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Modelling decomposition in the solid state: stability of salsalate in suspension in the presence of excipients

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Summary

The effect of excipients on the stability of salsalate in suspension is studied in an attempt to model the decomposition of drugs in the solid state. The zero-order rate of formation of salicylic acid is shown to be increased by the addition of alkali stearates, an effect which is produced by alkaline impurities rather than by the pure stearates. Thus, a direct relationship between the concentration of magnesium ions and the rate constants for salicylic acid formation, was found to be secondary to pH changes induced by impurities in the stearates. By following the decomposition of salsalate in both suspensions and solutions, it is shown that the first-order solution degradation rate constants, derived from zero-order suspension rate constants and solubility data, were close approximations to those observed. The potential and limitations of suspension systems for predicting solid state stability are discussed.

Introduction

Drug–excipient interactions in the solid state, leading to stability problems have attracted much attention in the literature. Most of the published studies have, however, tended to be qualitative or semi-quantitative. The paucity of quantitative information is partly explained by the complexity of reactions in solid state, the slow rate of decomposition and the lack of adequate models for predicting the behaviour of such systems. Despite these problems, several elegant attempts at modelling decomposition of drugs in the solid state have appeared in the literature and examples are described by authors such as Carstensen et al. (1972, 1975, 1980),

Guillory and Higuchi (1962), Leeson and Mattocks (1958) and Hasegawa et al. (1975). An interesting approach to accelerated stability testing of solids has been described by Kornblum and Zoglio (1955). By studying the decomposition of aspirin in a suspension system, they concluded that alkali stearates accelerated the decomposition of the drug by forming a buffer system detrimental to aspirin stability. This report describes the use of such a model for studying the stability of salsalate in the solid state and to further explore the model's potential and limitations.

Salsalate or salicyl salicylic acid is a prodrug of salicylic acid. In vivo, it is rapidly hydrolyzed to two molecules of salicylic acid and the same decomposition pathway is observed when the drug is improperly stored (Riker, 1981). One of its claimed advantages over aspirin is its longer plasma half-life. The drug is also claimed to produce less gastric irritation than aspirin (Riker, 1981). Salsalate is promoted for the treatment of conditions such as rheumatoid arthritis when long-term salicylate therapy is beneficial.

Materials and Methods

Salsalate and colloidal silica (Aerosil 200V) were used as received from Riker Laboratories (U.K.). The alkali stearates used were as previously described and characterized by gas liquid chromatography (Mroso et al., 1982). Analytical grade *o*-phosphoric acid, potassium chloride, magnesium chloride, salicylic acid, citric acid and disodium hydrogen phosphate were obtained from British Drug Houses (U.K.) while HPLC grade methanol was purchased from Fisons (Loughborough).

High-performance liquid chromatography (HPLC)

Analyses were performed by high-performance liquid chromatography using the system previously developed for monitoring aspirin decomposition in the solid state (Mroso et al., 1982).

Sample preparation and storage

The decomposition studies were carried out in doubled-distilled water or in McIlvaine's buffer solutions adjusted to the desired ionic strength with potassium chloride. 100 ml of the vehicle were preheated to 50°C in a shaking thermostated water bath and the drug with or without additives were transferred into the reaction vessel at time zero. 2 ml aliquots were withdrawn at predetermined intervals, and filtered through 3 μm membrane filters. The resultant solutions were assayed by HPLC after suitable dilution with water. To avoid precipitation of the drug from the solutions on cooling, sampling syringes and collecting vessels for the filtrates were preheated to 60°C. Known volumes of the filtrates were assayed after dilution to ensure that all the drug present was in solution.

Acid-washed magnesium stearate

1 g of magnesium stearate was added to 200 ml of water, vigorously shaken and filtered through Whatman no. 1 filter paper. The residues were washed twice more

by the same procedure and a third time with 200 ml of distilled water acidified with hydrochloric acid (pH 2.3). The magnesium stearate was then shaken with 200 ml of 95% ethanol to remove any stearic acid precipitated out during the acid wash. The solids were then dried overnight on filter paper and finally at 50°C for 0.5 h before storage in well-closed containers. A 10% suspension of the washed lubricant in distilled water gave a pH of 6.3.

Assay of magnesium ions

Magnesium ions were assayed by atomic absorption spectrometry using a Pye SP 90A meter and magnesium nitrate solutions as standards. Measurements were carried out at 285.2 nm with a slit-width of 0.05 mm and a current of 4 A. The burner was set at 1 cm, the acetylene gas at 0.7 $kg \cdot cm^{-2}$ and the compressed air flow at 4.5 $l \cdot min^{-1}$.

Results and Discussion

High-performance liquid chromatography (HPLC) was chosen for quantitation of salsalate and salicylic acid formed during the decomposition because of its selectivity and because of ease of sample preparation. Although not specifically described for the analysis of salsalate in the presence of salicylic acid, several published methods appear to be suitable for this purpose (Patel et al., 1967; Bundgaard; 1974; Reepmeyer and Kirchoefer, 1979; Irwin et al., 1979). Under the conditions used in this study, salsalate was well resolved from the chosen internal standard, propyl paraben, and from the decomposition product, salicylic acid (Fig. 1). During this assay, care was taken to ensure identical, sample and standard solution, preparation, since it has been shown that the addition of different amounts of organic solvent to the solutions prior to injection, produced significantly altered peak heights (Williams et al., 1980). Analysis of the salicylic acid formed in the suspension systems showed that its rate of formation followed zero-order kinetics. This apparent zero-order profile can be rationalized on the basis of the salsalate decomposition being much higher in solution than in the solid state and on decomposition rather than dissolution being the rate-limiting step. The suspensions were continuously shaken throughout the experiments.

The addition of magnesium stearate significantly increased the rate of decomposition of salsalate. The addition of other alkali stearates revealed that the stearate used apparently also had a strong influence on the rate of decomposition of the drug (Fig. 2). Although the stearates of the divalent metals produced the biggest changes, there was no clear relationship between the cationic charge and the observed effects. The addition of 0.1% magnesium stearate to a 1% suspension of salsalate produced more than a 10-fold increase in the rate of formation of salicylic acid with both batches used while the addition of the same amount of aluminium stearate only led to a doubling in decomposition rate.

Several explanations could account for the observations made so far. The presence of catalytic impurities could explain the batch to batch variation while a direct

Fig. 1.

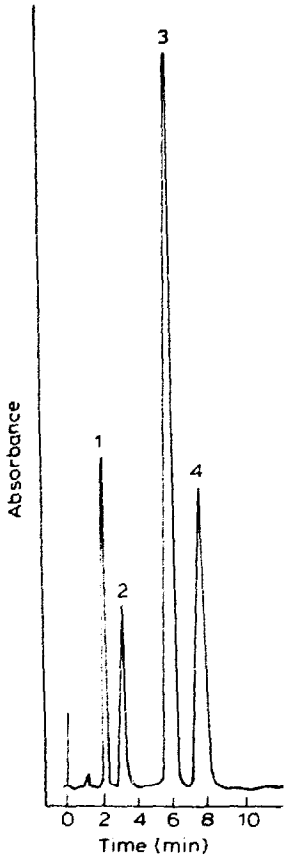

Fig. 2.

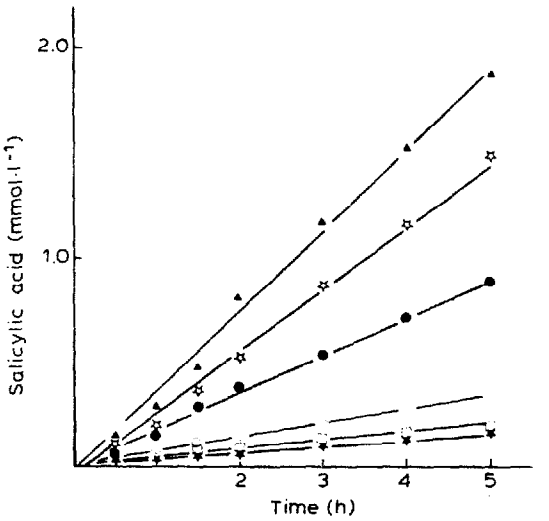

Fig. 1. HPLC separation of aspirin (1), salicylic acid (2), propyl paraben (3) and salsalate (4).

Fig. 2. Effect of alkali stearates and colloidal silica on the rate of formation of salicylic acid from salsalate suspensions at 50°C. ▲, +0.1% w/v magnesium stearate; ☆, +0.1% w/v calcium stearate; ●, +0.1% w/v sodium stearate; ○, +0.1% aluminium stearate; □, +0.03% w/v colloidal silica (Aerosil); ★, salsalate only.

catalytic effect by the metal ions and catalysis on the surface of the excipients could rationalise the effects seen upon changing the alkali stearate. The addition of colloidal silica had no effect on the decomposition of salsalate in suspension (Fig. 2), although such an approach was found to lead to improved stability in solid matrixes (Gore and Banker, 1979). This is to be expected as the mechanism of stabilization in these matrixes is most probably the absorption of free moisture (Gore and Banker, 1979).

In an attempt to provide possible explanations for the observations made, the decomposition of salsalate in the presence of different concentrations of magnesium stearate in solution was studied. A saturated solution of magnesium stearate was prepared by shaking 2 g of the lubricant with 2 litres of distilled water and filtering the suspension through 3 μm membrane filters. The filtrate was then diluted with varying amounts of distilled water to give magnesium concentrations ranging from 15 parts per million (ppm) to 0.15 ppm. A plot of the observed rate constant for

salicylic acid formation against the magnesium ion concentration showed that the two were apparently linearly related and could be described by the equation:

$$K_0 = 7.6 \times 10^{-3}C + 3.3 \times 10^{-3} \quad (\gamma = 0.997)$$

where K_0 = observed rate constant in $mmol \cdot l^{-1} \cdot h^{-1}$ and C is concentration of magnesium ions in ppm.

The intercept should of course be equal to the rate constant in the absence of magnesium ions. Comparison of this value with the experimental value shows the high degree of concordance between the two. Both gave a decomposition rate constant of 3.3×10^{-2} $mmol \cdot l^{-1} \cdot h^{-1}$.

It is tempting on the basis of these results to suggest that magnesium ions exert a direct catalytic effect on the decomposition of salsalate. That hydrolysis is the mechanism of decomposition suggests that the explanation must be elsewhere. Proof of this was obtained by monitoring the decomposition of salsalate in suspension in the presence of 0.1% magnesium chloride. This showed that although a doubling in rate of decomposition was observed when compared with a control system containing no additive, the increase was several times less than that observed with magnesium stearate. This was so despite the fact that at the level used, the magnesium ion content in solution was 1000 ppm in the magnesium chloride system and only 15 ppm in the magnesium stearate system.

To investigate whether the magnesium chloride effect could be attributed to changes in ionic strength, the decomposition was studied in pH 4 buffer adjusted to different ionic strengths. The data showed a linear relationship between the logarithm of the observed rate constant for salicylic acid formation and the square-root of the ionic strength, a relationship which could be defined by equation:

$$\log K_0 = -0.49\sqrt{\mu} - 0.56 \quad (\gamma = 0.997)$$

The dependency was, however, opposite in sign to that observed upon the addition of magnesium chloride and stearates and could not therefore explain the changes induced by these compounds.

In their studies on aspirin suspensions, Kornblum and Zoglio (1955) suggested that alkali metal ions were important in establishing an aspirin–aspirin salt buffer system which then exerted an adverse effect on the stability of the drug. To test whether this mechanism also applies to the salsalate system, given the close similarity between the two, salsalate decomposition was followed in buffers with and without additives and the data compared with those obtained in distilled water. Fig. 3 illustrates the results. It can be seen that with buffering, magnesium stearate no longer accelerated the decomposition of salsalate in suspension. In this buffered system magnesium chloride exerted a small negative effect consistent with that attributable to ionic strength effects.

While the data so far point to the additives exerting their effect by changing the pH of the system, they do not show whether the stearate themselves or whether the impurities present in them are responsible. While it is possible for salsalate to react

with the stearates to produce a buffer system as suggested by Kornblum and Zoglio for aspirin, it seemed more plausible that impurities in magnesium stearate would be the more likely candidates in elevating the pH of the reaction medium. The United States Pharmacopoeial (1980) and the British Pharmacopoeial (1973) grades of magnesium stearate, for example, contained 6.5–8.5% of magnesium oxide although current specifications (British Pharmacopoeia, 1980) ensure a lower level of alkaline contaminants. Jaminet (1968) in fact claimed that magnesium oxide in magnesium stearate was responsible for the observed acceleration in decomposition of their aspirin tablets. To test the possibility that this may be important with salsalate too, its decomposition was monitored in the presence of magnesium stearate purified of some of its alkaline impurities by washing. It was observed that the rate constant for salicylic acid formation in the salsalate suspension was significantly lower using the washed magnesium stearate than using the unwashed product (Fig. 4).

Impurities in the additives therefore appear to be the main explanation for their effects on salsalate stability. The impurities alter the pH and this promotes decomposition. To verify this, the rate of salsalate decomposition as mirrored by the formation of salicylic acid was monitored as a function of pH in a series of salsalate suspensions. Fig. 5 shows the results obtained. The overwhelming role played by pH is illustrated by plotting the earlier data obtained with both buffered and non-buffered salsalate suspensions on the same graph (Fig. 5). It should be noted that the linear relationship between the log of the rate constant and the pH is only applicable over the pH range shown and deviations would be expected at lower and higher pH values (Edwards, 1950), and this is shown in Fig. 6 where the pH profile for the

Fig. 3.

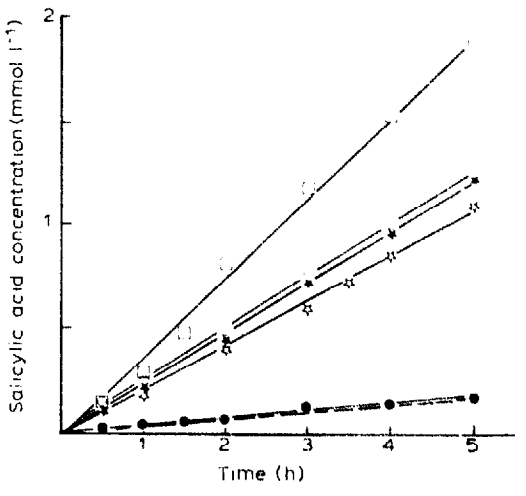

Fig. 4.

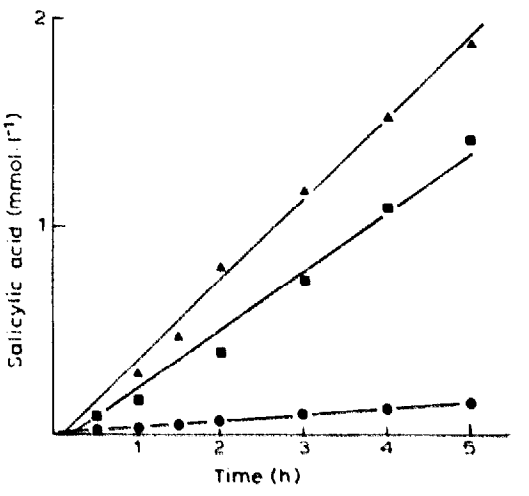

Fig. 3. Effect of magnesium chloride (●, ☆) and stearate (★, □) on the rate of formation of salicylic acid in buffered (☆, ★) pH 4.24 and non-buffered (●, □) salsalate suspensions. - - - - -, salsalate only in water; and ○, salsalate only in buffer (pH 4.24).

Fig. 4. Effect of washing magnesium stearate on the rate of formation of salicylic acid in non-buffered salsalate suspensions at 50°C. ●, salsalate only; ■, +0.1 % washed magnesium stearate; ▲, +0.1% unwashed magnesium stearate.

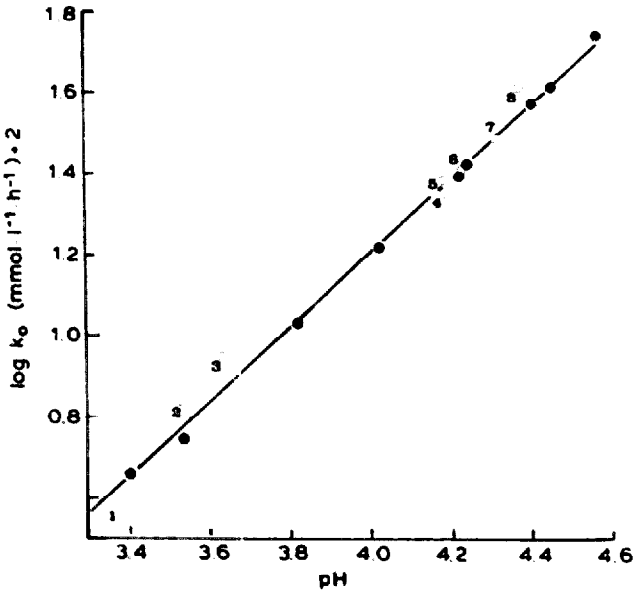

Fig. 5. Effect of pH on the rate constant of formation of salicylic acid in buffered and non-buffered salsalate suspensions. Salsalate in buffers without additive; (1), + $MgCl_2$ in water; (2, 4), + $MgCl_2$ in buffer; (3, 6), + magnesium stearate in buffer; (5,7), + washed magnesium stearate in water; (8), + magnesium stearate in water.

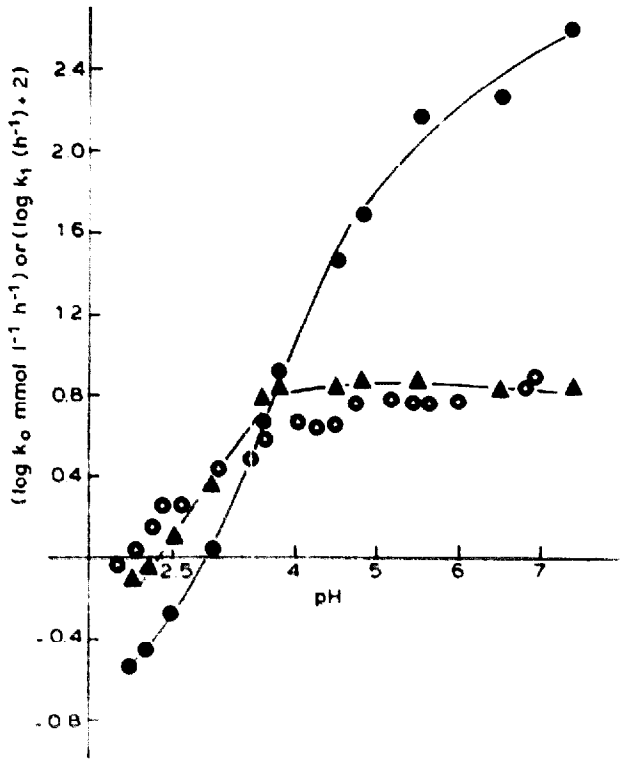

Fig. 6. pH decomposition rate constant for salsalate in buffered solutions (▲) and suspensions (●), ⊙, calculated first-order rate constants from zero-order constants and solubility data.

decomposition of salsalate is monitored over the pH range 2–7.4. Assuming that the decomposition of salsalate in the solid state is much smaller than in solution, and that the rate of dissolution is fast relative to the rate of decomposition, the zero-order rate constant for salsalate decomposition can be equated to the product of the first-order rate constant, K, and the solubility of salsalate in the medium studied. Knowing the solubility, the first-order rate constant can therefore be calculated. This was done at different pH values and the calculated K-values are plotted against pH in Fig. 6. The K_0 values were in mmol salsalate turnover per litre per hour. The K-values obtained by calculation were then compared to those obtained experimentally by following the decomposition of salsalate in solution rather than suspension over a range of pH (Fig. 6). It can be seen that although the trend was similar there was some discrepancy in the two sets of values. This can be rationalized on the basis of the difficulty in obtaining the same precision in the suspension results when compared to solution data.

Conclusion

The model proposed by Kornblum and Zoglio for studying the kinetics of solid state decomposition of hydrolabile drugs is an elegant approach to obtaining accelerated stability data. In this study, the model was used to study the decomposition of salsalate. In using such a model care must be taken to avoid erroneous conclusions being drawn. On the basis of the data presented, it would be reasonable to conclude that in the solid state alkaline impurities will adversely affect the stability of salsalate. It would, however, be unjustified to infer that removing these impurities will ensure compatability between magnesium stearate and salsalate. It has, for example, been shown (Mroso et al., 1982) that with aspirin decomposition this step did not improve compatibility in the solid state. Therefore, a major weakness of the suspension approach to modelling solid-state decomposition is that it will tend to magnify effects which are rapid in aqueous systems and will miss out effects such as transacylation which only take place in the solid state in the presence of limited amounts of moisture (Mroso et al., 1982).

In their work, Kornblum and Zoglio (1967) concluded that the alkaline stearates form buffers with aspirin and that these buffers have pHs detrimental to aspirin stability. The present work indicates that impurities in the alkaline stearates rather than the stearates themselves, are responsible for accelerating the hydrolysis. Reanalysis of Kornblum and Zoglio's data (1967) shows that in the pH 2.6–4.14 range the logarithm of the aspirin decomposition rate constant varied linearly with pH as predicted by earlier data reported by Edwards (1950). The relationship could be expressed by equation ($\log K_0 = 7.2 \times 10^{-1}\ pH - 2.79$) ($\gamma = 0.993$)

This conclusively shows that all the excipient effects described were solely mediated by changes in pH, an effect which is not necessarily true in the solid state where changes in melting point may be more critical (Mroso et al., 1982).

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