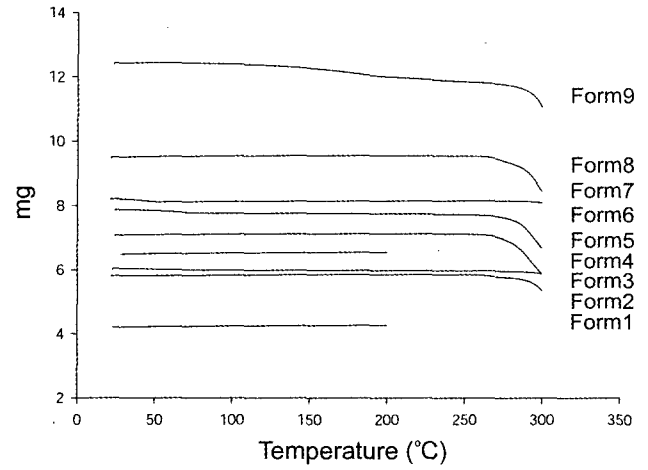

Fig. 4. TGA curves of nine doxazosin mesylate forms.

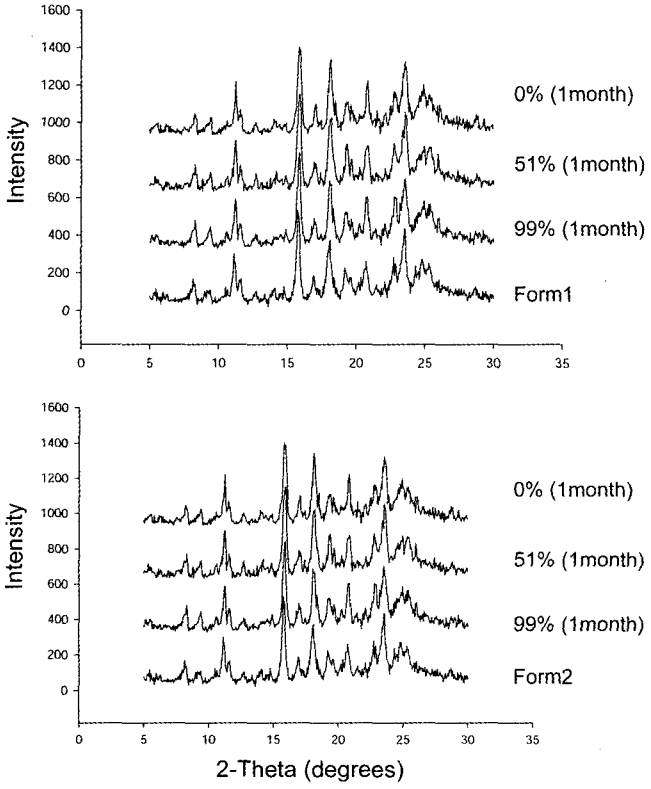

Fig. 5. Effect of relative humidity at room temperature on the transformation of Form 1 and Form 2

from chloroform and water. Form D was obtained by recrystallization of doxazosin mesylate from methanol. Form A was obtained either by crystallization or conversion from Form D. Grcman *et al.* (Grcman *et al.*, 2002) described seven polymorphic modifications of doxazosin mesylate, designed as Form A, Form D, Form E, Form F, Form G., Form H, and Form I. Five crystal forms, Form A, Form D, Form F, Form G, Form H were purchased by the various suppliers. Form E was obtained by thermal method in the mixture. The polymorph E was converted by heating to the more stable Form F. Form I was obtained by thermal method.

X-ray powder diffraction patterns of nine doxazosin mesylate forms are different from those reported in literature (Giridhar *et al.*, 2002; Grcman *et al.*, 2002).

In these literatures only the PXRD patterns of polymorphic forms were given, but their 2θ angles were not presented. And the peaks of polymorphic forms in PXRD patterns are low, because of their low crystallinity. So, the comparison of PXRD data of polymorphic forms is very difficult and practically not possible.

DSC curves of nine doxazosin mesylate forms are presented in Fig. 3. The thermal data of nine doxazosin mesylate forms are presented in Table X. The melting points and fusion energy of nine doxazosin mesylate forms are different from those reported in literature (Giridhar *et al.*, 2002; Grcman *et al.*, 2002). The fusion energy of Form 5 and Form 8 are 0.09 KJ/mol and 0.06 KJ/mol, respectively. This indicates that Form 5 and Form 8 are amorphous. The higher melting point and higher energy of fusion indicate that it is the more thermodynamically stable polymorph in that temperature region.

TG curves of nine doxazosin mesylate forms are presented in Fig. 4. TG curves show no change in mass in the temperature region corresponding to the DSC peaks at 200°C and it is proved that these forms are non-solvated forms.

The transformation of Form 1 and Form 2 is not observed with time and relative humidity (Fig. 5). So, it is confirmed that Form 1 and Form 2 purchased by two different suppliers are physically stable.

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