Pergamon

0731-7085(94)E0016-T

Journal of Pharmaceutical & Biomedical Analysis, Vol. 12, No. 8, pp. 1043–1046, 1994
Elsevier Science Ltd
Printed in Great Britain
0731-7085/94 $7.00 + 0.00

Crystallinity, hygroscopicity and dissolution of moricizine hydrochloride hemihydrate

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Abstract: A typical anhydrous moricizine hydrochloride, an antiarrhythmic agent, is a non-hygroscopic crystalline material. Three lots of moricizine hydrochloride were found to deliquesce within a day at 85% relative humidity, exhibit different X-ray powder diffraction (XRPD) patterns and have more rapid dissolution rate than that of typical anhydrous material. No change in XRPD pattern was observed when the solvent (ethanol) was removed from these lots by heating to 80°C. A two-step water release was observed by thermogravimetric analysis (TGA): a surface water release and a water of hydration release, for these heated samples. The stoichiometry of the water of hydration suggests that it is a hemihydrate. The dissolution rate of the hemihydrate was faster than that of typical anhydrous material. This hemihydrate could be converted to a typical anhydrous material by heating to 90°C. The granules obtained by a simulated wet granulation process on typical lots and typical lots containing up to 20% of hemihydrate exhibited similar physical behaviour to that of typical anhydrous material.

Keywords: *Moricizine hydrochloride; polymorphism; dissolution; hemihydrate.*

Introduction

Moricizine hydrochloride (Fig. 1) is an orally active phenothiazine derivative antiarrhythmic agent with potent local anaesthetic activity and a myocardial membrane stabilizing effect. Electrophysiological studies [1, 2] have demonstrated it to have properties similar to class 1A and 1B antiarrhythmic agents with minimal effects seen on the surface electrocardiogram.

Polymorphs are the same chemical entity having different molecular arrangements within the crystal lattice [3]. The pharmaceutical importance of polymorphism was reviewed by Haleblian and McCrone [4]. The impact of polymorphism on the physicochemical properties [5–7] and bioavailability [8, 9] was demonstrated and is of great concern in the pharmaceutical industry. In this study, three lots of Moricizine hydrochloride found to have different physical properties from those of typical lots of material were investigated by X-ray powder diffraction (XRPD), differential scanning calorimetric analysis (DSC) and thermogravimetric analysis (TGA). The dissolution profiles for these lots and typical lots of material were compared. The impact of the presence of this new hydrated crystalline form in a typical anhydrous crystalline material is discussed.

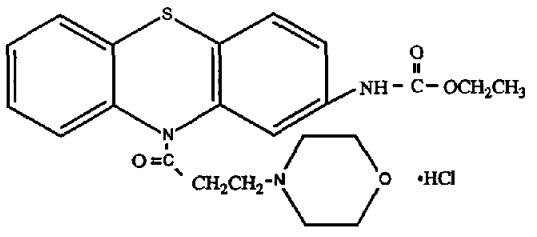

Figure 1
Chemical structure of moricizine hydrochloride.

Experimental

Materials

Moricizine hydrochloride (hydrochloride salt of 2-carbethoxyamino-10-(3-morpholyl-propionyl)-phenothiazine), here referred to as lots A, B, C, D, E, F and G were received from Chem Process R&D in The DuPont Merck Pharmaceutical Company. Lots D, E and F are typical anhydrous material, and lots A, B and C exhibit different physical properties. Lot G is a recrystallized material of lot A.

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Differential scanning calorimetry (DSC)

The thermal analysis instrument DSC model 910 equipped with Thermal Analyzer model 1090 was used. Moricizine hydrochloride was placed in a hermetically sealed pan with its cover reversed and heated under a nitrogen stream from 50 to 250°C at a heating rate of 10°C min^{-1}. Thermal transitions were recorded.

X-Ray powder diffractometry (XRPD)

A modified Philips X-Ray Diffractometer APD 3500 with XRG 3000 generator was used to examine moricizine hydrochloride crystals. A selected receiving slit of 0.2 mm and CuK$\propto$ radiation (40 kV, 30 mA) were employed. The sample was scanned from 4 to 50° (2θ) with 0.02° increments. The intensity of the diffracted radiation was automatically detected every 10 s by a scintillation detector.

Thermogravimetric analysis (TGA)

The thermal analysis instrument TGA model 951 equipped with Thermal Analyzer model 1090 was used. The drug substance was heated under a nitrogen stream from 30 to 170°C at a heating rate of 10°C min^{-1}. The weight loss representing the volatile content was recorded.

The water content was determined by the Karl Fischer titration method. About 10–15 mg of sample was weighed out accurately, and placed in Brinkman model 684 KF coulometer. Water level was recorded for the samples stored at 75% relative humidity at various intervals.

Intrinsic dissolution test was conducted using Wood's Rotating Disk dissolution apparatus [10, 11] at 100 rpm, room temperature (~25°C). The shafts were equipped with dyes, which allowed a constant surface of the moricizine hydrochloride pellet to be exposed to the dissolution medium (0.1 N HCl solution). Moricizine hydrochloride pellets were prepared by pressing 300 mg of the compound with 5000 lb for 5 min. The drug concentrations at various dissolution intervals were analysed using a spectrophotometer at a wavelength of 268 nm.

Granules of moricizine hydrochloride were prepared by adding an appropriate amount (20–25%) of water into moricizine hydrochloride powder and blending with a pestle. The moistened granules were then sieved through a #12 mesh screen and dried at 25°C overnight.

The impact of hemihydrate level on the hygroscopicity of anhydrous material was evaluated by adding 2.5–20% of lot A to the typical material, which was then stored at 85% relative humidity. The water level was monitored by Karl Fischer titration at various time intervals.

Results and Discussion

Moricizine hydrochloride lots A, B and C exhibited a similar XRPD pattern (Fig. 2b) which was different from that of typical material, lot D (Fig. 2a). However, lots A, B and C gave different DSC thermograms (Fig. 3a, b and c), which were different from that of typical lots of material with a melting-decomposition peak temperature of 213–218°C (Fig. 3e). Lots A, B and C contained various levels of residual ethanol (1.25, 1.83 and 2.95%, respectively). After the majority of ethanol was eliminated by heating these three lots of material to 80°C, a similar DSC thermogram (Fig. 3d) and no change in XRPD pattern was observed among them. These results suggest that lots A, B and C have the same crystalline structure, and the differences in DSC thermograms were possibly caused by residual ethanol.

The typical lot (D) was non-hygroscopic and exhibited non-detectable volatile weight loss as determined by TGA. However, lots A, B and C were hygroscopic and deliquesced within a day at 85% relative humidity. The total weight loss upon heating was about 6–7%, suggesting that water as well as solvent are present in

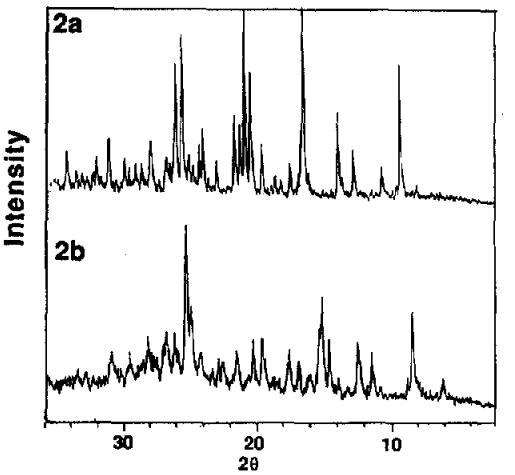

Figure 2
X-ray powder diffraction patterns of moricizine hydrochloride, typical lot D (2a) and lot A (2b).

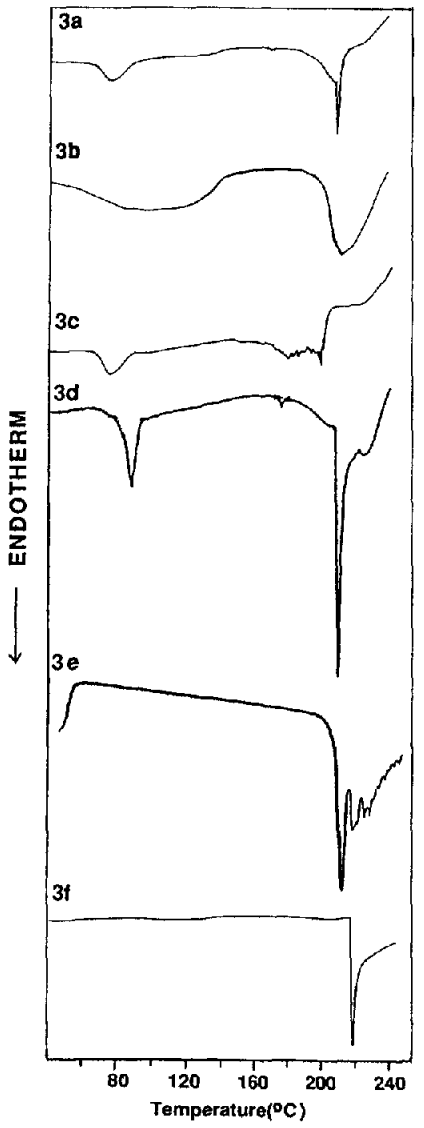

Figure 3
Differential scanning calorimetric thermograms of moricizine hydrochloride, log A (a); lot B (b); lot C (c); lot A heated to 80°C (d); lot D (e); lot A heated to 90°C (f).

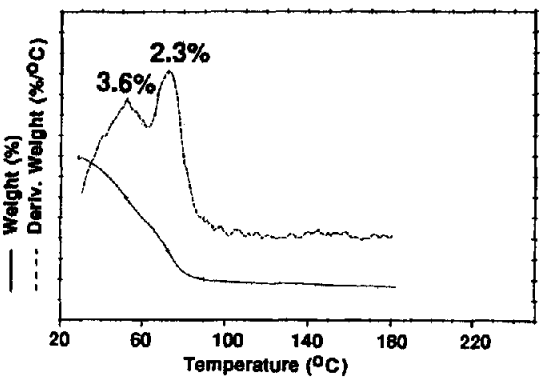

Figure 4
Thermogravimetric profile of moricizine hydrochloride lot A after heating at 80°C under vacuum overnight. A two-step weight loss was observed. The first step represented surface water release (3.6%) and the second step represented the release of water of hydration (2.3%).

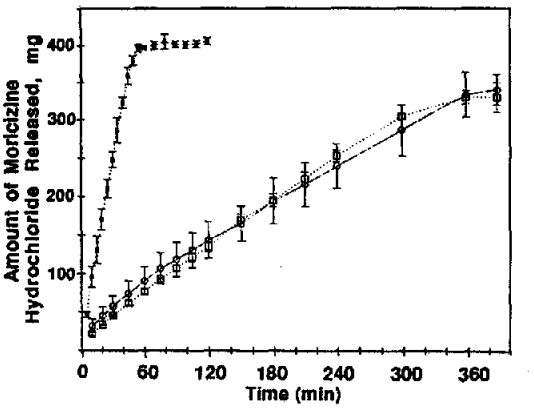

Figure 5
Dissolution profiles of moricizine hydrochloride at 25°C. —○— Typical lot (D); ---□--- reworked lot (G); ---★--- hemihydrate lot (A).

these lots of material. Since these crystals are hygroscopic, they reabsorbed water during the cooling period after heating at 80°C under vacuum and gave a two-steps water release profile by TGA (Fig. 4). The first (from 30 to 65°C) and second (from 65 to 90°C) step weight losses are probably due to the unbound water (~3%) and water of hydration (~2%), respectively. Stoichiometry suggests that 2% water of hydration represents a hemihydrate. Since this hemihydrate exhibited a different XRPD pattern compared to that of typical anhydrous material, it is a polymorphic hydrate.

After lot A was heated in a DSC pan to 90°C and cooled down to room temperature, it gave a typical moricizine hydrochloride thermogram with a DSC melting-decomposition peak temperature of 218°C (Fig. 3f) and exhibited a similar XRPD pattern to that of anhydrous material. It appears that both surface water and water of hydration were released and the crystals converted to the typical anhydrous material after the sample was heated to 90°C.

The intrinsic dissolution profiles for the anhydrous and hemihydrate are shown in Fig. 5. The reworked and the typical lots of material have similar dissolution rate profiles with initial dissolution rate of 1.1 mg min^{-1}. The hemihydrate material exhibits a much more rapid initial dissolution rate (8.0 mg min^{-1}). Generally, a hydrated material pro-

Table 1
Hygroscopicity of moricizine hydrochloride granules stored at 85% relative humidity

Sample	Water content (%)*		
	As is	13 days	24 days
Typical lot E	0.28	0.27	0.33
Typical lot F	0.27	0.26	0.39

*The water content was determined by Karl Fischer titration method.

Table 2
Hygroscopicity of typical anhydrous moricizine hydrochloride mixed with various levels of hemihydrate and stored at 85% relative humidity

Sample†	Water content (%)*			
	As is	1 day	9 days	16 days
2.5%	0.74	ND‡	0.77	0.87
5.0%	0.80	ND	1.02	0.90
10.0%	1.02	0.74	0.87	0.87
20.0%	1.40	1.20	1.08	0.17
Lot A	4.50	liquified		

* Water content was determined by Karl Fischer titration method.
†The samples were the mixtures of typical lot E and hemihydrate lot A at various levels.
‡Not done.

vides slower dissolution rate than anhydrous material [12], which is not the case here. This could be due to a less tightly packed hemihydrate crystals, with weaker hydrogen bonding (β type), than the anhydrous material [3].

The granules, prepared by adding 20–25% water into typical lot of material, remained non-hygroscopic at 85% relative humidity (Table 1), and exhibited a typical DSC thermogram. This result suggests that the wetting process does not convert the material to the hemihydrate form.

The mixtures of typical material and hemihydrate (lot A) at various levels (2.5–20%) are also non-hygroscopic. No significant change in water content (Table 2) and physical appearance was observed over a 16-day period.

In conclusion, the typical anhydrous and hemihydrate moricizine hydrochloride samples have different hygroscopicity, XRPD patterns, DSC thermograms and dissolution profiles. The dissolution rate was faster for this hemihydrate material than for the anhydrous material, which is different from what is normally observed.

Acknowledgements — Determination of ethanol content by Dr Jonathan Green is greatly appreciated.

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[Received for review 12 November 1993; revised manuscript received 24 January 1994]