Oxytetracycline tablet formulations: preformulation stability screening using differential thermal analysis

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The stability testing of developed dosage forms is expensive. Often a number are developed and subjected to a stability testing program with the view of marketing only the most stable. If this operation can be simplified, considerable economies might be made in the development of new drug products. Differential thermal analysis at the preformulation stage offers a possible help in the solution of the problem. By comparing the thermal reaction of the drug and each of a number of excipients with mixtures of drug and excipient, it is possible to select the most promising excipients for use in the development program. Differential thermal analysis will show where an excipient is compatible with a drug. Where an unexpected thermogram results, an excipient may show incompatibility with the drug on storage of the dosage form. While this is not conclusive, because of the elevated temperatures used, the analysis can distinguish between those excipients unlikely to cause a problem and those that may cause instability.

Any chemical reaction either evolving or absorbing heat will be monitored by the analysis. Change of crystalline structure and physical instability caused by eutectic formation will also be observed. Differential thermal analysis has been correlated with stability of oxacillin and dicloxacillin in formulations with stearic acid (Jacobson & Reier, 1969). A modified reheating technique was used by Hentze & Voege (1971) for studying the incompatibility of ampicillin and glucose. The ease and rapidity of eliminating possible incompatible excipients makes differential thermal analysis a useful tool in preformulation work and the relatively small quantities of materials necessary are also an advantage.

In the current study, oxytetracycline was examined for possible incompatibility with a variety of excipients in tablet formulations. The solid-solid instability of various oxytetracline mixtures had previously been studied by Lach & Bornstein (1965, 1966) using diffuse reflectance spectroscopy, which served as a useful basis for this investigation. Additionally, the work of Chalmers & Elworthy (1976), evaluated the effect of various binders and excipients on the mechanical properties of the granules and tablets as well as on the granulation method. Since a formulation might be chosen as a result of this work, it appeared to be worthwhile to evaluate the excipients used, for their possible effect on the stability of the formulation.

A Mettler TA 2000 differential thermal analyser was used with a constant heating rate of 6° min^{-1}. The samples were heated in an atmosphere of nitrogen flowing through the furnace at a flow rate of 20 to 25 cm^3min^{-1}. Samples between 1 and 2 mg were heated in an aluminium crucible using an empty crucible as a reference. The sensitivity range used was 100 μV. The individual substances and mixtures were heated over the temperature range, 30° to 300°.

Samples of oxytetracycline dihydrate and oxytetracycline hydrochloride were supplied by Pfizer (Australia) Pty. Ltd. The excipients used were those normally supplied for use in dosage form development work. No further elucidation of their properties was made.

Fig. 1 shows the rather complex differential thermograms of oxytetracycline hydrochloride (A) and oxytetracycline dihydrate (B). Thermograms of each of the individual excipients were also obtained. Thermograms of mixtures of an excipient with the respective tetracycline were then obtained and compared with those of the individual substances. Loss of the tetracycline peaks or new peaks was taken as evidence of possible incompatibility. The downward shift of peaks, due to depression of melting points, etc. was expected and occurred in many of the traces. Such depressions were not indicative of incompatibility, although severe depression may be indicative of physical instability on storage at room temperatures.

The results of the study are shown in Table 1. The possible incompatibility of sodium alginate with oxytetracycline dehydrate is the result of a severe test, since the excipient was present in the mixture in an equal weight ratio. Chalmers & Elworthy (1976) used a maximum of 3% by weight of alginic acid. The changes observed only occurred above 200° and may not be a problem at room temperature. However, if the reaction

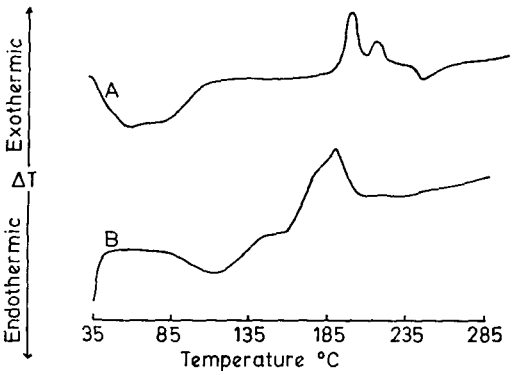

FIG. 1. D.T.A. thermogram of (A) oxytetracycline hydrochloride, (B) oxytetracycline dihydrate.

* Correspondence.

Table 1. *Compatibility of excipients with oxytetracyclines*

Oxytetracycline used	Excipient	Compatible + incompatible −	Range °C incompatibility observed
Hydrochloride	Polyvinyl-pyrrolidone	+	−
Dihydrate	,,	+	−
Hydrochloride	Micro-crystalline cellulose	+	−
Dihydrate	,,	+	−
Hydrochloride	Sodium alginate	+	−
Dihydrate	,,	(−)	> 200
Hydrochloride	Magnesium stearate	−	> 180
Dihydrate	,,	−	> 200
Hydrochloride	Magnesium oxide	−	235
Dihydrate	,,	−	240
Hydrochloride	Calcium gluconate	−	130–200
Hydrochloride	Mannitol	−	195–205
Dihydrate	,,	+	−
Hydrochloride	Anhydrous dextrose	−	185–235
Dihydrate	,,	−	185–235

does proceed at room temperature, it would only be observed after prolonged storage.

With magnesium stearate, the presence of small peaks above 180° for the hydrochloride and above 200° for the dihydrate indicate a degradation reaction. Whilst the test is once again a severe one, it is interesting to note that, using diffusion reflectance spectroscopy, Lach & Bornstein (1966) obtained results indicative of an interaction between oxytetracyclines and magnesium stearate.

Magnesium oxide is a component of commercial magnesium stearate. In equal weight mixtures with oxytetracycline hydrochloride a loss of the endotherm is observed at 235°, whereas a new endotherm at 240° is observed with oxytetracycline dihydrate. These results indicate the possible interaction of magnesium oxide with oxytetracycline in formulations, in agreement with the results of Lach & Bornstein (1966). Albert (1953) and Albert & Rees (1956) have demonstrated the high affinity of oxytetracycline for metallic ions and the absorption of oxytetracycline is known to be impaired by the simultaneous intake of antacids or other drugs containing calcium or magnesium (Sweeney, Hardy & others, 1957; Harcourt & Hamburger, 1957). For this reason, calcium gluconate was chosen for evaluation of its affect on the thermograms of oxytetracycline. Some of the endothermic peaks due to the oxytetracline hydrochloride are lost when heated with an equal weight of calcium gluconate. A new endothermic peak is observed between 130° and 200°. Thus, the known incompatibility is observed using this technique.

These results demonstrate the utility of differential thermal analysis as a quick and rapid method of ascertaining if an excipient is likely to be suitable in a formulation. Although it cannot be conclusive that an interaction incompatibility will occur during storage at room temperature, there are often sufficient excipients available in a preformulation program to choose only those unlikely to cause trouble.

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