ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
15 (1996) 131–138

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Short communication

Application of differential scanning calorimetry and X-ray powder diffraction to the solid-state study of metoclopramide

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Received for review 2 August 1995; revised manuscript received 6 February 1996

Keywords: Differential scanning calorimetry; Metoclopramide; Polymorphism; X-ray powder diffraction

1. Introduction

Thermal analysis is one of the most widely used methods for studying the solid state of pharmaceutical substances. Among the methods available, differential scanning calorimetry (DSC) is used for investigating the thermodynamic changes which occur on heating a substance; these comprise polymorphic transitions, melting and desolvation, which can all show endothermic or exothermic peaks on the DSC curves [1–4]. The X-ray powder diffraction (XRD) technique can also be used to study the solid state of pharmaceutical substances [5,6].

In the present work, commercial samples of metoclopramide as the dihydrochloride, the monohydrochloride and the free base [7], were examined using DSC and XRD.

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2. Materials and methods

Metoclopramide samples from Medichem were used as received.

Thermal analyses in a flow of air at atmospheric pressure were conducted using a DS-Polymer calorimeter. Approximately 4 mg samples were weighed directly into aluminium sample pans. The thermal conditions were previously defined in order to study metoclopramide dihydrochloride, monohydrochloride and base under the same conditions. Scans were made from 25 to 200°C at a heating rate of 10°C min^{-1} using standard open pans. A minimum of three runs were performed for each type of metoclopramide: dihydrochloride, monohydrochloride and free base. For calorimetric and temperature calibration, ultrapure indium was used. The experimental conditions were detailed in Table 1.

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PII S0731-7085(96)01812-2

X-ray powder diffraction patterns were obtained by exposing 300 mg of each sample to Ni-filtered Cu Kα radiation in a Philips wide-angle diffractometer over the range 5–70°.

3. Results and discussion

The results of the DSC analyses of metoclopramide dihydrochloride, monohydrochloride and free base are shown in Fig. 1.

The DSC curve of metoclopramide dihydrochloride (Fig. 2) showed two endothermic peaks, one at 118.5°C and the other at 145.4°C, which is due to melting [7]. By means of thermogravimetry (TG), it was verified that the first endothermic reaction was accompanied by a 5% loss of weight (Fig. 3). This proportion of water is the same as that determined by the Karl Fischer method. When a sample of metoclopramide dihydrochloride was heated at 110°C to constant weight and then scanned at 10°C min^{-1}, only the second endothermic peak appeared (Fig. 2b). Thus it can be deduced that the first endothermic reaciton at 118.5°C is due to the evaporation of water of crystallization. Complete removal of this water of crystallization by heating metoclopramide dihydrochloride, led to the recrystallization of the anhydrous form with a melting point of 145–146°C. Table 2 shows the sequence of reactions that occurred on heating metoclopramide dihydrochloride. On reheating a sample that had been previously melted and cooled, no peaks appeared on the DSC curve (Fig. 2c); this result indicates that this substance does not recrystallize after melting since it solidifies as an amorphous substance.

Table 1
Experimental conditions for thermal analysis by DSC

Start temperature (°C)	25
End temperature (°C)	200
Scanning rate (°C min^{-1})	10
Purge gas	Nitrogen
Pan type	Aluminium

Fig. 4 shows DSC curves of metoclopramide monohydrochloride. When the monohydrochloride was heated at 105°C and then scanned, only the second endothermic peak appeared (Fig. 4b); this indicates that the first endothermic peak is due to the evaporation of water of crystallization, as can be seen on the TG curve (Fig. 3). On reheating, no peaks appeared on the DSC curve (Fig. 4c); this means that the monohydrochloride does not recrystallize after melting since it solidifies as an amorphous substance.

The DSC thermogram of metoclopramide base showed two marked endothermic reactions at 130.7 and 148.0°C (Fig. 5). On reheating, only the second peak was apparent (Fig. 5b). After cooling and storing the sample pan for 3 days at room temperature (22°C), the first peak reappeared on the thermogram. This suggested that the first endothermic peak corresponded to a solid–solid transition, whereas the second peak was due to melting. In accordance with published work [8], metoclopramide base occurs in two enantiotropic polymorphic forms with transition occurring at 130°C for Form I (stable at low temperature) to Form II of m.p. 148°C (stable at high temperature).

Fig. 6 shows X-ray powder diffractograms of the three substances studied. The differences in the interplanar spacings, relative diffraction peak intensities and diffraction angles confirm that metoclopramide dihydrochloride, monohydrochloride and free base have different crystalline structures.

4. Conclusions

The DSC thermograms of metoclopramide dihydrochloride, monohydrochloride and the free base are complex. The dihydrochloride does not show polymorphism, anhydrous metoclopramide monohydrochloride shows monotropic polymorphism whereas metoclopramide base shows enantiotropic polymorphism.

The present study illustrates the importance of combining DSC with XRD in the study of the solid state of pharmaceutical substances.

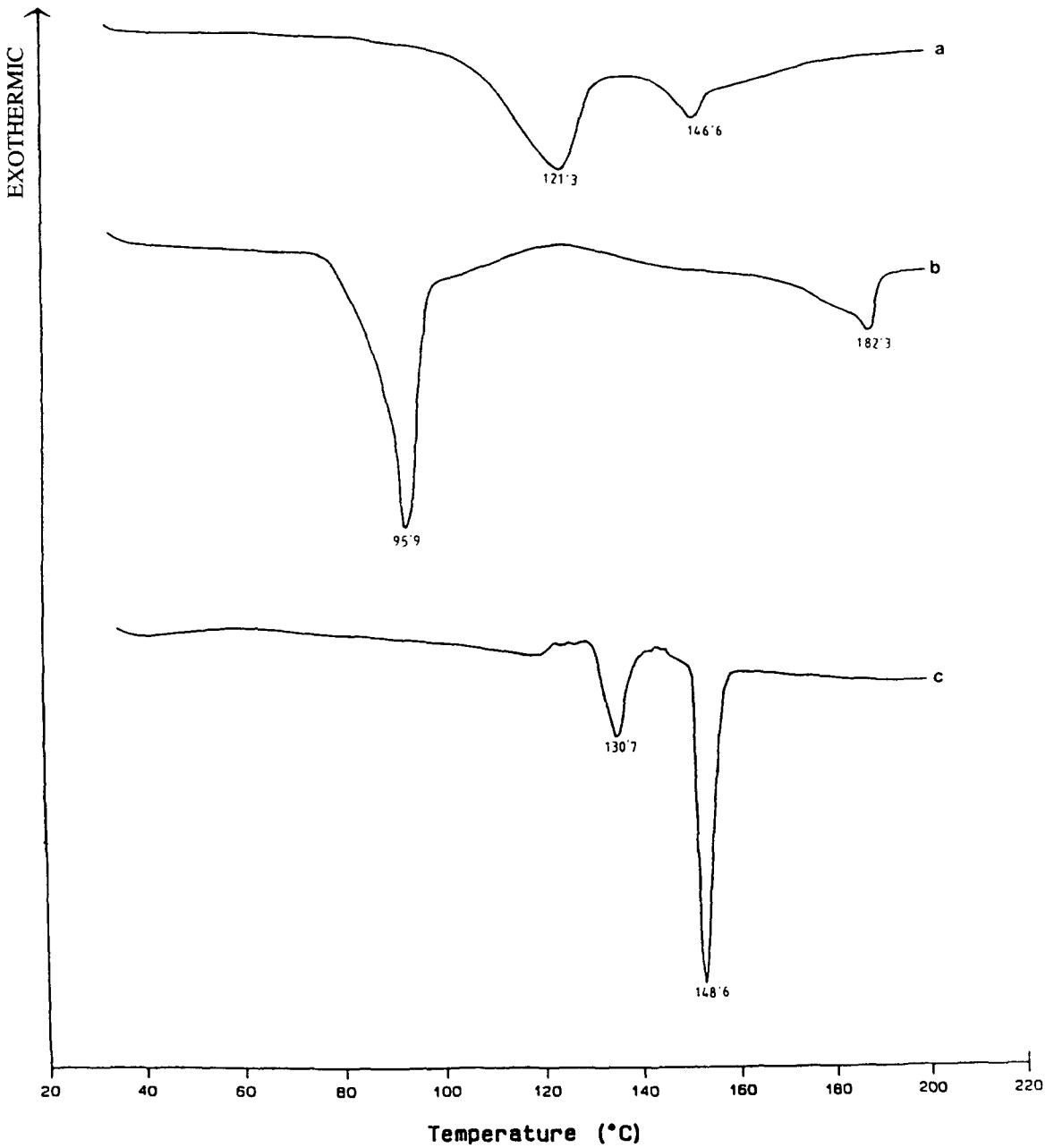

Fig. 1. DSC curves for (a) metoclopramide dihydrochloride (b) metoclopramide monohydrochloride and (c) metoclopramide base

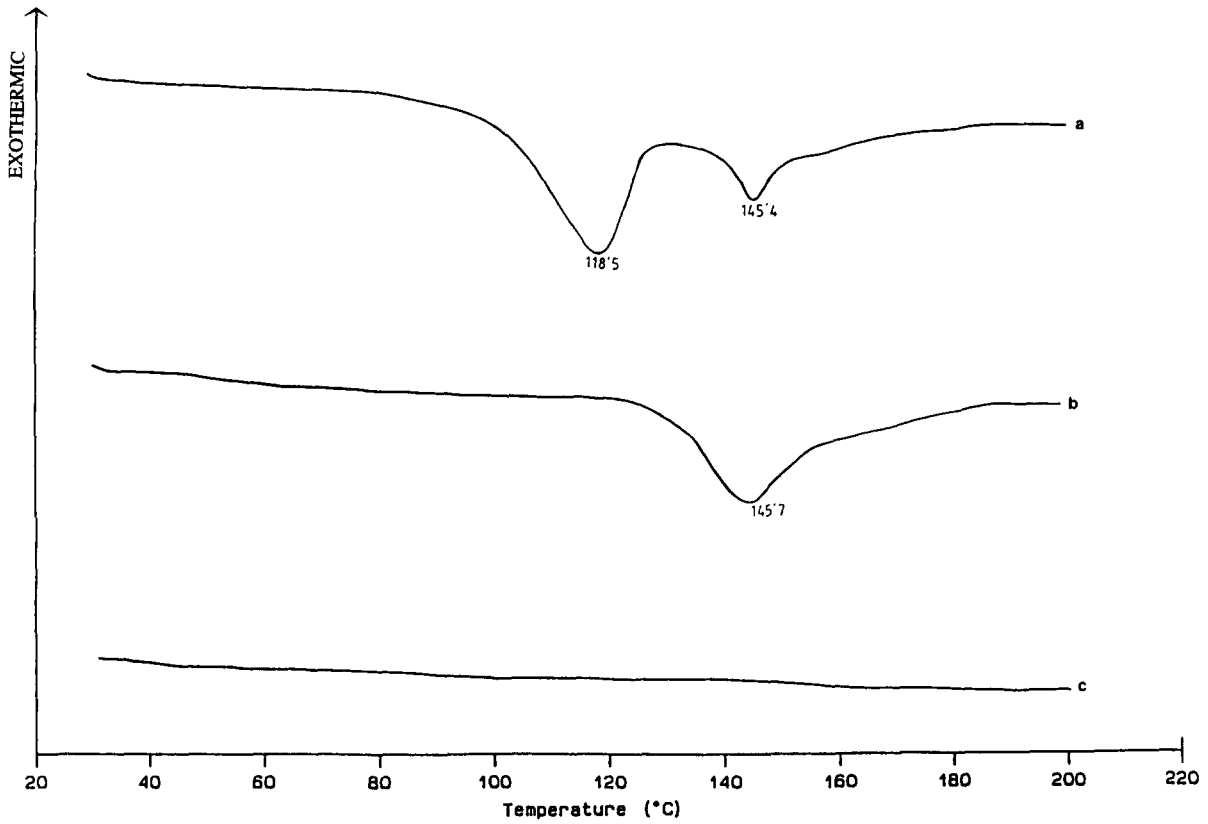

Fig. 2. DSC curves for (a) metoclopramide dihydrochloride (b) preheated at 110°C and (c) reheated.

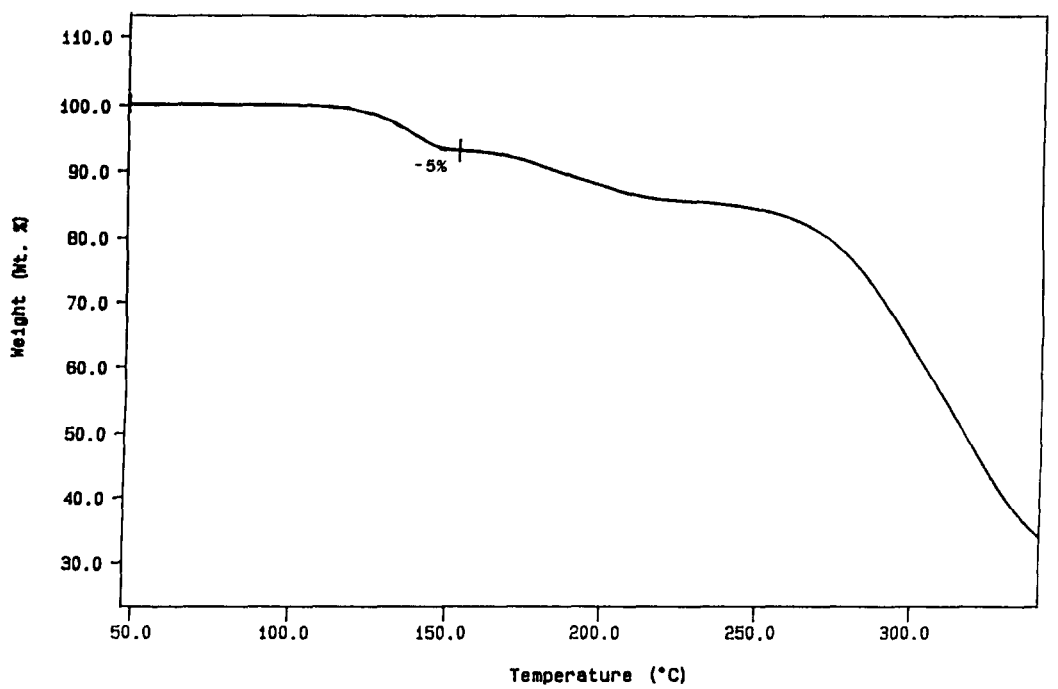

Fig. 3. Thermogravimetric curve for metoclopramide dihydrochloride.

Table 2
Thermal analysis of metoclopramide dihydrochloride

Reaction	T (°C)	ΔH (mcal mg^{-1})
MCP·2HCl·H_2O (solid) → MCP·2HCl (solid) + H_2O (gas)	121.39	32.76
MCP·2HCl (solid) → MCP·2HCl (liquid)	146.66	5.86

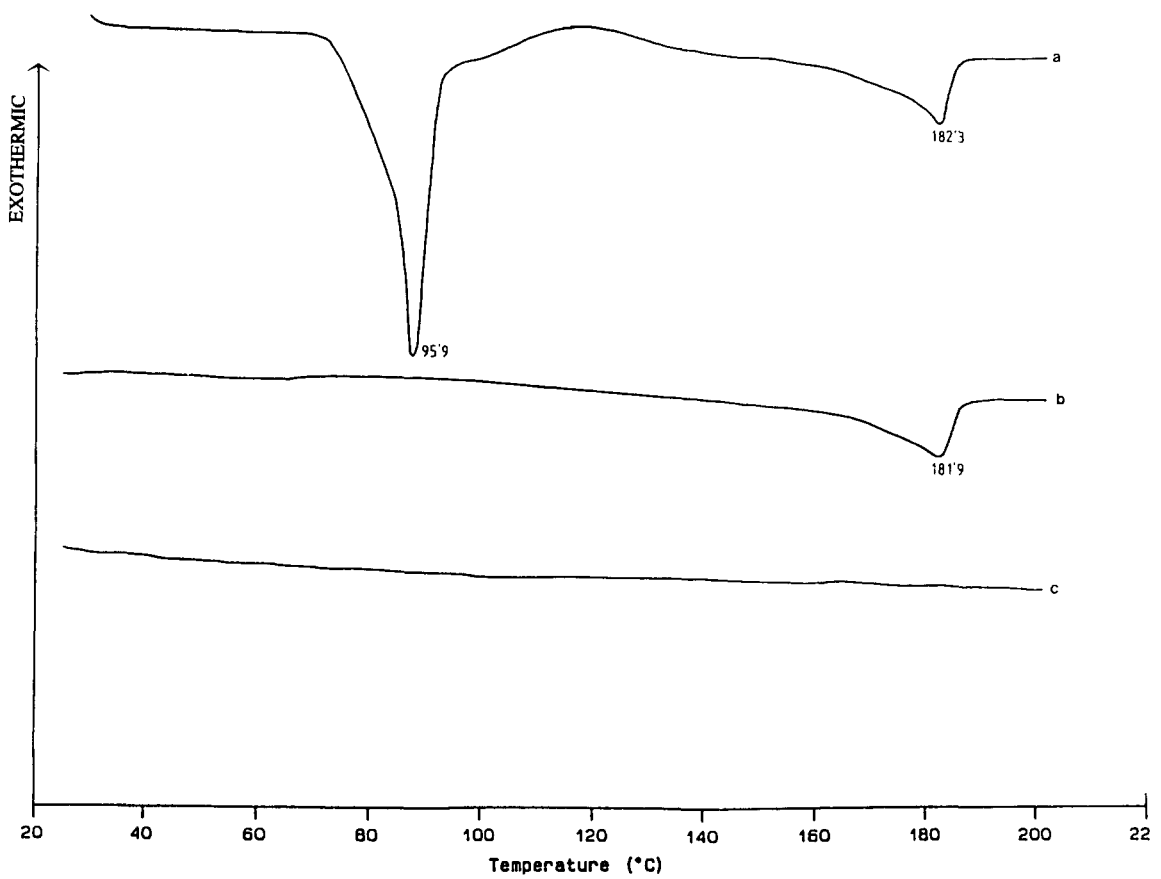

Fig. 4. DSC curves for (a) metoclopramide monohydrochloride (b) preheated at 105°C and (c) reheated.

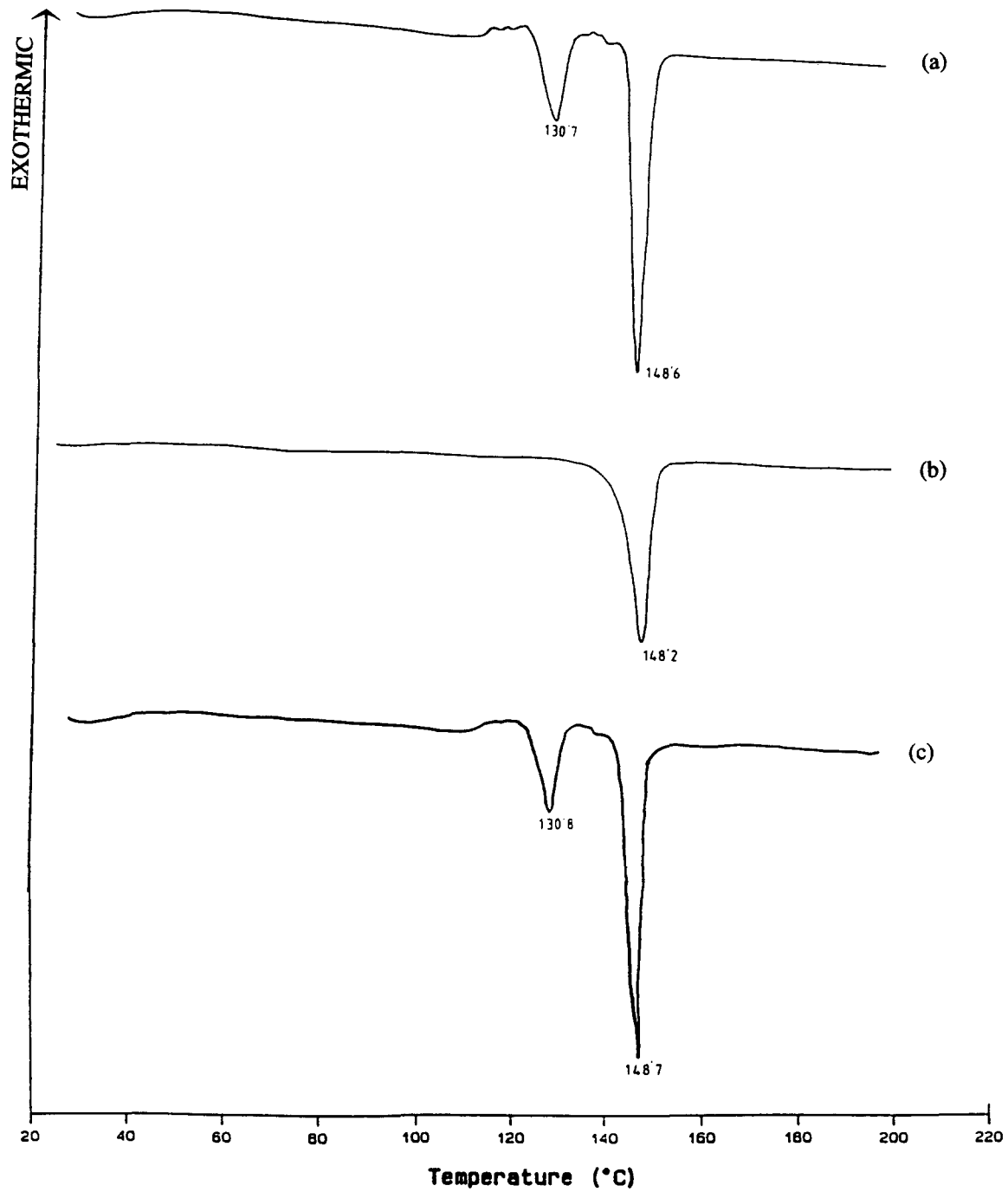

Fig. 5. DSC curves for (a) metoclopramide base (b) reheated and (c) reheated after storage for 3 days at room temperature.

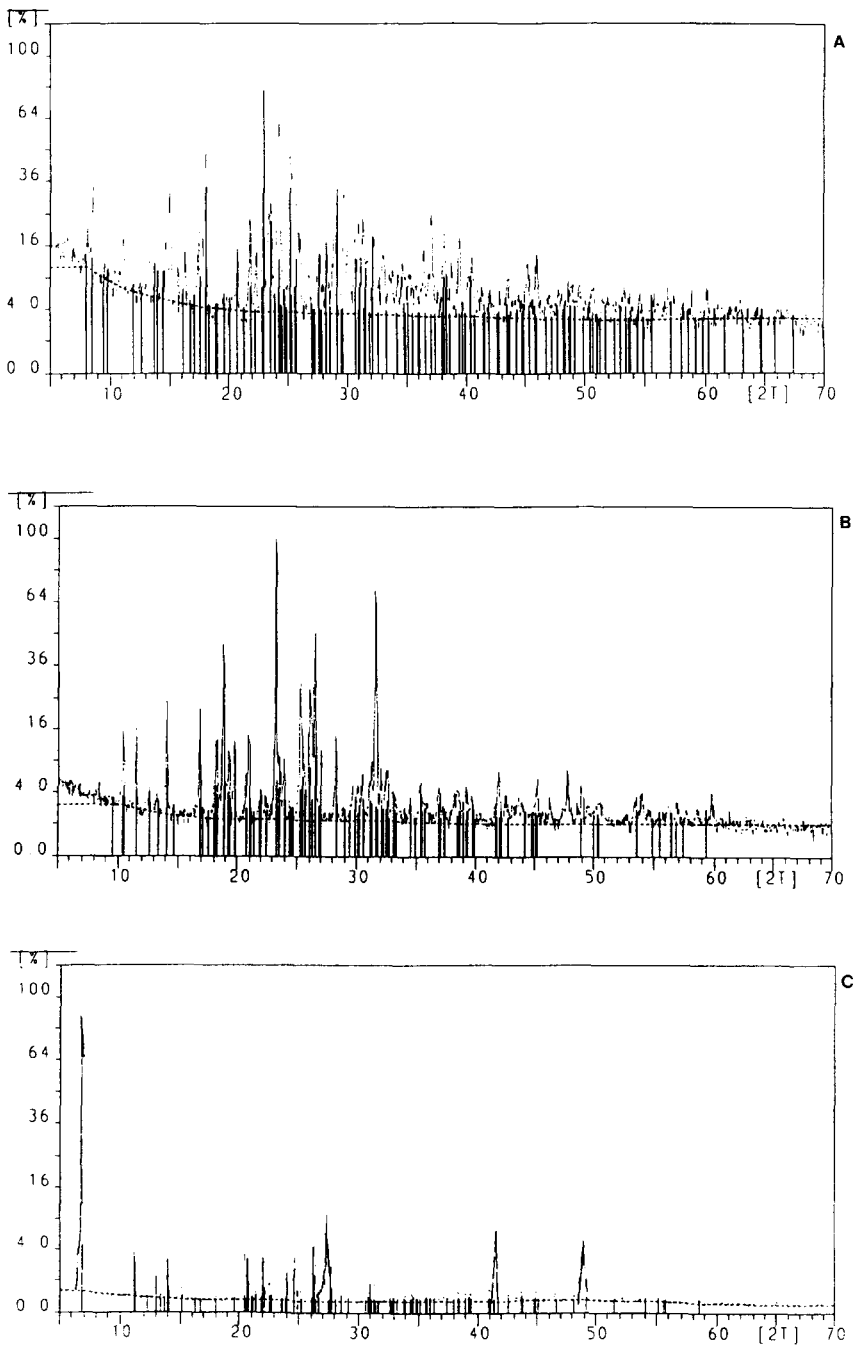

Fig. 6. X-ray powder diffractograms of (A) metoclopramide dihydrochloride, (B) monohydrochloride and (C) base.

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