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COMPATIBILITY STUDY BETWEEN ATENOLOL AND TABLET EXCIPIENTS USING DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

In order to improve the formulation of atenolol the physico-chemical compatibility between the drug and various excipients, commonly used in tablet manufacturing, was studied with the aid of Differential Scanning Calorimetry (DSC).

Using this method, it was found that atenolol is compatible with starch, Sta-Rx®, Primojel®, Avicel PH®, Ac-Di-Sol®, cross-linked PVP, magnesium stearate, calcium sulphate dihydrate, dicalcium phosphate and icing sugar. Interactions of atenolol with PVP, lactose and the lubricant stearic acid were found, although it cannot be conlusively stated that interaction incompatibilities will occur during storage at room temperature.

INTRODUCTION

This study was undertaken to establish the compatibility of atenolol, 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 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 chose methods for the evaluation of the solid state stability that give fast en reliable information about possible interactions. A number of techniques can be used to indicate interactions in drug-excipient systems, namely diffuse reflectance techniques[3], TLC and IR 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] concluded that DTA 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 imcompatibilities between the formulation compounds derived from appearance, shift or disappearance of peaks and/or variations in the corresponding ΔH. Thermal analysis does not replace the chemical methods for determination of the concentration of a drug in a dosage form and does not replace stability tests, but it does

represent a valuable tool in the first step of a formulation[12]. Van Dooren[13] recommended the use of DSC in combination with short time stress in order to evaluate DSC curves easier.

EXPERIMENTAL

Materials

The following materials were used: atenolol (supplied by Twins-Propan, Isando, S.A.); 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®); icing sugar; lactose; magnesium stearate; stearic acid; calcium sulphate dihydrate; polivinylpyrrolidone (PVP); polivinylpyrrolidone cross-linked; dicalcium phosphate.

Differential Scanning Calorimetry

Samples (3 - 8 mg) were measured and hermetically sealed in flatbottomed aluminum pans. These samples were heated in an atmosphere of nitrogen and thermograms were obtained with a Du Pont 910 DSC system equipped 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.

Thermograms were obtained by heating at a constant rate of 5°C per minute and recorded at a constant chart speed of 10 mm per minute. The individual substances, as well as 1:1 physical mixtures of atenolol and excipients prepared by mortar and pestle, were heated over the temperature range of 30 - 250°C, under nitrogen purge.

RESULTS AND DISCUSSION

Trace 1 of figure 1 is that of atenolol, showing an endothermic melting peak with an onset of 150°C and a maximum occuring at

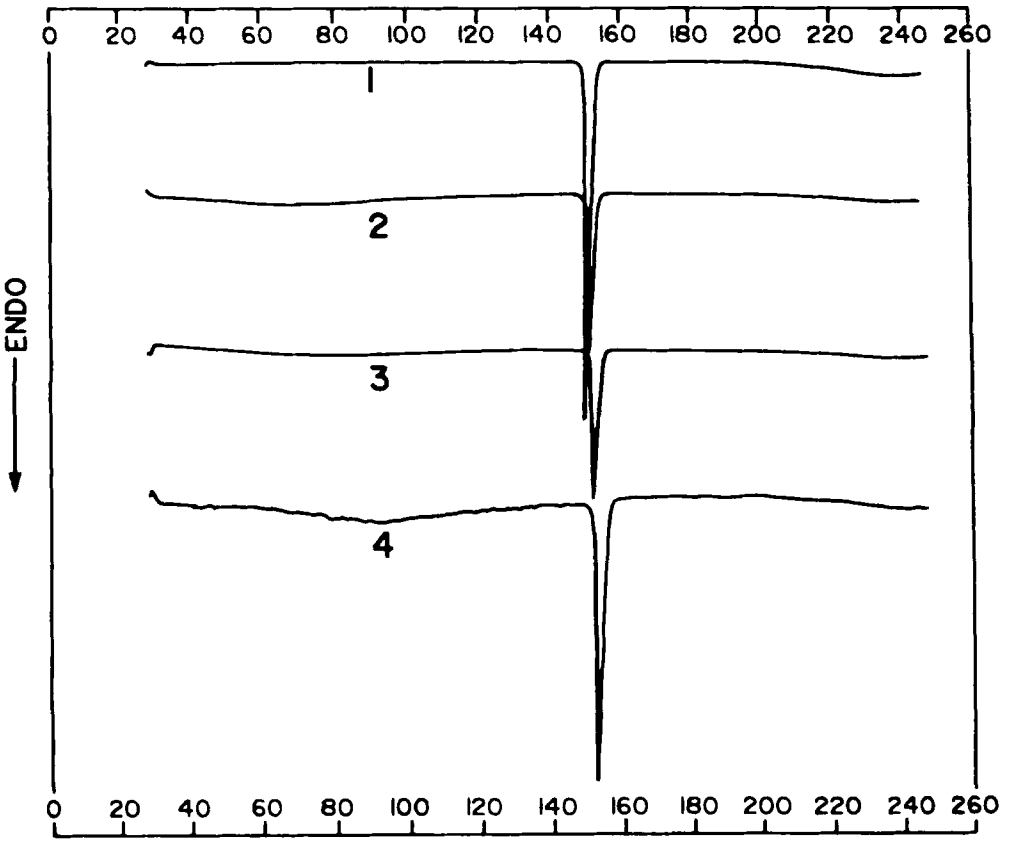

FIGURE 1
DSC thermograms of atenolol (1) and 1:1 physical mixtures of atenolol with Sta-Rx (2), Starch (3) and Primojel (4).

152°C. Traces 2 - 4 of fig. 1 are the thermograms of 1:1 physical mixtures of atenolol with Sta-Rx, starch and Primojel respectively. These excipients exhibit no transition when scanned individually over the temperature range of 30 - 250°C. Therefore, DSC thermograms of mixtures of these excipients with atenolol will reflect the characteristic feature of atenolol if no interaction occured. This is indeed the case as can be seen in fig. 1. Some changes

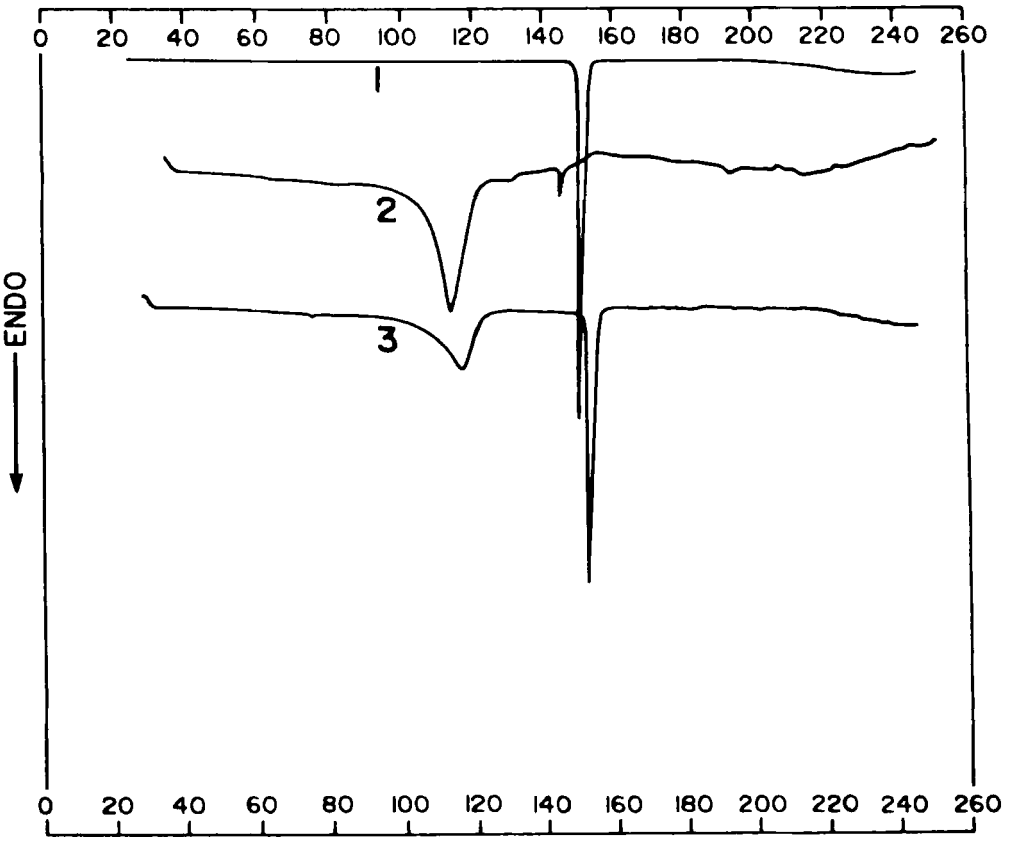

FIGURE 2
DSC thermograms of atenolol (1), magnesium stearate (2) and 1:1 physical mixture of atenolol:magnesium stearate (3).

in peak shape and height-to-width ratio were expected because of possible differences in the mixture sample geometry[14]. Similarly, no interactions are observed with physical mixtures of atenolol and Avicel PH 101, Ac-Di-Sol and cross-linked PVP.

The thermogram of atenolol-magnesium stearate mixture (Trace 3 of fig. 2), combines the features characteristic of the thermograms of each component. Also, combinations of atenolol with calcium sulphate dihydrate, dicalcium phosphate or icing sugar show

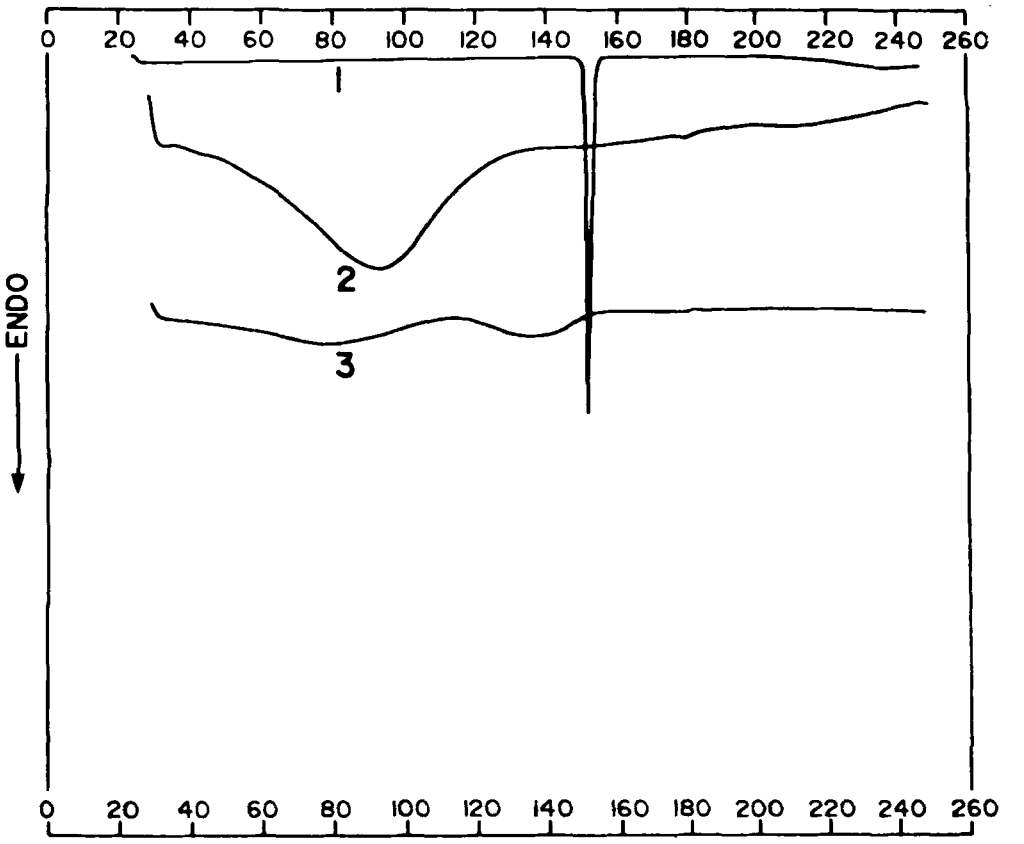

FIGURE 3
DSC thermograms of atenolol (1), PVP (2) and 1:1 physical mixture of atenolol:PVP (3).

no interactions; a slight shift to a higher atenolol melting temperature (158 - 160°C) is observed in the case of atenolol-icing sugar mixture.

Trace 2 of fig. 3 is the thermogram of PVP, which shows a broad endotherm (53 - 96°C) due to adsorbed water. Trace 3 of fig. 3 is the thermogram of atenolol-PVP physical mixture - apart from the adsorbed water endotherm, a second broad endotherm with an onset of 118°C can be seen, while the endotherm characteristic

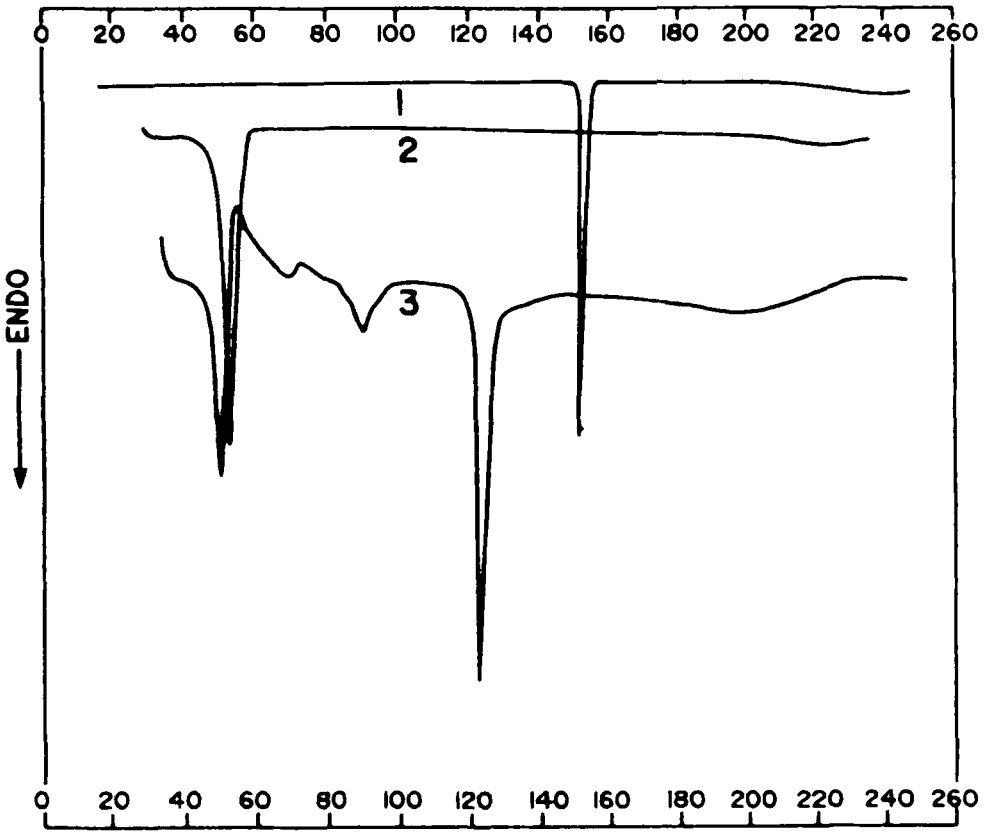

FIGURE 4
DSC thermograms of atenolol (1), stearic acid (2) and 1:1 physical mixture of atenolol:stearic acid (3).

of atenolol has been obliterated. This indicates an interaction of PVP with atenolol.

In the trace of an atenolol - stearic acid mixture (trace 3; fig. 4) the characteristic endotherm of stearic acid (49 - 54°C) can be seen, as well as two smaller endothermic peaks (60 - 72°C; 88 - 93°C) and a larger endotherm at 123 - 127°C, while the melting endotherm of atenolol (150 - 152°C) is absent.

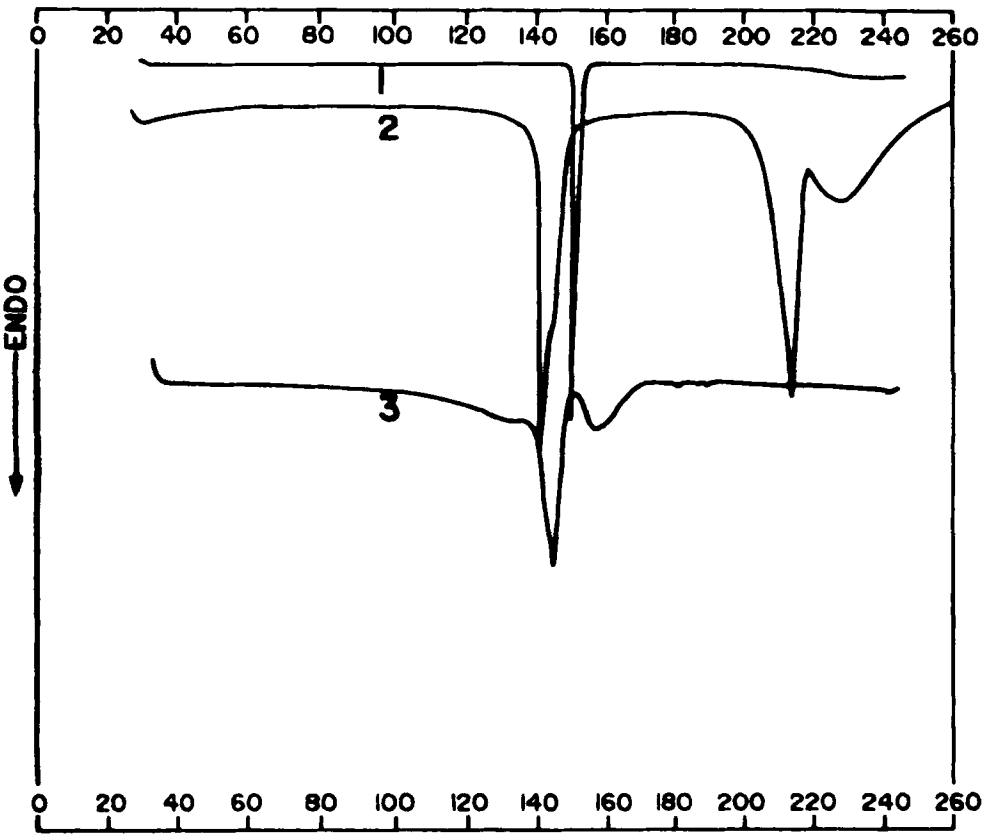

FIGURE 5
DSC thermograms of atenolol (1), lactose (2) and 1:1 physical mixture of atenolol:lactose (3).

The combination of atenolol - lactose (trace 3; fig. 5) shows three peaks with transition onset temperatures of 102, 141 and 157°C, while the trace of lactose (trace 2) shows transition endotherms at 137 and 207°C. Thus, the first characteristic endotherm of lactose, as well as that of atenolol, although smaller than expected, can be recognised, with the feature of an addisional peak at 102°C and the loss of a lactose endotherm at 207°C. This

result was anticipated, since the browning of lactose in the presence of amines is well-documented[14]

Hardy[15] and Smith[16] warn against accepting that interactions thus discovered are detrimental but state that DSC can be an invaluable tool in avoiding excipients with interacton potential.

CONCLUSIONS

The incompatibility between atenolol and lactose or stearic acid was derived by DSC. Thus, this technique could usefully be employed to optimise the atenolol formulations, leading to better storage stability.

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