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COMPATIBILITY STUDY BETWEEN OXPRENOLOL HYDROCHLORIDE AND TABLET EXCIPIENTS USING DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

Differential scanning calorimetry (DSC) was used to investigate the physico-chemical compatibility between oxprenolol hydrochloride and a number of commonly used tablet and capsule excipients.

Oxprenolol hydrochloride was found to be compatible with starch, Sta-Rx 1500®, Primojel®, Avicel PH 101®, Ac-Di-Sol® and cross-linked PVP. Interactions of oxprenolol hydrochloride with PVP, lactose and the lubricants magnesium stearate and stearic acid were found, although it cannot be conclusively stated that interaction incompatibilities will occur during storage at room temperature.

INTRODUCTION

This study was undertaken to establish the compatibility of oxprenolol hydrochloride, a beta-adrenolytic cardioselective drug, with a number of commonly used tablet excipients.

The stability of a formulation depends, amongst other factors, on the compatibility of the active components with the excipients. It is of importance to detect any possible interactions, since it has been shown that certain interactions can either change the bioavailability[1] or stability[2] of a product. The excipients can affect the solid state stability of a drug in various ways; this may occur directly as a chemical reaction between the drug and the excipients, or mostly indirectly by sorption of moisture and/or catalysis.

Unless incompatibility is evident, it is necessary to carry out a stability study that usually requires months or years. Thus, it is important to choose methods for the evaluation of the solid state stability that give fast and reliable information about possible interactions. A number of techniques can be used to indicate interactions in drug-excipient systems, namely diffuse reflectance techniques[3], thin-layer chromatography and infrared spectrometric techniques[4] and thermal analysis. Thermal analysis, both DTA[5-6] and DSC [7-9] are now well developed techniques used in the detection of incompatibilities in drug-drug and drug-excipient interactions. Guillory et al.[10] have concluded that DTA used at the preformulation stage offers a possible help in the solution of the problem of drug-drug and drug-additive interactions. DSC yields data which are inherently more quantitative and more amenable to theoretical interpretation than the technique of DTA[11] and allows the fast evaluation of possible incompatibilities between the formulation compounds. The incompatibilities may be deduced from the appearance, shift or disappearance of peaks and/or variations in the corresponding ΔH values. Thermal analysis does not replace the chemical methods for determination of the concentration of a drug in a dosage form and stability tests, but it does represent a valuable tool in the first step of a formulation[12]. Van Dooren[13] has recommended the use of DSC in combination with short time stress in order to evaluate DSC curves more easily.

In this study, the compatibility of oxprenolol hydrochloride with a number of excipients commonly used in tablet manufacture was investigated. This was achieved by comparing the DSC curves of oxprenolol hydrochloride and each of the investigated excipients with curves for 1 : 1 mixtures of oxprenolol hydrochloride and excipients. Although it cannot be conclusively stated that an interaction will occur during storage at room temperature, there are normally sufficient excipients available to choose only those unlikely to cause problems[14].

EXPERIMENTAL

Materials

The following materials were used: oxprenolol hydrochloride (supplied by Twins-Propan, Johannesburg, S.A.); corn starch; directly compressible starch (Sta-Rx 1500®); sodium carboxymethyl starch (Primojel®); microcrystalline cellulose (Avicel PH 101®); a cross-linked form of sodium carboxymethylcellulose (Ac-Di-Sol®); lactose; magnesium stearate; stearic acid; polivinylpyrrolidone (PVP); cross-linked polivinylpyrrolidone.

Differential Scanning Calorimetry

Samples (3 - 8 mg) were measured and hermetically sealed in flat bottomed aluminum pans. Samples of the individual substances, as well as1 : 1 physical mixtures of oxprenolol hydrochloride and excipients prepared by grinding in a mortar and pestle, were heated over the temperature range of 30 - 200°C in an atmosphere of nitrogen at 5°C min^{-1} in a Du Pont 910 DSC system equipped

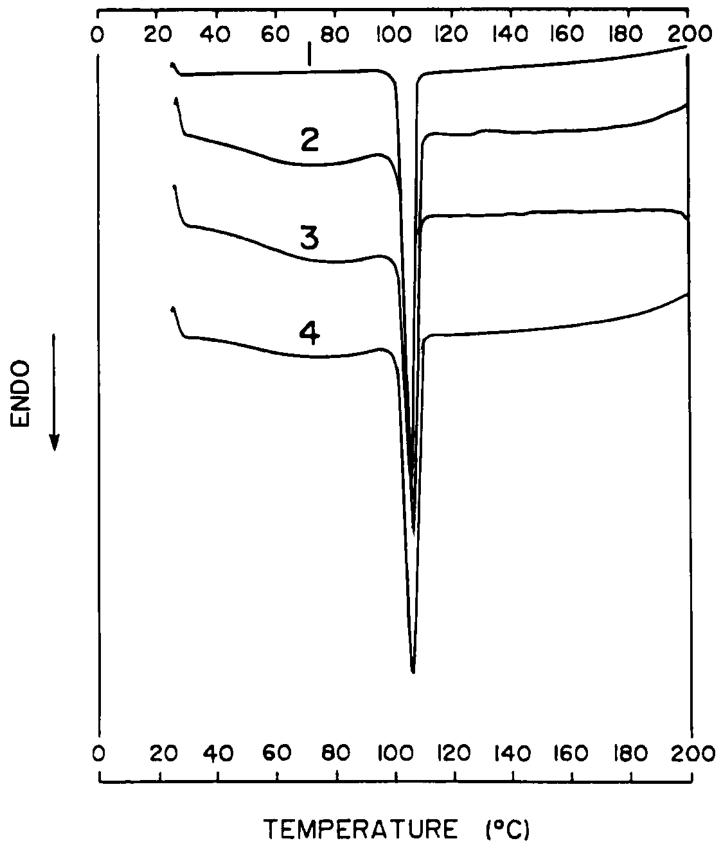

FIGURE 1

DSC thermograms of oxprenolol HCl (1) and 1 : 1 physical mixtures of oxprenolol HCl with Ac-Di-Sol (2), starch (3) and Avicel PH 101 (4).

with a Du Pont Series 99 Thermal Analyzer programmer. A Hewlett-Packard X-Y recorder was used. The instrument was calibrated with an indium standard.

RESULTS AND DISCUSSION

Trace 1 of figure 1 is that of oxprenolol hydrochloride, showing an endothermic melting peak with an onset of 104°C and a

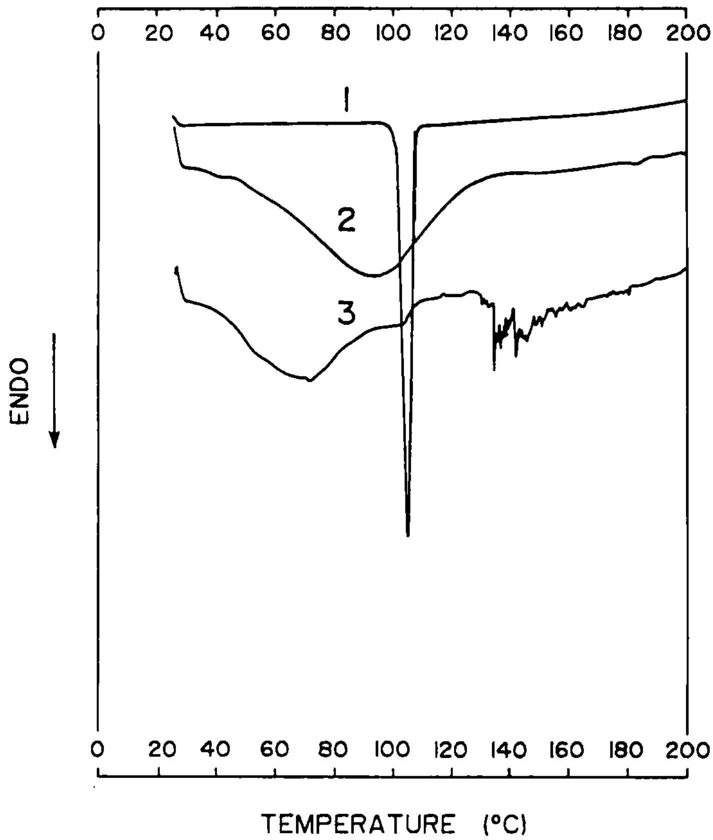

FIGURE 2

DSC thermograms of oxprenolol HCl (1), PVP (2) and 1 : 1 physical mixture of oxprenolol HCl : PVP (3).

maximum occurring at 108°C. Traces 2 - 4 of fig. 1 are the curves of 1:1 physical mixtures of oxprenolol hydrochloride with Ac-Di-Sol, corn starch and Avicel PH 101 respectively. These excipients exhibited a shallow broad endotherm that was completed at 145°C when scanned individually over the temperature range of 30 - 200°C. This might correspond to the volatilization of adsorbed water, since it was reported that the thermal analysis of cellulose[15] and wheat starch[16] showed endotherms above 100°C that were attributed to water vapor. It is probable that a similar dehydration reaction

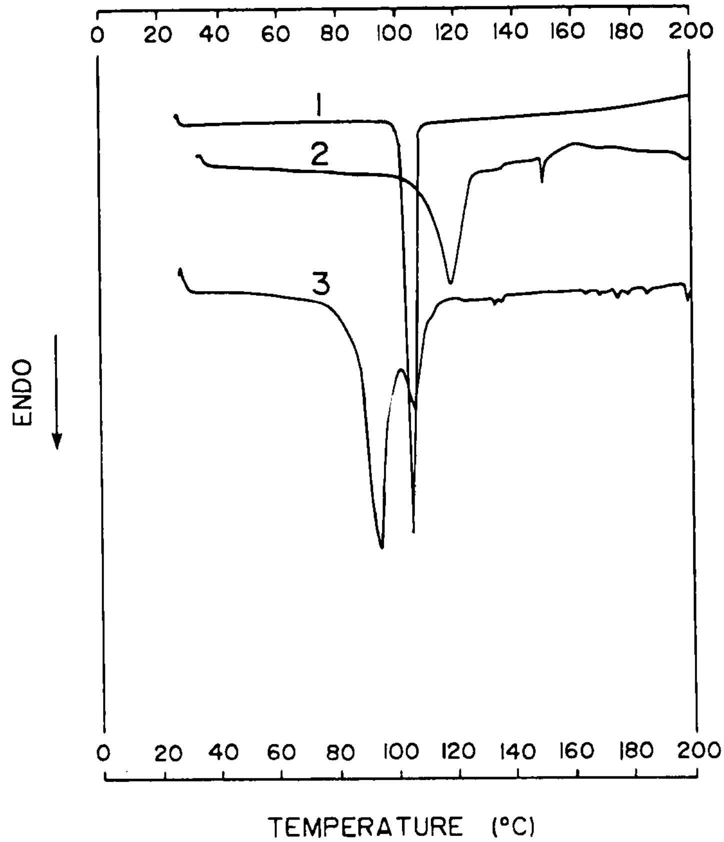

FIGURE 3

DSC thermograms of oxprenolol HCl (1), magnesium stearate (2) and 1 : 1 physical mixture of oxprenolol HCl : magnesium stearate (3).

occurred in Ac-Di-Sol. Therefore, DSC curves of mixtures of these excipients with oxprenolol hydrochloride will reflect the characteristic feature of oxprenolol hydrochloride if no interaction occurred. This is indeed the case as can be seen in fig. 1. As expected, some changes in peak shape and height-to-width ratio can be seen because of possible differences in the mixture sample geometry[17]. Similarly, no interactions are observed with physical mixtures of oxprenolol hydrochloride and Sta-Rx 1500, Primojel and cross-linked PVP.

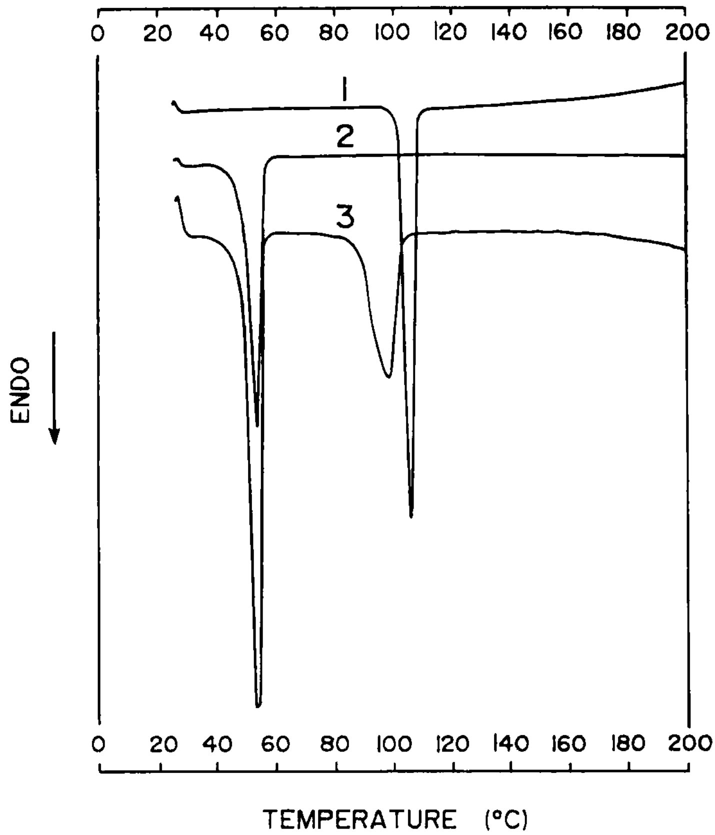

FIGURE 4

DSC thermograms of oxprenolol HCl (1), stearic acid (2) and 1 : 1 physical mixture of oxprenolol HCl : stearic acid (3).

Trace 2 of fig. 2 is that of PVP, which shows a broad endotherm over the temperature range 53 - 140°C due to adsorbed water (12% of water, as determined by the Karl Fischer titration method). Trace 3 of fig. 2 is the curve of oxprenolol hydrochloride-PVP physical mixture - apart from the adsorbed water endotherm, a second broad endotherm, followed by degradation and/or vaporization can be seen, while the endotherm characteristic of oxprenolol hydrochloride has been obliterated. This indicates an interaction of PVP with oxprenolol hydrochloride.

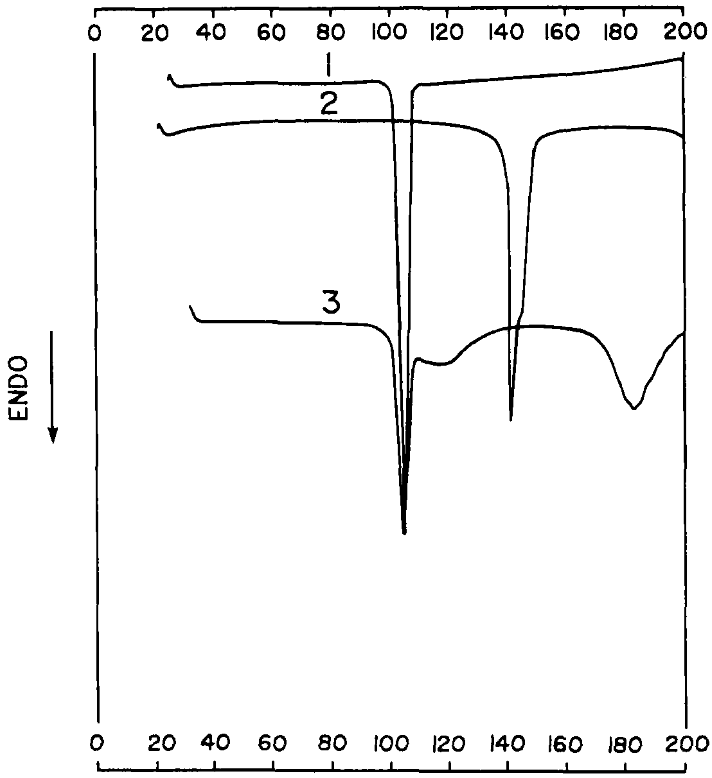

FIGURE 5

DSC thermograms of oxprenolol HCl (1), lactose (2) and 1 : 1 physical mixture of oxprenolol HCl : lactose (3).

Two overlapping endothermic peaks are found in the case of an oxprenolol hydrochloride-magnesium stearate mixture (trace 3 of fig. 3), with onsets of transitions at 85 and 96°C. The trace of magnesium stearate (trace 2; fig. 3) shows a broad melting endotherm at 110 - 118°C, which is absent in the trace of the combined products. Extra thermal effects in a thermogram before the peak of the lower melting component might be indicative of an incompatibility[13].

In the trace of an oxprenolol hydrochloride - stearic acid mixture (trace 3; fig.4) the characteristic endotherm of stearic acid

(49 - 55°C) can be seen, as well as an endothermic peak at a temperature of 88 - 99°C, probably the melting endotherm of oxprenolol hydrochloride. When two substances are mixed, the purity of each may be reduced and generally slightly lower melting points result. If the solid-solid interaction is weak or non-existent, the reduction of the melting point is usually inconsequential. On the other hand, any large shift in melting point signifies that a strong solid-solid interaction has occurred, although it does not necessarily indicate an incompatibility.

The combination of oxprenolol hydrochloride - lactose (trace 3; fig. 5) shows two endotherms with onset temperatures of 101 and 170°C, as well as a broad overlapping endotherm with a maximum at 113°C. The trace of lactose (trace 2; fig. 5) shows a transition endotherm at 137°C. Thus, the endotherm of oxprenolol hydrochloride can be recognized, with the feature of an additional peak at 170 - 181°C and the loss of the characteristic lactose endotherm. The reaction between lactose and primary amines is well-documented[18-19] and although oxprenolol hydrochloride is a secondary amine, this result might be indicative of an interaction.

Hardy [20] and Smith[21] have warned against accepting that interactions thus discovered are detrimental but state that DSC can be an invaluable tool in avoiding excipients with interaction potential.

CONCLUSIONS

The incompatibility between oxprenolol hydrochloride and PVP, magnesium stearate, stearic acid and lactose was demonstrated by DSC. Starch, Sta-Rx 1500, Primojel, Avicel PH 101, Ad-Di-Sol and cross-linked PVP exhibited no interactions with oxprenolol hydrochloride. Thus, this technique could usefully be employed to optimize oxprenolol hydrochloride formulations, leading to better storage stability.

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