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Polymorphism in metoclopramide hydrochloride and metoclopramide

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Metoclopramide hydrochloride ($MCPHCl.H_2O$) and metoclopramide base (MCP) have been studied by DSC, thermomicroscopy, X-ray diffraction and infrared spectroscopy. $MCPHCl.H_2O$ does not readily lose water of crystallization either from the solid state or from the melt, but depending on the conditions, dehydration can give rise to two anhydrous polymorphs, MCPHCl/Form I (mp 187 °C) and MCPHCL/Form II (mp 155 °C). Form I crystallizes from the melt of Form II and not by a reversible solid–solid transition. The anhydrous hydrochloride therefore shows monotropic polymorphism where Form I is the stable polymorph and Form II, a metastable polymorph. Thermal analysis of MCP shows that the base exists as two enantiotropic polymorphs. The transition of the form stable at room temperature (MCP/Form I) to the form stable at high temperatures (MCP/Form II mp 147 °C) occurs extremely rapidly at 125 °C but the reverse process requires one month at room temperature (≈22 °C). It is therefore possible to compare the X-ray diffraction powder patterns and infrared spectra of MCP Forms I and II.

The thermal behaviour of metoclopramide hydrochloride ($MCPHCl.H_2O$) has been examined using hot stage microscopy by Kuhnert-Brandstatter et al (1978). Its crystal structure has been determined, using single crystal X-ray diffraction, by Blaton et al (1980), and that of metoclopramide base (MCP) by Cesario et al (1981) and by Shin et al (1983).

In the present work, commercial samples of metoclopramide hydrochloride hydrate (BP) and its free base have been examined using differential scanning calorimetry (DSC), hot stage microscopy, powder X-ray diffraction and infrared spectroscopy with particular reference to the identification of polymorphic forms.

MATERIALS AND METHODS

$MCPHCl.H_2O$ and MCP both from Secifarma were used as received: assay by the method of BP 1982 gave 99·6% and 100·4% for $MCPHCl.H_2O$ and MCP, respectively.

Thermal analyses in a flow of nitrogen at atmospheric pressure were made using a Perkin Elmer differential calorimeter (DSC 1B); a Du Pont 1090 with a DSC module was used for scans under reduced pressure. Approximately 5 mg samples were weighed on a Cahn Gram electrobalance directly into Perkin Elmer aluminium sample pans. Scans were made at various rates using standard open pans, sealed pans and sealed pans with a 0·1–0·2 mm pinhole. A minimum of three runs was made for each set of experimental conditions and standard indium scans were made using the same scanning rates and sensitivities. The sample scan was then overlaid on the appropriate indium scan with the indium leading edge passing through the peak maximum. The temperature at which each phase change occurred was read where the indium leading edge intersected with the sample base line (Perkin Elmer Thermal Analysis Newsletter No. 5). Vaporization and recrystallization peaks tended to be broad, and the range of temperatures at the peak is reported for these phase changes. Thermomicroscopic analyses were made using a Mettler FP2 hot stage, and the samples, mounted either dry or in mineral oil, were examined using transmitted or polarized light.

Powder X-ray diffraction patterns were obtained by exposing 300 mg of each sample to Ni-filtered CuKα radiation (40 kV, 15 mA) in a Philips wide angle diffractometer over a range of 2θ from 10° to 60°.

Infrared spectra were obtained using a Unicam SP 1000 spectrophotometer using either compressed discs containing about 2–3 mg of sample in 200 mg of dried potassium bromide, or a mull in mineral oil.

RESULTS AND DISCUSSION

The results of the DSC thermal analysis of $MCPHCl.H_2O$ are summarized in Table 1. Three distinct thermograms, designated 1–3, were obtained, depending on experimental conditions such as the type of sample pan, the scanning rate and pressure. In all three types of sample pan, at scanning rates of 5 °C min^{-1} and faster, one endothermic reaction with no weight loss was

Table 1. Thermal analysis of metoclopramide hydrochloride.

Thermogram	Pan	Rate °C min^{-1}	Peak	Reaction	Temp.[a] °C
1	A, B, C	5–20	1.	MCPHCl.H_2O (solid) → MCPHCl.H_2O (liquid)	90–94[b]
2a	A, C	5	1.	MCPHCl.H_2O (solid) → MCPHCl.H_2O (liquid)	90–94[b]
				MCPHCl.H_2O (liquid) → MCPHCl (I) + H_2O (gas) (heat at 105 °C to remove water of crystallization)	
			5.	MCPHCl (I) → MCPHCl (liquid)	186–188
2b	A, B, C	0·625–2·5	1.	MCPHCl.H_2O (solid) → MCPHCl.H_2O (liquid)	90–94[b]
	A, B, C		2.	MCPHCl.H_2O (liquid) → MCPHCl (I) + H_2O (liquid)	98–102P
	A, C		5.	MCPHCl (I) → MCPHCl (liquid)	186–188
3	D	1–10[c]	1.	MCPHCl.H_2O (solid) → MCPHCl (liquid) + H_2O (gas)	73–75P
			2.	MCPHCl (liquid) → MCPHCl (II)	85–89P
			3.	MCPHCl (II) → MCPHCl (liquid)	154–156
			4.	MCPHCl (liquid) → MCPHCl (I)	156–158P
			5.	MCPHCl (I) → MCPHCl (liquid)	186–188

A = standard pan: B = sealed pan; C = sealed pan with small pinhole; D = as A but under a vacuum of ≃ 130 Pa.
[a] Intersection of indium leading edge with sample base line (see text), except for broad peaks, P, where the temperature is the range of the peak maxima.
[b] Using A, the peak broadened, often with a shoulder, due to partial vaporization of water.
[c] Temperatures given are for scans under vacuum at 1 °C min^{-1} from 30–100 °C followed by cooling and then scanning at 5 °C min^{-1} from 30–200 °C under nitrogen.

obtained at 90–94 °C (Thermogram 1). Continued heating to higher temperatures gave an unstable base line, and liquid was often observed on the lid of the standard pans. Hot stage microscopy showed that the endotherm at 90–94 °C corresponded to the melting of the monohydrate, while the absence of bubbles when the crystals were heated in mineral oil, confirmed that melting occurred without concurrent evaporation of water of crystallization.

When MCPHCl.H_2O in standard pans or sealed pans with a pinhole was heated at 105 °C in the DSC to constant weight, then scanned at 5 °C min^{-1}, a second endotherm appeared at 186–188 °C (Thermogram 2a, peak 5). Although peak 5 was also obtained when these pans were scanned from room temperature at rates of less than 5 °C min^{-1}, peak 1 was followed immediately by an exothermic reaction, presumably due to the recrystallization of anhydrous MCPHCl at these slow scanning rates (Thermogram 2b, reaction 2). Evaporation of water of crystallization from the melt was not necessary for this recrystallization since (a) reaction 2 occurred in sealed sample pans from which water vapour could not escape, and (b) the decrease in weight using standard pans after reaction 2 was less than that required for the loss of one molecule of water. However, unless most of the remaining water was vaporized before about 180 °C, no final melting endotherm was subsequently observed. Thus, peak 5 was missing when sealed pans were used.

Complete removal of the water of crystallization by scanning MCPHCl.H_2O in standard pans under vacuum led to the recrystallization of an anhydrous form with a melting point of 154–156 °C (Thermogram 3, reaction 3). Melting was followed immediately by recrystallization (reaction 4) and a final melting at 186–188 °C. Heating under vacuum shifted reaction 1 to lower temperatures with peak broadening. Complete removal of the water of crystallization was confirmed gravimetrically by weighing the sample pan after peak 1. The stability of the DSC base line and the definition of peaks 3–5 was markedly improved if vacuum was used only up to the recrystallization reaction (peak 2) and the scan then continued under nitrogen in the normal manner.

The sequence of reactions given in Table 1, Thermogram 3, was confirmed by hot stage microscopy. Recrystallization from a melt of MCPHCl.H_2O occurred after holding at 120 °C to evaporate the water of crystallization and then cooling. The resulting spherulites melted at 150 °C and immediately recrystallized to a form which melted at 181 °C. Together with the DSC thermograms, this suggests that the higher melting point form of MCPHCl (Form I) is produced from a melt of MCPHCl.H_2O under conditions which promote slow recrystallization, whereas the lower melting point form of MCPHCl (Form II) is formed as a result of rapid recrystallization from the dehydrated melt. Thermogram 3 shows that Form I crystallizes from a melt of Form II and not by a reversible solid–solid transition. It is concluded that anhydrous MCPHCl shows monotropic polymorphism, where

Form I is the stable and Form II a metastable polymorph.

Attempts were made to isolate Forms I and II. The former (mp 187 °C) was readily prepared either by heating MCPHCl.H_2O on a boiling water bath to constant weight or by heating in a vacuum oven at 90 °C until bubbling ceased. Heating at lower temperatures under vacuum caused only partial dehydration and recrystallization of a mixture of Forms I and II (see later). Attempts to recrystallize Form II from solutions of Form I in various solvents were unsuccessful. DSC thermograms of the crystals recovered from acetone suggested a MCPHCl acetone solvate which desolvated between 70–90 °C and then recrystallized as Form I; crystals from chloroform desolvated at 85 °C leaving a mixture of Forms I and II. The solid which recrystallized from both MCPHCl.H_2O (partially dehydrated by heating in vacuo) and the desolvated chloroform solvate, was identified by thermomicroscopy as a mixture of the metastable and stable forms in which not all the crystals melted between 154–156 °C with unmelted crystals clearly acting as seeds for the rapid recrystallization of Form I (mp 187 °C). Although the metastable polymorph Form II was not isolated, other metastable polymorphs of MCPHCl undoubtedly exist, since the DSC Thermogram of an acetone solvate recrystallized from MCPHCl.H_2O (to be distinguished from the solvate obtained from an acetone solution of MCPHCl described above) showed the existence of a third polymorphic form (mp 142 °C) followed by recrystallization to Form II (mp 155 °C) and finally to Form I (mp 187 °C).

MCPHCl.H_2O does not readily lose its water of crystallization either from the solid or from the melt. This is shown by thermomicroscopic analysis and from the observation that on scanning to 105 °C at 10 °C min^{-1} in a standard pan and then holding the temperature constant, about 4 h was required to evaporate completely the water of crystallization; on continuing the scan, the Form I melting endotherm appeared at 186–188 °C. Furthermore, there was no weight loss on storing MCPHCl.H_2O in a desiccator over phosphorus pentoxide; conversely, MCPHCl/Form I did not rehydrate when stored at 25 °C at controlled relative humidities. At rh $\geq$ 66% however, Form I turned a bright yellow-green colour within 24 h, indicating a chemical reaction. Similarly, MCPHCl.H_2O showed a less marked colour change after 24 h at rh = 66%. No attempt was made to identify the chemical decomposition process.

Recent studies (Mitchell & Down 1984) have shown that, after compaction in a tablet press, several drug substances, including MCPHCl.H_2O, undergo extensive recrystallization on the tablet surface and at crystal interfaces. It was suggested that compaction leads to the creation of lattice defects accompanied by an increase in thermodynamic activity and that crystal growth occurs as a result of the decrease in surface free energy necessary to restore equilibrium.

A DSC thermogram in standard pans of material scraped from the surface of a freshly compacted tablet compressed without excipients or lubricant, and from a similar compact stored for 3 months at 25 °C over phosphorus pentoxide, showed reactions 1 through to 5. By contrast, uncompacted material under the same experimental conditions gave reaction 1 only (Table 1). DSC thermograms of MCPHCl.H_2O ground for varying times in an electromagnetic micro-pulveriser (Fritsch Pulverisette 0) with an agate mortar and ball and sieved to give the +100 −140 sieve fraction for analysis, showed reactions 1 and 2. Marked broadening was apparent in peak 1 with the dehydration/melting endotherm starting as low as 62 °C. At higher temperatures, the base line became unstable, although with occasional samples, there was evidence for the metastable and stable polymorphic forms. It is suggested that, by increasing the number of crystal defects, mechanical stress accelerates the dehydration reaction and thereby induces recrystallization of the anhydrous polymorph or polymorphs. The effect of mechanical stress on solid–solid transformations has not been widely reported for drugs although phase transformation on compression and grinding have been noted for succinylsulphathiazole hydrates and for phenylbutazone polymorphs by Rankell (1969) and Ibrahim et al (1977), respectively.

The DSC thermogram of MCP base showed two marked endothermic reactions at 124–126 °C and 146–148 °C. An exothermic reaction occurred on cooling, but on reheating, only the second peak was apparent. After cooling and storing the sample pan for 3 days at room temperature ($\simeq$22 °C), the first peak reappeared in the thermogram. Thermomicroscopy showed that the first endothermic peak corresponded to a solid–solid transition, while the second endotherm was due to melting. It is concluded that MCP base occurs in two enantiotropic polymorphic forms with transition occurring at 125 °C from Form I (stable at low temperature) to Form II, mp 147 °C (stable at high temperature). The transition MCP/Form I $\rightarrow$ MCP/Form II was extremely rapid, and the melting point of Form I could not be determined

even at very fast heating rates. However, the reverse transition, Form II → Form I, takes place relatively slowly, and depends on the previous heat treatment of the sample. After melting and cooling, the DSC results indicate that the transition Form I → Form II takes about 3 days at room temperature. However, when Form I was heated to between 125 °C and 147 °C (i.e. above the transition temperature, but below the melting point of Form II), then cooled and stored at room temperature, the transition Form II → Form I required over 1 month for completion, i.e., at room temperature, the transition Form II → Form I occurs far more rapidly when Form II has crystallized from a melt than when it has been formed by a solid–solid transition. It was possible therefore to obtain the X-ray diffractogram and infrared spectrum of MCP/Form II by carrying out the analyses immediately after heating a sample of MCP/Form I in a hot air oven at 135 °C and then cooling.

Interplanar spacings and relative intensities of the ten most intense X-ray diffraction peaks of MCPHCl.H_2O, MCPHCl/Form I (mp 187 °C), MCP/Form I (transition temperature 125 °C) and MCP/Form II (mp 147 °C) are given in Table 2. The differences in interplanar spacings confirm that MCP Forms I and II are polymorphic.

Table 2. X-ray powder diffraction data for 10 most intense peaks.

MCPHCl.H_2O		MCPHCl		MCP (I)		MCP (II)	
d[a]	I/Io[b]	d	I/Io	d	I/Io	d	I/Io
3·33	89	3·10	23	2·89	18	3·30	21
3·40	35	3·24	24	3·23	47	3·44	68
3·46	17	3·44	40	3·40	100	3·48	29
3·49	100	3·50	49	3·61	42	3·60	100
3·81	35	4·09	39	3·70	35	4·21	18
4·46	39	4·66	37	4·03	59	4·33	31
4·59	25	5·46	19	4·29	68	4·46	88
4·69	66	6·19	22	6·32	61	5·06	62
5·24	45	6·65	100	6·80	26	5·12	61
6·23	58	7·13	38	7·89	76	6·91	15

[a] d = Interplanar spacing Å.
[b] I/Io = Relative intensity %.

The infrared spectra of MCP/Forms I and II were identical except that the spectra of the latter showed the appearance of an additional band at 3480 cm^{-1}, indicating less hydrogen bonding in the form metastable at room temperature compared with MCP/Form I.

Further evidence for polymorphism was the observation that dissolution and recrystallization occurred on adding a saturated solution of MCP/Form I in xylene to Form II on a microscope slide due to the greater solubility of Form II at room temperature whereas no dissolution occurred on adding the saturated solution to crystals of the original material, i.e. MCP/Form I.

CONCLUSIONS

The DSC thermograms of MCPHCl.H_2O are complex, due to the recrystallization of either a stable anhydrate alone or in admixture with a metastable monotropic anhydrous polymorph, depending on the scanning conditions.

The commercial MCP base was the room temperature stable form, Form I.

Anhydrous metoclopramide hydrochloride, MCPHCl, shows monotropic polymorphism while the base, MCP, shows enantiotropic polymorphism.

The present study illustrates the importance of combining DSC under a variety of experimental conditions with thermomicroscopy to identify the nature of the phase changes.

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