Journal of Thermal Analysis and Calorimetry, Vol. 56 (1999) 1317-1322

DSC SCREENING OF POTENTIAL PROCHLORPERAZINE-EXCIPIENT INTERACTIONS IN PREFORMULATION STUDIES

M. E. Brown, E. M. Antunes, B. D. Glass, M. Lebete and R. B. Walker

Department of Chemistry, Rhodes University, Grahamstown, 6140 South Africa

Abstract

Differential scanning calorimetry was used to examine the thermal behaviour of mixtures of the drug prochlorperazine with standard excipients, to assess potential interactions, and of mixtures with cyclodextrins, to investigate inclusion complexation which could increase the photostability of the drug. For most of the excipients (magnesium stearate, stearic acid, Explotab®, Ac-Di-Sol®, Encompress® and Ludipress®, lactose and Starch 1500) disappearance or broadening of the melting endotherm of the drug indicated interactions. Lubritab® was the only 'inert' excipient tested. Mixtures of prochlorperazine and the cyclodextrins gave incomplete inclusion complexation as shown by only partial disappearance of the melting endotherm of the drug.

Keywords: cyclodextrins, drugs, DSC, excipients, prochlorperazine

Introduction

During the development of a solid dosage form, assessment of possible incompatibilities between a drug and different excipients is an important part of the preformulation stage prior to large scale development trials. Excipients are required to facilitate administration, to promote consistent release and bioavailability of the drug, and to protect the active ingredient from the environment. Even though excipients are usually regarded as medically inert, physical and chemical interactions with drugs are commonplace [1, 2]. Techniques for screening drug-excipient mixtures for compatibility include: a) isothermal stress testing [3] and b) thermal analysis using DSC or DTA [4, 5]. Thermal analysis has the advantage over conventional isothermal stress testing in that long-term storage of mixtures and chromatographic analysis are not required and only a few milligrams of sample are needed per individual experiment. Results obtained by DSC screening have, however, been criticized as being inconclusive [6–9] because moisture stress testing is usually not included and the temperatures and heating rates used are not characteristic of normal storage conditions so there is difficulty in interpreting and extrapolating the thermal results. DSC should thus be used in conjunction with other techniques [3, 10, 11]. In this paper, only preliminary DSC screening is reported [12].

1418–2874/99/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

Prochlorperazine is a member of the piperazine subclass of phenothiazines (used as an anti-emetic) and is sensitive to light-induced oxidative degradation in the solid state and in solution [13]. Because of this potential instability, the purpose of this study was to examine the thermal behaviour of the drug (in the form of prochlorperazine mesylate) in mixtures with standard tabletting excipients to assess possible drug-excipient interactions, and (in the form of prochlorperazine maleate) in mixtures with β- or γ-cyclodextrin to explore inclusion complexation which could result in photoprotection of the prochlorperazine salt.

Experimental

Equipment

A Perkin Elmer DSC 7 differential scanning calorimeter was used. Samples (2–8 mg) were weighed into standard aluminium pans with lids and heated in flowing nitrogen at 10°C min^{-1} over the range 50 to 300°C.

Materials

Prochlorperazine mesylate was supplied by Intramed, Port Elizabeth, South Africa, prochlorperazine maleate by Lennon Ltd, β-cyclodextrin by Sigma Chemicals, and γ-cyclodextrin by Cyclolab, Budapest. The excipients (USP or BP grade), grouped according to their main tabletting function were as follows.

Diluents: lactose, modified lactose (Ludipress®), croscarmellose sodium (Ac-Di-Sol®), microcrystalline cellulose (Avicel PH101®, Avicel PH102®, Emcocel®), dextrose-combination-maltose (Emdex®), different grades of methylcellulose (Methocel®: A4M, A15LV, E4M, E5, E5M, E10M CR, E15LV, E50LV, K4M, K4M CR, K15M CR, K100LV CR and K100M CR), dibasic calcium phosphate (Encompress®) and pregelatinized starch (Starch 1500®),

Lubricants: magnesium stearate, sodium lauryl sulphate, stearic acid, hydrogenated vegetable oil (Lubritab®),

Disintegrants: sodium starch glycolate (Explotab® and Primojel®).

Sample preparation

Physical mixtures (1:1 molar ratios) of the salts of the drug and the cyclodextrins were gently ground in a mortar as dry powders and stored in dark airtight containers. Further quantities were kneaded in a mortar for 30 min with 50% aqueous ethanol to form a paste and then dried for 24 h at 45°C under reduced pressure and stored as above.

Preliminary screening was done using mixtures of prochlorperazine mesylate with the other excipients in 1:1 mass ratios. Those excipients that showed the least interactions were then selected and combined in a 3:3:4 (drug:lubricant:diluent) mass ratio for further screening. Mixtures were prepared by blending approximately 100 mg of the powders in a glass vial for 20 min using a Gallenkamp shaker.

The final formulations for testing were prepared as tablets, containing 25:4:71 mass ratios of drug:lubricant:diluent, using direct compression as opposed to wet granulation. The lubricant was only added before compression.

Results and discussion

The DSC curve for prochlorperazine mesylate on its own (Fig. 2, curve a) showed a broad endotherm below 100°C characteristic of removal of adsorbed moisture, and a sharp melting endotherm with extrapolated peak onset temperature at 240°C. The trace for prochlorperazine maleate (Fig. 1, curve c) shows a more complex melting endotherm with extrapolated peak onset temperature at about 210°C. The DSC curve for β-cyclodextrin (Fig. 1, curve a) is in agreement with reported behaviour [14] with loss of water up to 160°C and an endotherm at 220°C due to a reversible phase transformation. Melting, with decomposition, is observed at about 300°C. The trace for γ-cyclodextrin (Fig. 1, curve b) is similar but is without the transformation endotherm

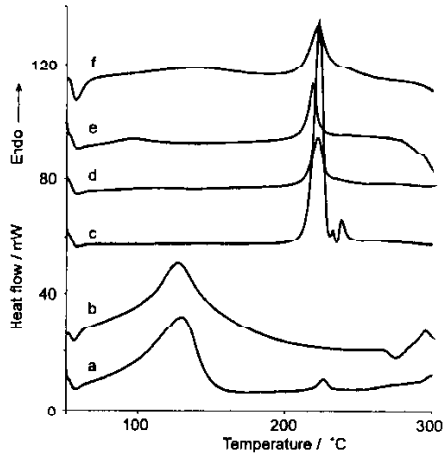

Fig. 1 DSC traces for prochlorperazine maleate, the cyclodextrins, and their mixtures. a – β-cyclodextrin; b – γ-cyclodextrin; c – prochlorperazine maleate; d – prochlorperazine maleate-β-cyclodextrin physical mixture; e – prochlorperazine maleate-β-cyclodextrin kneaded mixture; f – prochlorperazine maleate-γ-cyclodextrin

The physical mixture of prochlorperazine maleate and β-cyclodextrin (Fig. 1, curve d) shows a decreased endothermic contribution (65%) from melting (at an unaltered temperature) of the proportion of drug. After the kneading treatment (Fig. 1, curve e), this endothermic contribution was 61% and the melting temperature was slightly decreased. A similar mixture with γ-cyclodextrin (Fig. 1, curve f) resulted in an endothermic contribution of only 40%. The decrease in the endotherm, without complete disappearance, is an indication that partial inclusion complexation of the drug in the cyclodextrins has occurred. The greater decrease observed for γ-cyclodextrin is attributed to the larger cavity and thus superior inclusion complexation. These conclusions were confirmed by X-ray diffraction studies [15].

The other excipients when heated separately showed a variety of behaviours. Comparison could be made on the basis of both their thermal behaviour and their

pharmaceutical function. Those which showed no significant thermal events in the range 50 to 300°C were croscarmellose sodium (Ac-Di-Sol), microcrystalline cellulose (Avicel PH101, Avicel PH102, Emcocel), the different grades of methylcellulose (Methocel: A4M, A15LV, E4M, E5, E5M, E10M CR, E15LV, E50LV, K4M, K4M CR, K15M CR, K100LV CR and K100M CR) and pregelatinized starch (Starch 1500). When these excipients were tabletted with prochlorperazine mesylate, the melting endotherm of the pure drug (onset approximately 240°C) was broadened and shifted to slightly lower temperatures. Stearic acid melts at 70°C dissolving the drug so that there was no separate melting endotherm.

The individual DSC traces of magnesium stearate, sodium lauryl sulphate, dextrose-combination-maltose (Emdex), sodium starch glycolate (Explotab and Primojel), and dibasic calcium phosphate (Encompress) all showed significant thermal events (Fig. 2).

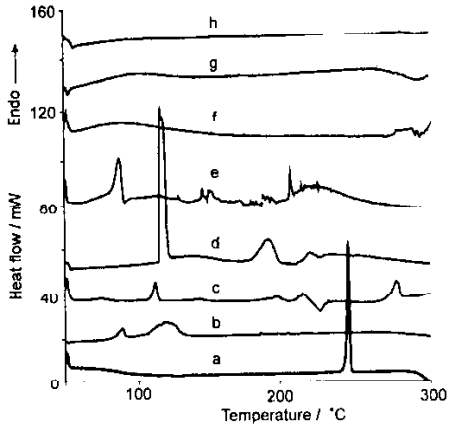

Fig. 2 Individual DSC traces for prochlorperazine mesylate and various excipients. a – prochlorperazine mesylate; b – magnesium stearate; c – sodium lauryl sulphate; d – dibasic calcium phosphate (Encompress); e – dextrose-combination-maltose (Emdex); f – Starch 1500; g – Explotab; h – Primojel

The DSC trace of the commonly used lubricant, magnesium stearate (Fig. 2, curve b), shows two broad, shallow endotherms in the 80 to 120°C range which may correspond to the different hydrated states or pseudo-polymorphs [3]. Only one peak (at approximately 80°C) remained in the trace for the physical mixture with the drug, while the trace for a tablet showed the disappearance of all endotherms. Incompatibilities involving magnesium stearate are frequently observed [3], even though glidants or lubricants often make up only 1 to 4% of the tablet. An alternative lubricant, Lubritab, was found to be superior in terms of lack of interaction. The melting endotherm of the drug in the DSC trace for the mixture with Lubritab had onset at approximately 238°C and was only slightly broadened.

The DSC trace of sodium lauryl sulphate (Fig. 2, curve c) showed endothermic activity around 100 to 110°C and 190 to 220°C that was sensitive to sample form. In-

teraction on mixing with the drug was sufficient to suppress the melting endotherm completely. The behaviours of dibasic calcium phosphate (Encompress) and of dextrose-combination-maltose (Emdex) were similar (Fig. 2, curves d and e) although the temperature ranges of endothermic activity of these excipients were slightly different, but still occurring below the melting point of the drug.

Pregelatinized starch (Starch 1500) exhibits a broad endotherm between 60 and 140°C (Fig. 2, curve f), probably due to the loss of bound water. In mixtures, the drug endotherm is broadened into overlapping peaks. The sodium starch glycolates (Primojel and Explotab) showed broad endotherms across the approximate range 60 to 200°C (Fig. 2, curves g and h) that appear to contribute to the suppression of the melting endotherm of the drug in mixtures.

The results of the DSC compatibility screening can be summarized as follows:

No or little incompatibility: Lubritab, Avicel PH101, Avicel PH102, Emcocel, Methylcellulose A15LV, -E4M, -E5, -E15LV, -K4M and -K4M CR.

Possible incompatibility: Starch 1500, Methylcellulose E50LV, -E5M, -E10M CR, -K15M CR, -K100LV CR and -K100M CR.

Probable incompatibility: Ac-Di-Sol, Emdex, Encompress, Explotab, Primojel, lactose, Ludipress, magnesium stearate, sodium lauryl sulphate and stearic acid.

Conclusions

DSC screening has proved to be a reliable indicator of major incompatibilities by several workers [3, 5]. This method detects but does not indicate the extent of the destabilizing effects of the excipients. Interpretation of the effects observed in DSC screening is not straightforward, because many types of drug-excipient interaction are possible. These include eutectic formation, solid-solid reactions (possibly complicated by solid-phase transformations), solid-liquid reactions and solid-gas reactions (particularly hydrolysis by evolved water vapour). Those excipients that undergo thermal events at temperatures below those of importance in the behaviour of the drug, are expected to produce incompatibilities, through one or more of the interactions listed above.

Results for mixtures of prochlorperazine maleate with β- or γ-cyclodextrin indicated partial inclusion complexation of the drug in the cyclodextrins with the effect being greater in the larger cavity of γ-cyclodextrin. Because even partial inclusion complexation may confer stability on a drug molecule, tests are in progress to determine the mode of complexation and whether the photostability of the drug is increased [15].

References

1 D. C. Monkhouse, Drug Dev. Ind. Pharm., 10 (1984) 1373.
2 A. R. Fassihi and P. H. R. Persicaner, Int. J. Pharm., 37 (1987) 167.
3 T. Durig and A. R. Fassihi, Int. J. Pharm., 97 (1993) 161.
4 J. L. Ford and P. Timmins, Pharmaceutical Thermal Analysis, Ellis Horwood, Chichester, UK 1989.
5 P. Mura, M. T. Faucci, A. Manderioli, S. Fulanetto and S. Pinzauti, Drug Dev. Ind. Pharm., 24 (1998) 747.

6 A. Smith, Anal. Proc., 19 (1982) 559.
7 A. A. Van Dooren, Drug Dev. Ind. Pharm., 9 (1983) 43.
8 R. E. Gorden, C. J. Van Koevering and D. J. Reits, Int. J. Pharm., 21 (1984) 99.
9 F. A. Chrzanowsky, L. A. Ulissi, B. J. Fegehy and A. C. Newman, Drug Dev. Ind. Pharm., 12 (1986) 783.
10 S. Motola and S. Agharkar, in Pharmaceutical Dosage Forms: Parenteral Medications, Vol. 1, (Eds K. E. Avis, L. Lachman and H. A. Lieberman) Dekker, New York 1984, pp. 89-133.
11 K. A. Connors, G. L. Amidon and V. J. Stella, Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists, 2nd Edn, Wiley, New York 1986, pp.148-150.
12 E. M. Antunes, M. Sc. Thesis, Rhodes University, 1998, in preparation.
13 D. E. Moore and S. R. Tamat, J. Pharm. Pharmacol., 32 (1980) 172.
14 J. Sztatisz, S. Gál, J. Kőmives, A. Stadler-Szöke and J. Szejtli, Thermal Analysis, Vol. 2, (Ed. W. Hemminger), Birkhaeuser Verlag, Basel 1980, pp. 487-493.
15 M. E. Brown, M. Lebete, B. D. Glass and E. M. Antunes, in preparation.