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COMPATIBILITY STUDY BETWEEN OXPRENOLOL HYDROCHLORIDE, TEMAZEPAM 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, temazepam and a number of commonly used tablet and capsule excipients.

Oxprenolol hydrochloride was found to be compatible with starch, Sta-Rx 1500®, Avicel PH 101®, Elcema G250®, Ac-Di-Sol® Sterotex® and cross-linked PVP while temazepam was found to be compatible with starch, Sta-Rx 1500®, Primojel®, Elcema G250®, Explotab®, Sterotex® and lactose. Interactions of oxprenolol hydrochloride with Primojel®, Explotab®, PVP, lactose, Emcompress® and the lubricants magnesium stearate, stearic acid and Precirol Ato 5® were found. Temazepam was found to interact with cross-linked PVP, PVP, Precirol Ato 5®, stearic acid, magnesium stearate, Emcompress® and possibly Avicel PH 101® and Ac-Di-Sol®.

INTRODUCTION

This study was undertaken to establish the compatibility of oxprenolol hydrochloride, a beta-adrenolytic cardioselective drug and temazepam, a pharmacologically active metabolite of diazepam indicated for the management of anxiety disorders, with a number of commonly used tablet excipients. Tablet formulations typically contain diluents, binders, disintegration agents and lubricants, therefore compatibility screening must be considered with selected excipients from each group.

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. Although a number of methods are available for routine drug-excipient interaction studies[3-7], differential scanning calorimetry (DSC) has become the screening method of choice, since DSC allows the fast evaluation of possible incompatibilities 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 stability tests, but it does represent a valuable tool in the first step of a formulation[8]. Van Dooren[5] 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 and temazepam with a number of excipients commonly used in tablet manufacture was investigated. This was achieved by comparing the DSC curves of the active ingredients and each of the investigated excipients with curves for 1 : 1 mixtures of the actives 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[9].

EXPERIMENTAL

Materials

The following materials were used: oxprenolol hydrochloride, temazepam (supplied by Twins-Propan, Johannesburg, S.A.); corn starch; directly compressible starch (Sta-Rx 1500®); sodium carboxymethyl starch (Primojel®, Explotab®); microcrystalline cellulose (Avicel PH 101®); microfine cellulose (Elcema G250®); a cross-linked form of sodium carboxymethylcellulose (Ac-Di-Sol®); lactose; magnesium stearate; stearic acid; polivinylpyrrolidone (PVP); cross-linked polivinylpyrrolidone; hydrogenated cotton seed oil (Sterotex®); glyceryl palmitostearate (Precirol Ato 5®); dicalcium phosphate dihydrate (Emcompress®).

Differential Scanning Calorimetry

Samples (3 - 8 mg) were measured and hermetically sealed in flat bottomed aluminum pans. Samples of the individual substances, as well as 1 : 1 physical mixtures of oxprenolol hydrochloride/temazepam and excipients prepared by grinding in a mortar and pestle, were heated in an atmosphere of nitrogen at 5°C min^{-1} in 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. A temperature range of 30 - 200°C was used in the case of oxprenolol hydrochloride mixtures, while a range of 30 - 250°C was used in the case of temazepam mixtures.

RESULTS AND DISCUSSION

Trace 1 of fig. 1 is that of oxprenolol hydrochloride, showing an endothermic melting peak with an onset of 104°C and a maximum occurring at 108°C. The DSC thermogram of temazepam (trace 2 of fig. 1) shows a sharp melting endotherm with an onset of 158°C and a maximum occuring at 159°C, followed by a degradation exotherm at a temperature of ± 220°C.

The excipients corn starch, Sta-Rx 1500, Primojel, Explotab, Avicel PH 101, Elcema G250, and Ac-Di-Sol all exhibit a shallow broad endotherm that is completed at 145°C. This might correspond to the volatilization of adsorbed water, since it was reported that the thermal analysis of cellulose[10] and wheat starch[11] showed endotherms above 100°C that were attributed to water vapor. It is probable that similar dehydration reactions occurred in Primojel, Explotab and Ac-Di-Sol. The combination of oxprenolol hydrochloride / temazepam with each of these excipients exhibits the characteristic features of the actives, indicating compatibility, although the degradation exotherm is more pronounced in the temazepam : Avicel PH 101 and temazepam : Ac-Di-Sol mixtures and absent in temazepam : Primojel and temazepam : Explotab physical mixtures. A slight downward shift of the oxprenolol hydrochloride melting endotherm in mixtures with Primojel and Explotab, namely to 96 - 104°C and 93 - 103°C respectively, is found. 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 extremely weak or non-existent, the reduction of the

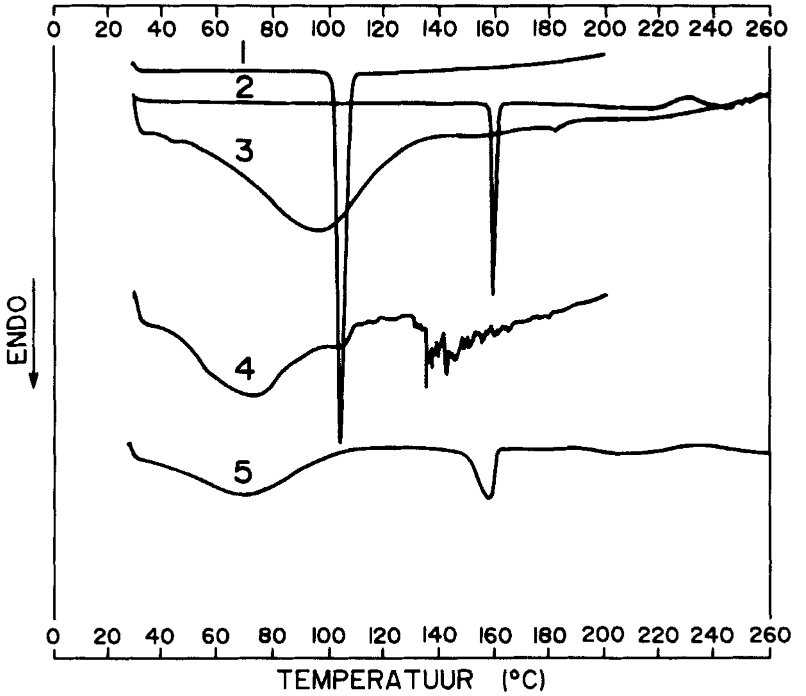

FIGURE 1

DSC thermograms of oxprenolol HCl (1), temazepam (2), PVP (3), 1 : 1 physical mixtures of oxprenolol HCl : PVP (4) and temazepam : PVP (5).

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. As expected, some changes in peak shape and height-to-width ratio can be seen because of possible differences in the mixture sample geometry[12].

The thermograms of both oxprenolol hydrochloride : Sterotex and temazepam : Sterotex physical mixtures combine the features characteristic of the thermograms of each component indicating that no interaction occurred.

Trace 3 of fig. 1 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 4 of fig. 1 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. A mixture of temazepam : PVP (trace 5; fig.1) shows a small endotherm with an onset temperature of 150°C. Interactions between PVP and diazepam, nitrazepam, donazepam, medazepam and chlordiazepoxide were investigated[13] and it is possible that the small temazepam endotherm could be due to a similar interaction.

Trace 3 of fig. 2 is the thermogram of cross-linked PVP, showing a broad endotherm (30 - 140°C) due to adsorbed water. The combination temazepam : cross-linked PVP shows, apart from the broad water endotherm and the characteristic temazepam endotherm, a lowered degradation exotherm which follows immediately on the temazepam endotherm (trace 5; fig. 2). This lowered exotherm might be indicative of an interaction. The combination oxprenolol hydrochloride : cross-linked PVP shows the characteristic feature of oxprenolol hydrochloride, indicating compatibility (trace 4; fig. 2).

The thermogram of oxprenolol hydrochloride : Precirol Ato 5 (trace 4; fig.3) shows a slight downward shift of the oxprenolol hydrochloride melting endotherm to a temperature of 95 - 104°C while the thermogram of temazepam : Precirol Ato 5 (trace 5, fig. 3) shows not only a downward shift of the temazepam melting endotherm to a temperature of 146 - 152°C, but the size of the peak is apprecially smaller than expected.

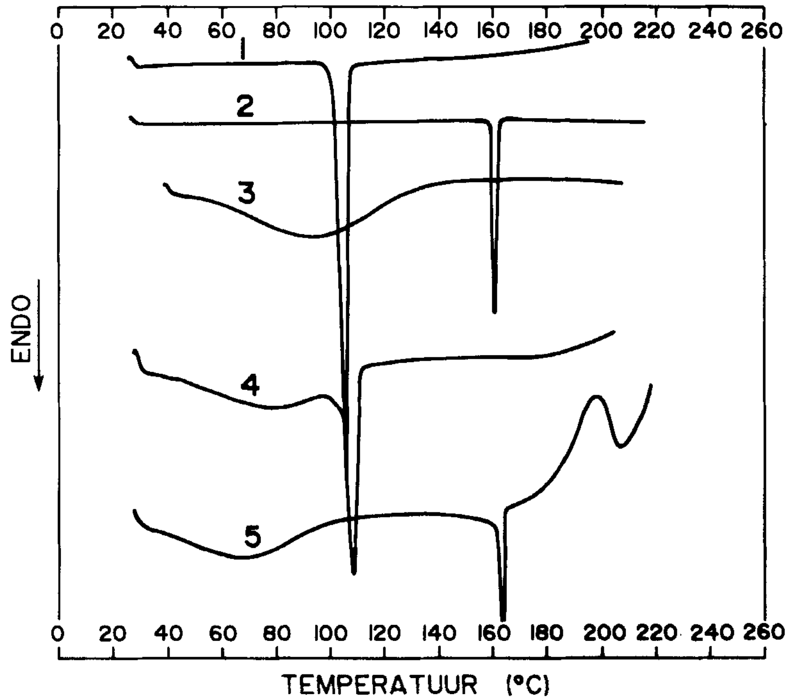

FIGURE 2

DSC thermograms of oxprenolol HCl (1), temazepam (2), cross-linked PVP (3), 1 : 1 physical mixtures of oxprenolol HCl : cross-linked PVP (4) and temazepam : cross-linked PVP (5).

Two overlapping endothermic peaks are found in the case of an oxprenolol hydrochloride-magnesium stearate mixture (trace 4; fig. 4), with onsets of transition at 85 and 96°C. The trace of magnesium stearate (trace 3; fig. 4) 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[5]. A temazepam-magnesium stearate combination (trace 5; fig.4), shows the typical magnesium stearate endotherm,

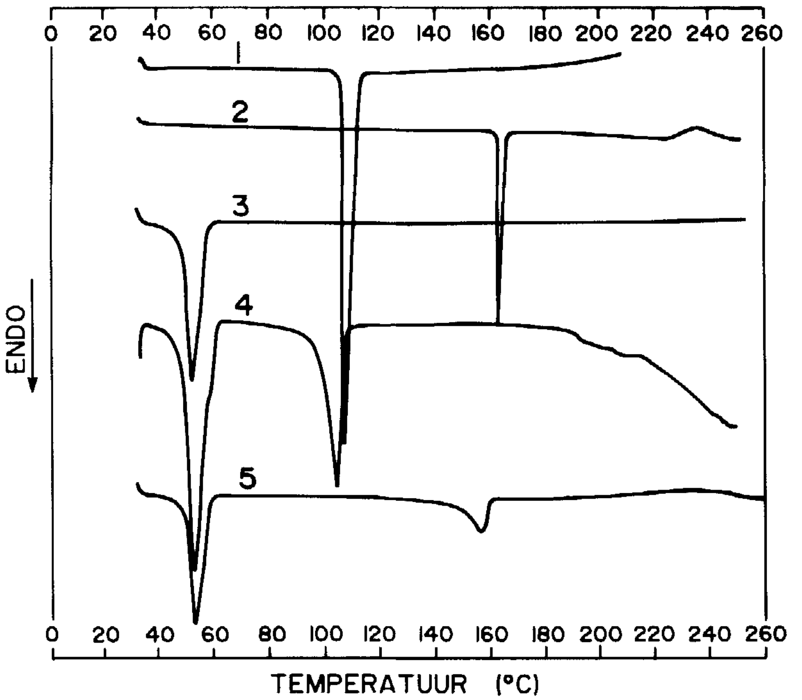

FIGURE 3

DSC thermograms of oxprenolol HCl (1), temazepam (2), Precitol Ato 5 (3), 1 : 1 physical mixtures of oxprenolol HCl : Precirol Ato 5 (4) and temazepam : Precirol Ato 5 (5).

followed by a somewhat deformed temazepam endotherm with an onset of transition at 149°C. Although no conclusive conclusions can be made, it seems as if, judging from the appearance of the thermogram, the possibility of an interaction might excist.

In the trace of an oxprenolol hydrochloride : stearic acid mixture (trace 4; fig. 5) 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. Any large shift in melting point signifies

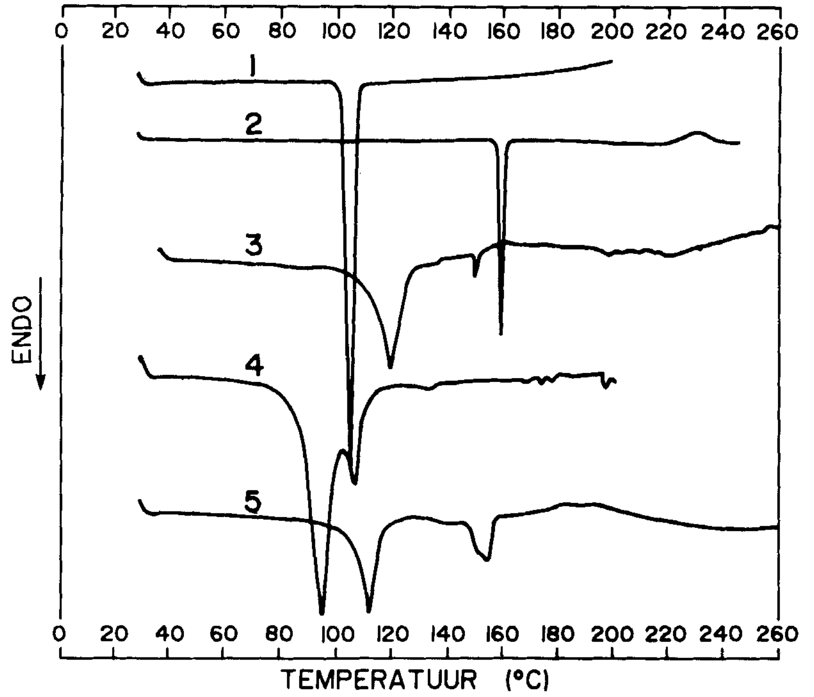

FIGURE 4

DSC thermograms of oxprenolol HCl (1), temazepam (2), magnesium stearate (3), 1 : 1 physical mixtures of oxprenolol HCl : magnesium stearate (4) and temazepam : magnesium stearate (5).

that a strong solid-solid interaction has occurred, although it does not necessarily indicate an incompatibility. The characteristic endotherm of stearic acid is followed by two shallow endotherms with onsets of 128 and 180°C respectively in the trace of a temazepam : stearic acid mixture (trace 5, fig. 5), while the characteristic temazepam endotherm disappears completely. Stearic acid is essentially stable when heated to 250°C, a temperature well beyond that where the other features of the thermogram are obtained. The disappearance of one of the component peaks in a

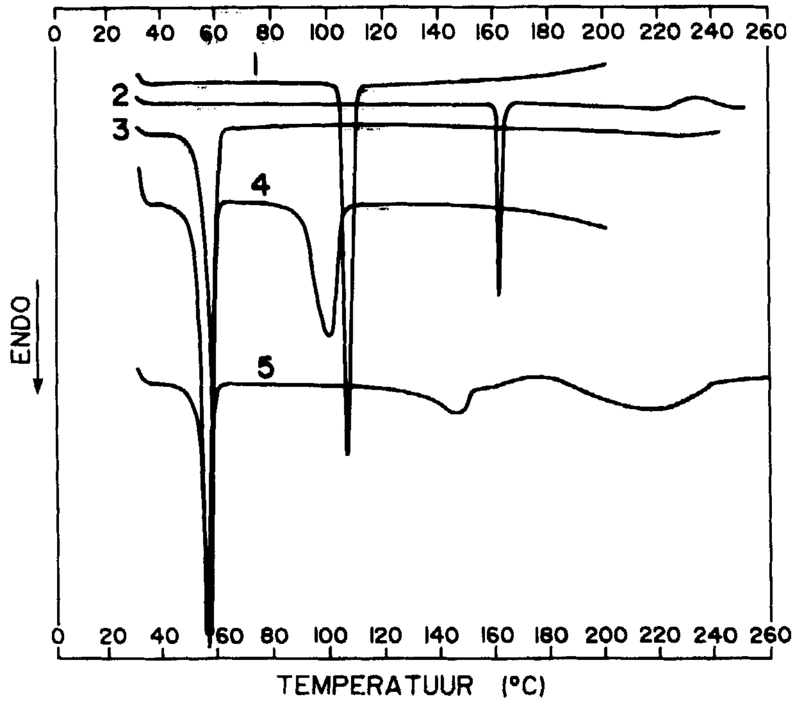

FIGURE 5

DSC thermograms of oxprenolol HCl (1), temazepam (2), stearic acid (3), 1 : 1 physical mixtures of oxprenolol HCl : stearic acid (4) and temazepam : stearic acid (5).

mixture might be indicative of an incompatibility[5]. Incompatibilities were also shown between stearic acid and potassium penicillin G[14], sodium oxacillin monohydrate[14], erythromycin[15] and cephalexin[16]. The interaction of stearic acid with ibuprofen was identified as an eutectic[17].

The thermogram of lactose shows two large endothermic transitions at 137 - 144°C and 207.5 - 217°C, followed by a third smaller endotherm (trace 3; fig. 6). The combination of oxprenolol hydrochloride : lactose (trace 4; fig. 6) shows two endotherms with

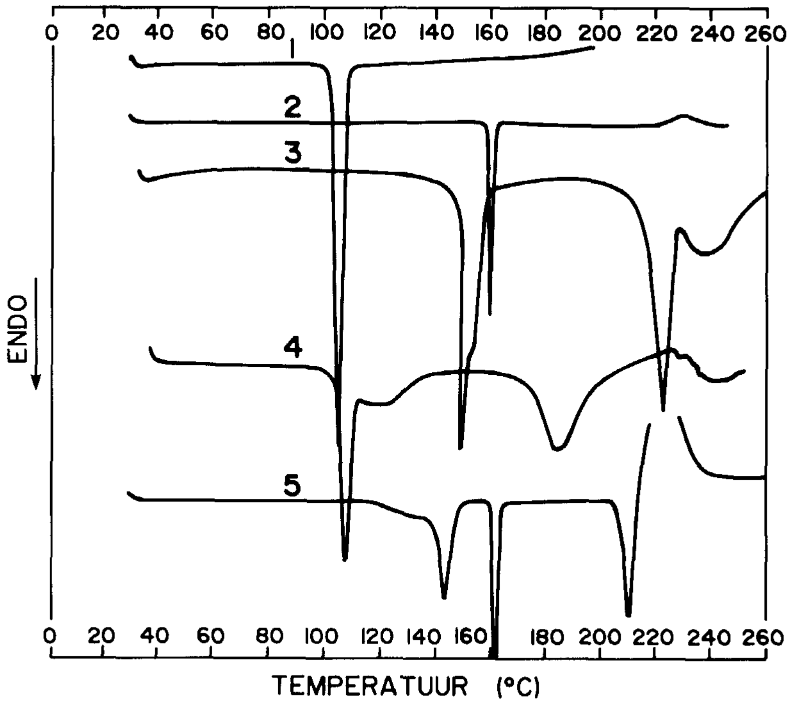

FIGURE 6

DSC thermograms of oxprenolol HCl (1), temazepam (2), lactose (3), 1 : 1 physical mixtures of oxprenolol HCl : lactose (4) and temazepam : lactose.

onset temperatures of 101 and 170°C, as well as a broad overlapping endotherm with a maximum at 113°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. The physical combination temazepam : lactose shows the lactose endotherms, as well as the characteristic

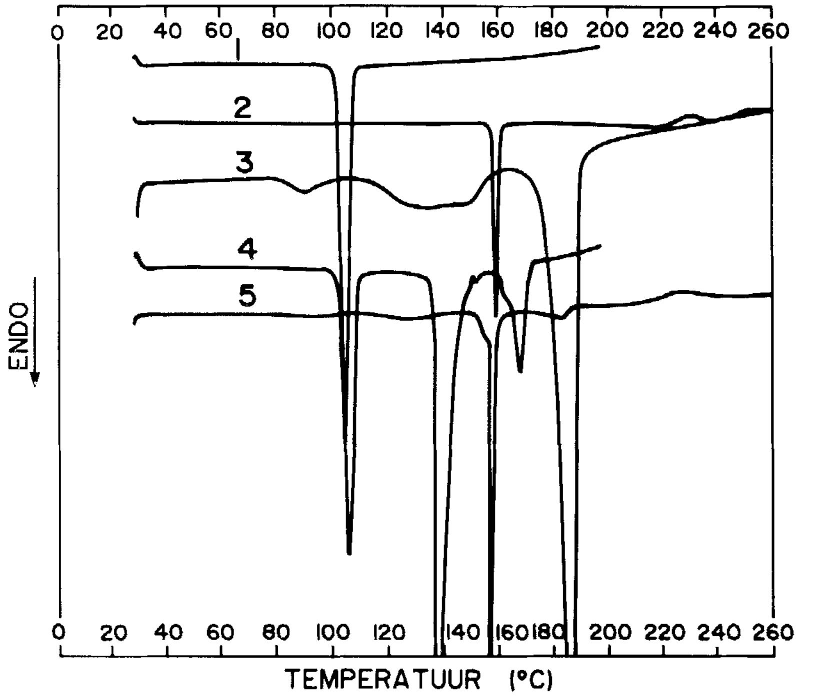

FIGURE 7

DSC thermograms of oxprenolol HCl (1), temazepam (2), Emcompress (3), 1 : 1 physical mixtures of oxprenolol HCl : Emcompress (4) and temazepam : Emcompress (5).

temazepam endotherm (trace 5; fig. 6), followed by an exotherm, which could be the normal temazepam exotherm.

Emcompress shows a melting endotherm with an onset of 176°C and a maximum at 187°C (trace 3; fig. 7) and a shallow broad endotherm ranging from 100 - 160°C, due to the volatilization of crystal water. The combination oxprenolol hydrochloride : Emcompress shows, apart from the characteristic oxprenolol hydrochloride endotherm, also an extra endotherm with an onset of 136°C (trace 4; fig. 7), which could be indicative of an interaction. A combination of temazepam : Emcompress shows a sharp endotherm with an onset of 155°C followed by a very shallow endotherm with an onset of 178°C (trace 5; fig. 7). This possible incompatibility was expected as the combination of an alkaline vehicle, such as Emcompress, with an acidic active ingredient such as temazepam (pKa 1,6), is contra-indicated[20]. Dicalcium phosphate dihydrate was found to be incompatible with erythromycin[15], cephalexin[16], nalidixic acid[21] and dexchlorpheniramine maleate[22].

Hardy[23] and Smith[24] 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, lactose and Emcompress was demonstrated by DSC. Starch, Sta-Rx 1500, Avicel PH 101, Elcema G250, Ac-Di-Sol, Sterotex and cross-linked PVP exhibited no interactions with oxprenolol hydrochloride. Since no conclusive interaction could be demonstrated in oxprenolol hydrochloride mixtures with Primojel, Explotab and Precirol Ato 5, it would be best to avoid these combinations. It was found that temazepam was compatible with starch, Sta-Rx 1500, Primojel, Elcema G250, Explotab, Sterotex and lactose. Interactions between temazepam and cross-linked PVP, PVP, Precirol Ato 5, stearic acid, magnesium stearate, Emcompress and possibly Avicel PH 101 and Ac-Di-Sol were found and although it cannot be stated that these interactions would indicate incompatibility, it would be best to avoid these combinations until the nature of these interactions is assessed.

REFERENCES

1. G. Levy and R.H. Reuning, J. Pharm. Sci., 53, 1472 (1964).

2. A. Li Wan Po and P.V. Mroso, Int. J. Pharm., 18, 287 (1984).

3. J.L Lach and M. Bornstein, J. Pharm. Sci., 54, 1730 (1965).

4. A.A. Kassem, S.A. Zaki, N.M. Mursi and S.A. Tayel, Pharm. Ind., 41, 1220 (1979).

5. A.A. van Dooren, Drug Devel. Ind. Pharm., 9, 43 (1983).

6. C. Ahlneck and P. Lundgren, Acta Pharm. Suec., 22, 305 (1985).

7. S.A. Botha, A.P. Lötter and J.L. du Preez, Drug Devel. Ind. Pharm., 13, 1197 (1987).

8. B.W. Muller, Acta Pharm. Technol., 23, 257 (1977).

9. K.C. Lee and J.A. Hersey, J. Pharm. Pharmacol., 29, 515 (1977).

10. F.J. Kilzer, High Polym., 5, 1015 (1971).

11. H. Morita, Anal. Chem., 28, 64 (1956).

12. E.S. Watson, M.J. O'Neill, J. Justin and N. Brenner, Anal. Chem., 36, 1233 (1964).

13. S. Keipert and R. Voigt, Pharmazie, 41, 400 (1986).

14. H. Jacobson and G. Reier, J. Pharm. Sci., 58, 631 (1969).

15. H.H. El-Shattawy, D.O. Kildsig and G.E. Peck, **Drug Dev. Ind. Pharm.**, **8**, 937 (1982).

16. H.H. El-Shattawy, D.O. Kildsig and G.E. Peck, **Drug Dev. Ind. Pharm.**, **8**, 897 (1982).

17. R.E. Gordon, C.L. VanKoevering and D.J. Reits, **Int. J. Pharm.**, 21, 99 (1984).

18. R.N. Duval, K.T. Koshy and J.W. Pyles, **J. Pharm. Sci.**, **54**, 607 (1965).

19. S.M. Blaug and W.-T. Huang, **J. Pharm. Sci.**, **61**, 1770 (1972).

20. E.J. Mendell, **Mfg. Chem.**, **43**(April), 40 (1972).

21. H.H. El-Shattaway, **Drug Dev. Ind. Pharm.**, **10**, 491 (1984).

22. E. Graff, A.A. Fawzy and I. Tsaktanis, **Acta Pharm. Technol.**, **30**, 25 (1985).

23. M.J. Hardy, **Anal. Proc.**, **19**, 556 (1982).

24. A. Smith, **Anal. Proc.**, **19**, 559 (1982).