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Drug–drug incompatibility in the solid state: kinetic interpretation, modelling and prediction

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Summary

Drug–drug incompatibility in the solid state is modelled using aspirin and mepyramine maleate as test compounds. A diffusional model previously used for describing interactions between drugs and excipients was found to be suitable for describing the kinetics of decomposition of aspirin in the presence of mepyramine maleate. This was so although the profiles of the decomposition products were qualitatively very different to those observed with magnesium stearate (1). No salicylic acid ester other than aspirin was detected during the course of the study with the aspirin–mepyramine maleate mixtures. Addition of mepyramine maleate to aspirin depressed its melting point and the extent of this effect was related to the observed rate constant of decomposition of aspirin in such mixtures. The usefulness and limitations of such mathematical modelling for predicting solid-state incompatibilities during work on the formulation of drugs are discussed.

Introduction

This study forms part of a series of experiments on the modelling of drug decomposition in the solid state. Previous reports have concentrated on drug–excipient incompatibilities using diffusional (Mroso et al., 1982) and suspension (Li Wan Po et al., 1983) models.

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In this report, drug–drug incompatibility is modelled and the kinetics of decomposition in such systems is described.

Products containing more than one active ingredient are widely used. Despite the many criticisms directed towards this practice (Drug and Therapeutics Bulletin, 1980), the convenience of these products to patients will no doubt ensure their continued popularity. Indeed in some cases, such as when synergistic drugs are used for the chemoprophylaxis of chloroquine-resistant malaria, combination products are often considered as first-line products (Hall, 1978). Co-formulation of active ingredients, however, introduces the possibility of drug–drug incompatibility and there is therefore a need for mathematical models for predicting and quantitating such interactions. Although numerous reports on drug–drug incompatibilities have appeared in the literature such as those by Wu et al. (1970) and Jacobs et al. (1966), most of these have tended to be qualitative or semi-qualitative and of those which have been quantitative, the emphasis has been on structural changes occurring during such interactions. Trans-esterification has received particularly close examination (e.g. Troup and Mitchner, 1964; Galante et al., 1979). Generally, little attention is given to the physical changes accompanying the decompositions. A few notable exceptions are described in the work of Guillory and Higuchi (1962), Carstensen et al. (1972) and Guillory et al. (1969). The model drugs chosen for studying this aspect of drug interaction in this study were aspirin and mepyramine, drugs which are potential combinations for products intended for the symptomatic relief of migraine and the common cold (Li Wan Po, 1982).

Theory

Jander's equation for decomposition in the solid state has previously been shown to apply for the decomposition of cylindrical aspirin crystals in the presence of magnesium stearate in the solid state (Mroso et al., 1982):

$$\left[1-(1-x)^{1/2}\right]^2 = \left[\frac{2K}{r_o^2}\right]t \qquad (1)$$

where x = fraction decomposed, t = time, r_o = initial radius of aspirin crystals and K is the rate constant for the thickening of the diffusion layer. The same equation is used in this study.

Experimental

Materials

Salicylic acid, orthophosphoric acid and *n*-propyl-*p*-hydroxybenzoate were obtained from the British Drug Houses (Poole, U.K.), aspirin from Sigma (U.K.), mepyramine maleate from May and Baker (U.K.) and sodium chloride B.P. from McCarthys (U.K.). The salicylsalicylic acid used was a gift from Riker 3M Laboratories (U.K.). The aspirin used came from the same bulk sample as that used previously (Mroso et al., 1982).

Sample preparation and storage

Aspirin crystals were mixed with fixed proportions of mepyramine maleate. 100 mg quantities of each of the mixtures or of pure aspirin were weighed into individual glass vials and loosely covered with cotton wool to prevent entry of condensed water droplets. The samples were then stored at 60°C and 75% relative humidity. To test for homogeneity of the powder mixtures, samples were analysed by high-performance liquid chromatography as described previously (Mroso et al., 1982). Mepyramine maleate eluted at the solvent front and did not interfere with the assay of aspirin and its decomposition products.

Melting point determinations

The melting points of aspirin and its mixtures were determined by the standard capillary tube method using an electro-thermal melting point apparatus (Electrothermal, London). A second set of melting points were also obtained using a Dupont Model 110 differential scanning calorimeter operated at a heating rate of $10°C \cdot min^{-1}$. 20–30 mg samples were used with aluminum as the reference material. The instrument was calibrated with indium.

Results and Discussion

Mepyramine maleate was found to accelerate the decomposition of aspirin. In contrast to magnesium stearate (Mroso et al., 1982), mepyramine maleate did not appear to accelerate the rate of formation of the minor decomposition products, salicylsalicylic acid and acetyl salicylsalicylic acid. Fig. 1 shows the chromatographs of aspirin stored alone and in the presence of mepyramine maleate and magnesium stearate. Although the salicylic acid content was higher than in the magnesium stearate sample, no salicyl salicylic acid or acetyl aspirin could be detected when aspirin was stored in the presence of mepyramine maleate under the same conditions. To explain this difference the effect of mepyramine maleate on aspirin decomposition was studied in closer detail. Increasing mepyramine maleate (Fig. 2) quite clearly increased the rate of decomposition of aspirin, an observation which is similar to that noted with magnesium stearate (Mroso et al., 1982). Again as in this previous study, microscopical examination revealed the rapid formation of a liquid layer around the aspirin crystals when stored with mepyramine maleate. (Fig. 3). Modelling of the rate data using the Jander equation, showed that as with magnesium stearate, a diffusional model seems to be the most appropriate one for the kinetic analysis of the aspirin–mepyramine maleate system (Fig. 4) despite the differences in the profiles of the decomposition products in the two systems (Mroso et al., 1982; and Fig. 1).

To investigate whether the similarities in modelling could be extended further, the effect of mepyramine maleate on the melting point of aspirin was studied. The previous study (Mroso et al., 1982) had shown that the rate constant of decomposition of aspirin in solid mixtures containing magnesium stearate was linearly related to the reciprocal of the melting points of the mixtures. Measurement of the melting

Fig. 1. HPLC of decomposed samples of aspirin stored on its own (a) and in the presence of 5% mepyramine maleate (b) or 5% magnesium stearate (c) for 10 days at 60°C and 75% relative humidity. Key: 0, solvent front; 1, aspirin; 2, salicylic acid; 3, interval standard, propyl paraben; 4, acetylsalicyl salicylic acid; 5, salicyl salicylic acid; and 6, unidentified product.

points of aspirin in mepyramine maleate admixtures revealed a complication which was not apparent with magnesium stearate–aspirin mixtures probably because of the lower concentration of additive used. Observation of the admixed crystals of aspirin and mepyramine during melting point determinations showed the presence of two melting points. The first corresponded to the depressed melting point of mepyramine maleate which in the pure state melts at 99–100°C (Merck Index, 1976) while the second was that of the depressed melting point of aspirin. Pure aspirin melts at 135°C (Merck Index, 1976). Separation of the two melting points was experimentally not difficult because of the large difference in particle size between the fine mepyramine maleate powder and the aspirin crystals which had a geometric mean of 280 ± 1.85 μm as measured by sieve analysis (Edmundson, 1967). Following melting of mepyramine maleate, the residual aspirin crystals were observed to melt at a

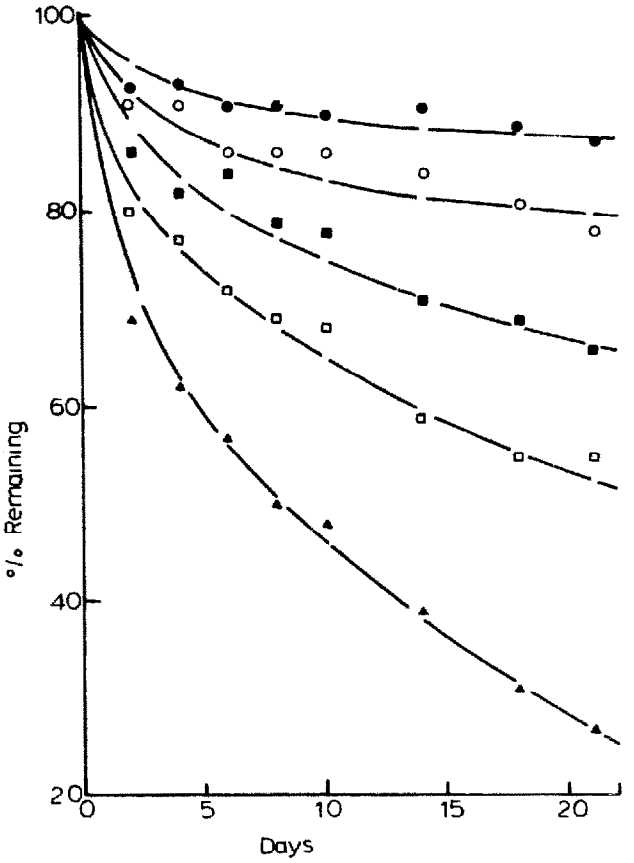

Fig. 2. Effect of concentration of mepyramine maleate on the decomposition of aspirin in the solid state. Key: ●, pure aspirin; ○, 5%; ■, 10%; □, 15%; and ▲, 20% mepyramine maleate.

temperature which was dependent on the percentage of mepyramine maleate present but which was always lower than that of pure aspirin. In the scanning differential calorimeter, the two-stage melting of the aspirin–mepyramine maleate mixtures was observed as two endothermic peaks (Fig. 5). Two sets of melting points could therefore be obtained as was the case with the capillary tube method. The values obtained by DSC were consistently lower than that observed by the capillary tube method.

Fig. 6 shows the effect of percentage composition of the physical mixtures on the melting points observed. It can be seen that at the aspirin/mepyramine maleate ratios used the temperature at which melting was first observed was approximately constant. This eutectic temperature was about 65°C and corresponded to a eutectic composition of about 53 : 47 aspirin to mepyramine maleate on a weight to weight basis or 0.72 : 0.28 on a mole fraction basis. Note that the eutectic temperature was only measurable at the intermediate mepyramine maleate to aspirin ratios in aspirin-rich mixtures and only at one point in the mepyramine maleate-rich mixtures because of broad melting ranges of the other mixtures.

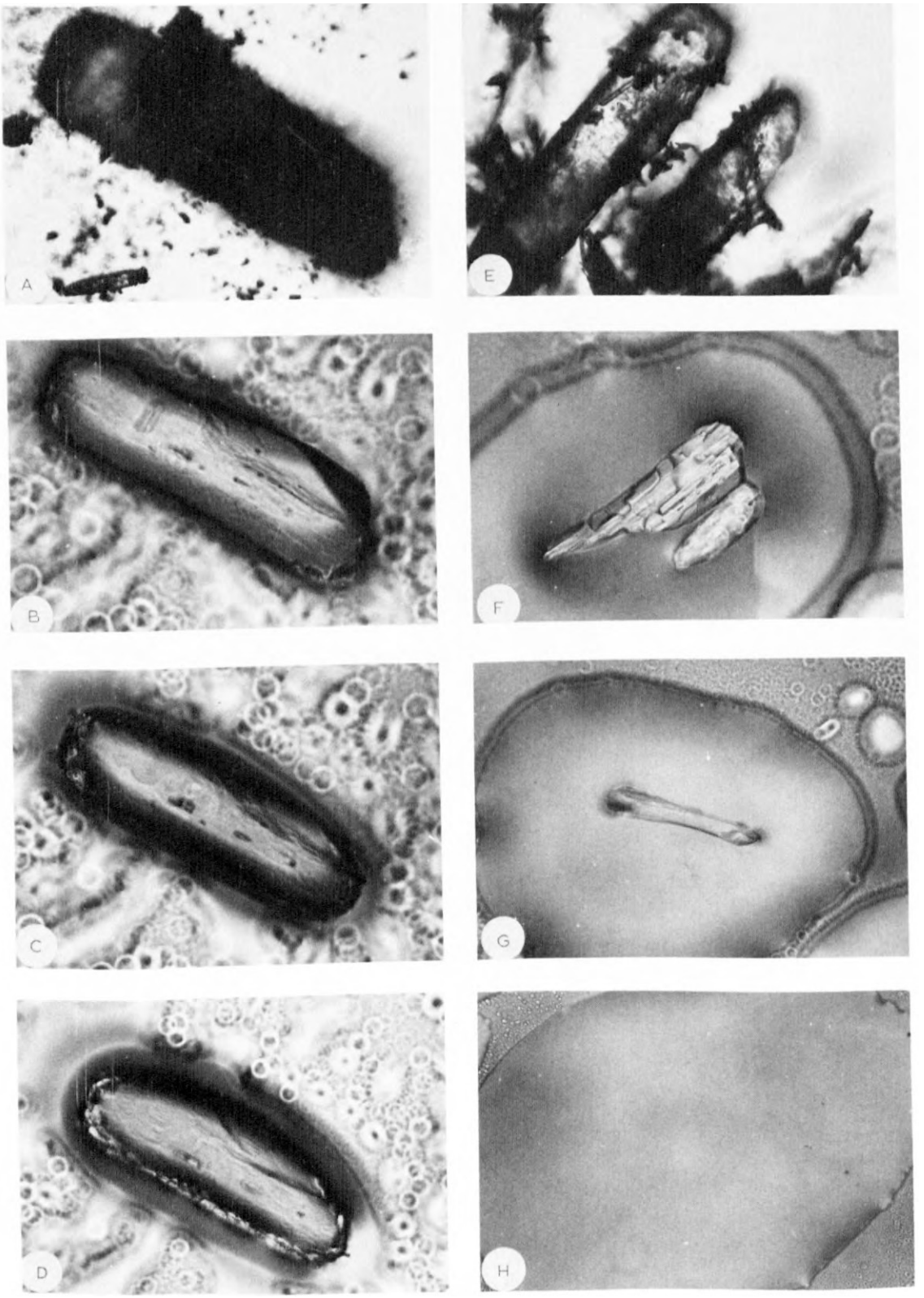

Fig. 3. A–H

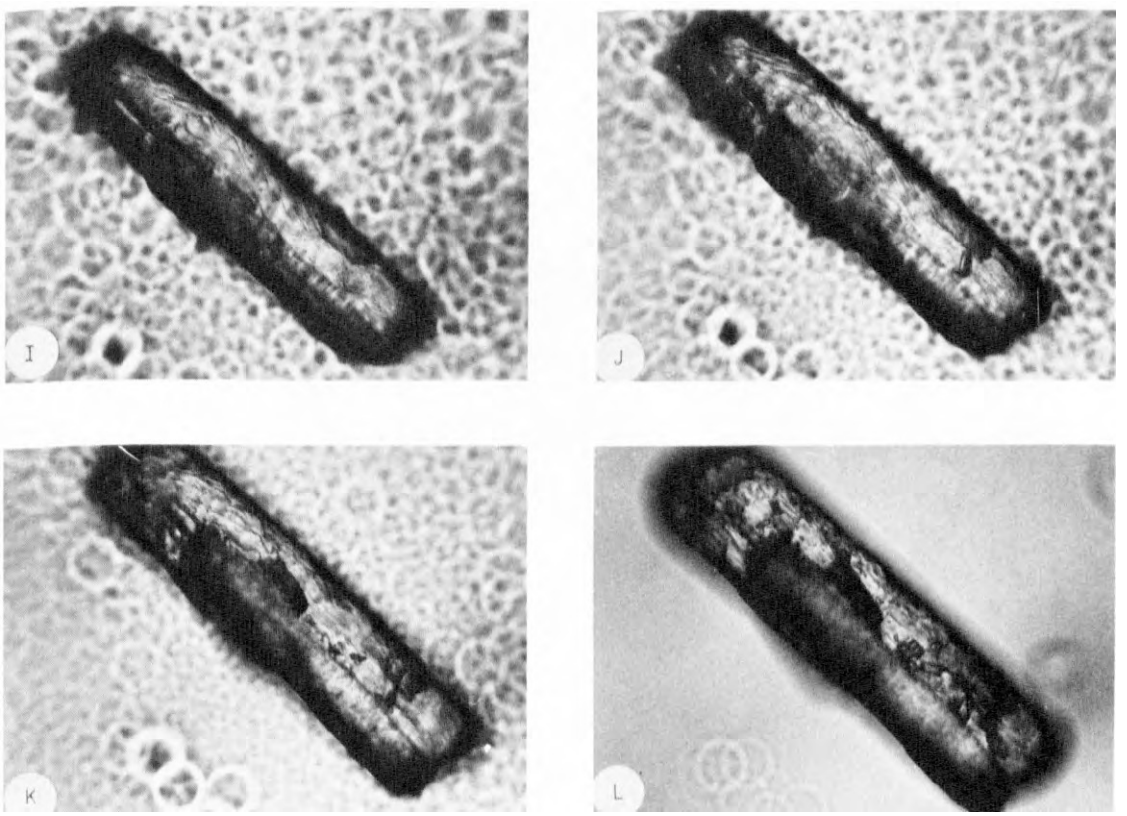

Fig. 3. Photomicrographs of samples of aspirin stored alone (a) and in the presence of mepyramine maleate (b) and magnesium stearate (c) at 60°C and 75% relative humidity. Key: Left column (A–D), aspirin + magnesium stearate; middle column (E–H), aspirin + mepyramine maleate; right column (I–L) aspirin alone—A, day 1; B, day 2; C, day 3; D, day 5; E, day 1; F, day 2; G, day 3; H, day 5; I, day 1; J, day 2; K, day 3, L, day 5.

In the present study, the effect of mepyramine maleate on aspirin melting point was important since aspirin decomposition was being monitored. The temperature corresponding to the second stage of the melting process in the aspirin-rich mixtures was therefore the most appropriate for quantitative correlation with rates of decomposition. Fig. 7 shows the results. The linear relationship between the rate constant, as given by logarithm of the slope of Jander's equation (Eqn. 1), and the reciprocal of the absolute temperature could be represented by equation

$$\log 2k/r_o^2 = 14110/Tm - 9 \qquad (2)$$

Inclusion of the results previously reported for aspirin–magnesium stearate mixtures shows that both sets of data could be modelled by the same equation. This is of great practical relevance since it indicates that screening for depression in melting points on addition of excipients or other drugs during formulation of a given drug is a rapid method for detecting potential incompatibilities. The data also suggest that the effect of any observed melting point depression can be predicted once the regression line has been constructed using a few mixtures.

Fig. 4.

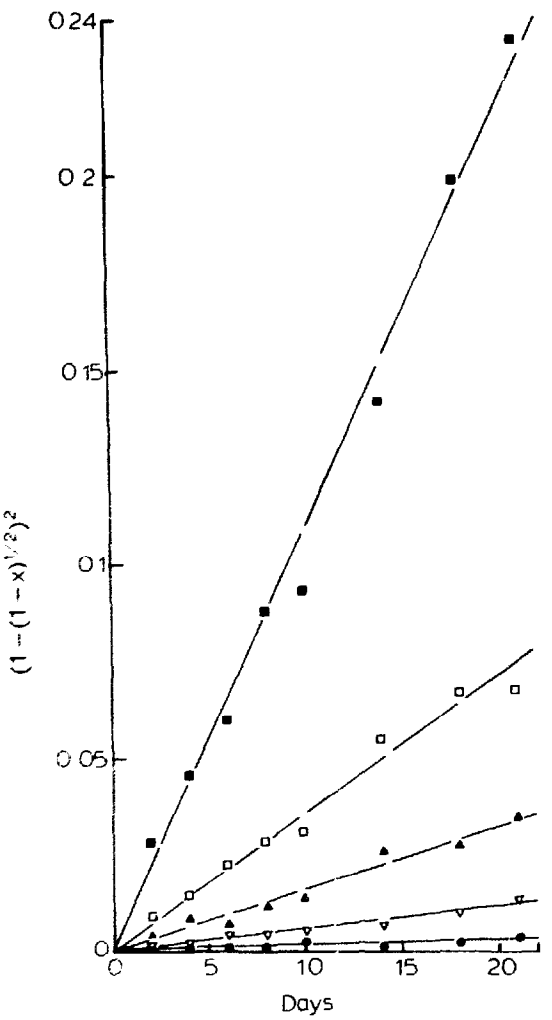

Fig. 5.

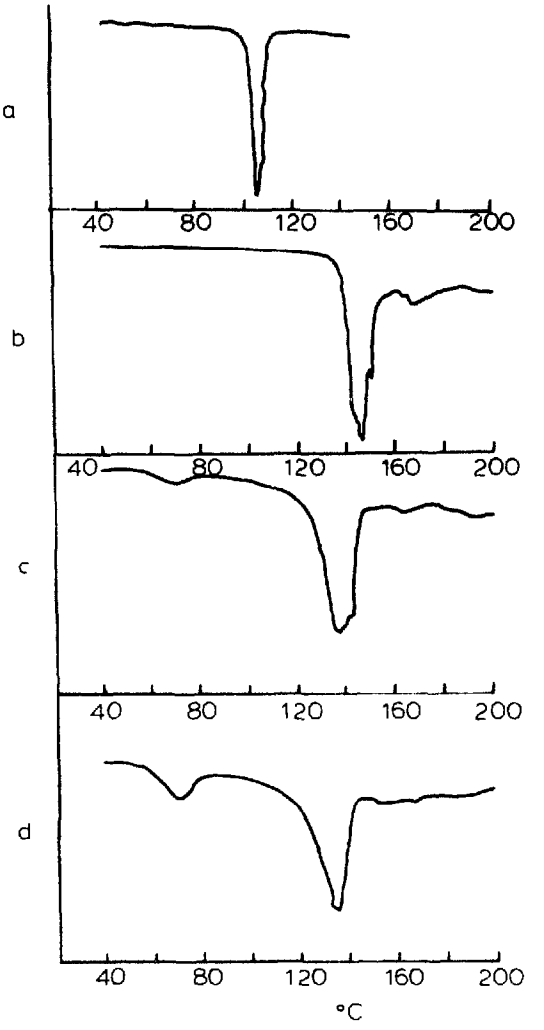

Fig. 4. Data for decomposition of aspirin in the presence of different concentrations of mepyramine maleate plotted according to Eqn. 1. Key: ●, control; ▽, 5%; ▲, 10%; □, 15%; and ■, 20% mepyramine maleate added.

Fig. 5. Melting behaviour of mepyramine maleate (a), aspirin (b), and 10% (c) and 20% (d) mepyramine maleate in aspirin mixtures as shown by differential scanning calorimetry.

Despite the fact that aspirin decomposition in the presence of both magnesium stearate and mepyramine maleate could be modelled by the same mathematical equation, microscopical examination of the two different types of admixtures indicated that there were real differences between them. In addition to the differences in the chemical composition of the decomposed samples (Fig. 1) as revealed by the HPLC analyses, aspirin crystals in mepyramine maleate–aspirin mixtures were found to develop liquid layers much more rapidly than crystals in the magnesium stearate–aspirin mixtures as shown in the photomicrographs (Fig. 3). Yet, the catalytic effects of magnesium stearate were more pronounced than those of

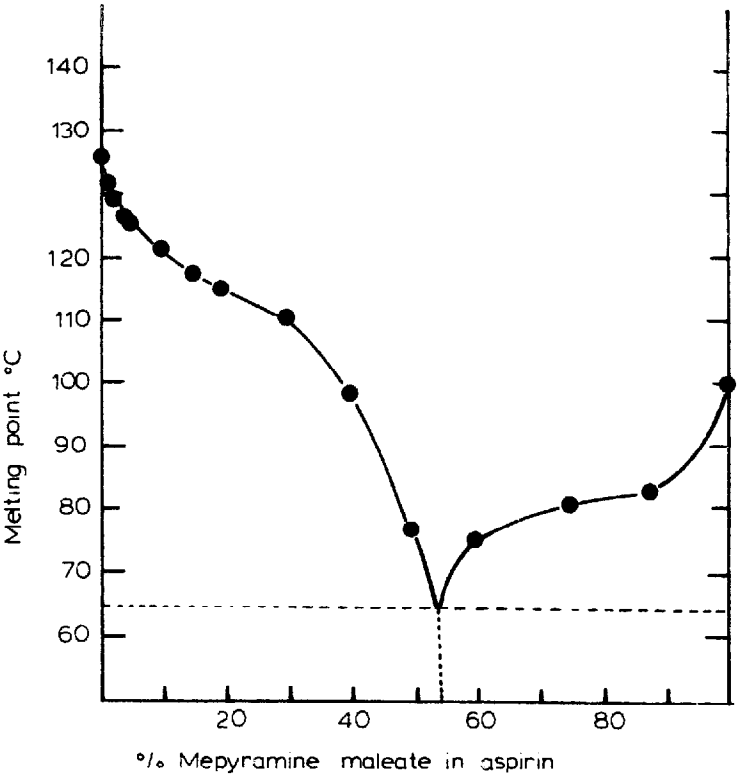

Fig. 6. Melting point characteristics of aspirin–mepyramine maleate mixtures.

mepyramine maleate. Intuitively, one would expect the converse to be true although Jander's model assumes that the rate of reaction is inversely proportional to the thickness of any liquid layer formed. This of course has to be balanced against a much more rapid rate of decomposition in the liquid than in the solid states. The sum of all competing effects is observed in the rate constants of decomposition obtained. The corresponding slopes for the decomposition of aspirin when admixed with either 5% mepyramine maleate or 5% magnesium stearate were 5.73×10^{-4} and 264.6×10^{-4} day^{-1}, respectively, when stored at 60°C and 75% relative humidity.

A possible explanation for the differences in observed behaviour of the aspirin–mepyramine maleate and aspirin–magnesium stearate mixtures is different rates of moisture uptake by the two. Mepyramine maleate is a highly water-soluble drug, having a solubility of 1 g in 0.4 ml of water (Merck Index, 1976) while magnesium stearate is an almost insoluble compound with well-known hydrophobic properties. Mixtures containing these two additives will therefore be expected to exhibit wide differences in water sorption properties. A rapid moisture uptake by the aspirin–mepyramine maleate mixtures would explain the rapid formation of liquid layers round the aspirin crystals (Fig. 3) and the absence of salicylic acid esters, other than aspirin (Fig. 1) in the decomposed samples. Preliminary results suggest that moisture uptake was indeed rapid in aspirin–mepyramine maleate mixtures, but more extensive kinetic experiments on moisture uptake are required to confirm this

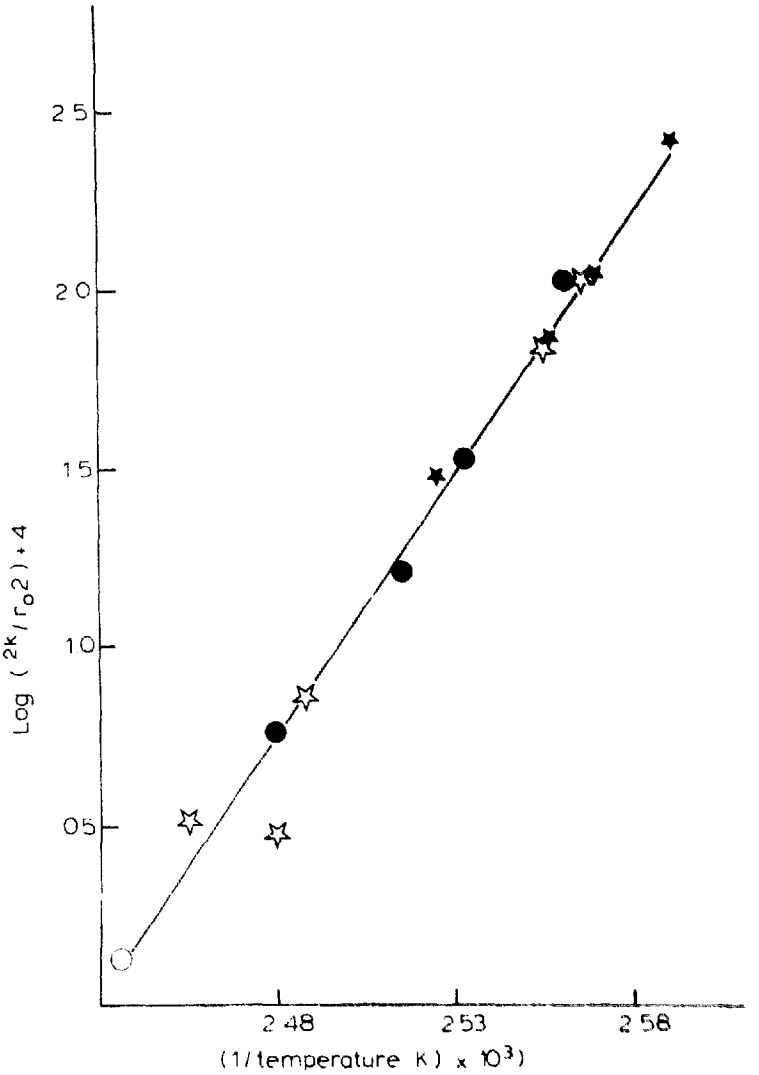

Fig. 7. Relationship between the rate constant (day^{-1}) for the decomposition of aspirin in admixtures with mepyramine maleate, as expressed by the slope of Eqn. 1, and the reciprocal of the melting point (1). Also shown are previously reported data (1) for aspirin decomposition in the presence of magnesium stearate. Key: (☆) magnesium stearate, (●) mepyramine maleate, (★) other metal stearates and (○) aspirin on its own.

explanation. All the evidence, however, still shows that depression in the melting point of aspirin induced by components which are added to it is the mechanism by which decomposition of the drug is enhanced.

Conclusion

Aspirin has now been used by numerous workers in attempts to model the kinetics of hydrolysis of drugs in the solid state. Two basic approaches have been

used. The first proposed the formation of a drug-saturated layer, of adsorbed moisture, in which hydrolysis takes place. This led to the experimental suspension models proposed by Leeson and Mattocks (1958). The second postulates the propagation of reaction nuclei which behaves much like free radical reactions in that a chain initiation step is followed by a chain propagation stage which itself reduces to one of chain termination (Carstensen, 1974; Hasegawa et al., 1975). Diffusion-control may be observed at certain temperatures but not others when decomposition product layers are observed (Nelson et al., 1974). Refinements to take into account the dynamic nature of adsorptions onto solid surfaces have also been reported (Yang and Brooke, 1982). To the student of solid-state kinetics of hydrolabile drugs and in particular of aspirin, the question must be, which then is the best model to use for predicting solid-state decomposition given that more than one model give good-fits. This study and the previous one in the series (Mroso et al., 1982) indicate that in aspirin admixtures, that is in systems usually encountered in practice, a model based on diffusion control across a liquid layer may be most appropriate. Not only is linearization of observed data possible using the mathematical description of the model but observed physical changes are also consistent with it (Fig. 3). These two studies have also demonstrated that depression in melting point may be a useful quantitative predictor of incompatibility (Fig. 7). They do not, however, show that absence of melting point depression is proof of compatibility. Models which only allow for the hydrolysis of aspirin and exclude the formation of other salicylic acid esters such as those identified by Reepmeyer et al. (1979 and 1983) are clearly inadequate for stability testing.

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