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Dissolution characteristics of benzoic acid-Tris mixtures

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Summary

The dissolution rates of mixtures of benzoic acid and a basic excipient, Tris, have been examined. Benzoic acid dissolution rates from benzoic acid-Tris compacts increased to a broad maximum in the Tris content range of 60–70% and then declined. Maximum relative enhancements of 22-, 15- and 7.8-fold were obtained in normal saline, 0.1 M HCl and phosphate buffer, respectively. Benzoic acid solubility increased with increasing Tris concentration in the range 5–50 mg/ml, the relationship being linear in phosphate buffer. The non-interacting model (Higuchi et al., *J. Pharm. Sci.*, 54 (1965) 1405–1410) was modified to account for the solubility enhancing effect of Tris at the solid/solution interface, setting the solubility of the salt as an upper limit. This modified model predicted a plateau in the rate vs composition plot. The experimental results obtained in phosphate buffer were in reasonable agreement with those predicted by the modified model.

Introduction

Solid dosage forms are generally multicomponent, containing excipients which may influence the dissolution rate of the drug. Previously, we have shown that an acid excipient can greatly influence the dissolution rate of an acidic drug. The magnitude of the effect was dependent on a range of factors including the pK_a(s), intrinsic solubilities and the proportions of each component present, the pH and buffering capacity of the dissolution medium as well as the hydrodynamic conditions (Ramtoola and Corrigan, 1987, 1988, 1989). The dissolution rate vs composition profiles obtained deviated from the predictions of the two-component non-interacting model (Higuchi et al., 1965). The deviations were explained in terms of the pH changes occurring in the microenvironment at the solid-liquid interface. The more rapid recession of one acid from the surface led to an increase in surface pH and hence solubility of the surface component. If the relationship between drug solubility and excipient concentration is known, the model may be modified using an iterative method to establish the limiting dissolution rates of the surface component. Good agreement was obtained between the experimental findings (benzoic acid and salicylic acid) and the predicted dissolution rates.

The objective of the current work was to investigate the dissolution of compacts consisting of an acid and a base. Benzoic acid was initially used as a model acidic drug and Tris (Tham) was chosen

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as the base since it is a solid at room temperature and has been suggested as a useful counterion for salt formation with acidic drugs (Gu and Strickley, 1987).

Materials and Methods

Solubility determinations

The effect of Tris on the solubility of benzoic acid in a range of media was determined at 37°C as previously described (Ramtoola and Corrigan, 1987). The solubility of the salt was also determined in isotonic phosphate buffer (pH 7.4) by the same method. Equilibrium was achieved within 48 h and samples filtered through 0.2 μm membrane filters (Gelman Sciences Inc.). On dilution, samples were assayed for benzoic acid by UV spectroscopy (Shimadzu UV. 160).

Dissolution rate method

Dissolution profiles were determined by the static disc method from compressed discs of drug mounted in paraffin wax (Ramtoola and Corrigan, 1987). Powders were ground to a sub 210 μm particle size before use. The pH of the dissolution medium was monitored using a pH meter (PHM 82 Radiometer).

Salt formation

The Tris-benzoate salt was prepared by precipitation from supersaturated ethanolic solution. The purity of the dried precipitate was established by UV spectroscopic assay, differential scanning calorimetry (Mettler) and powder X-ray diffraction analysis (XRD) (Philips).

Results and Discussion

Dissolution studies of compressed mixtures

Benzoic acid dissolution profiles were determined in the following media: normal saline, 0.1 M HCl and phosphate buffer pH 7.4. The effect of Tris content on the dissolution profiles of benzoic acid from mixed discs obtained in saline is shown in Fig. 1. The limiting dissolution rates of benzoic acid for low weight fractions of Tris

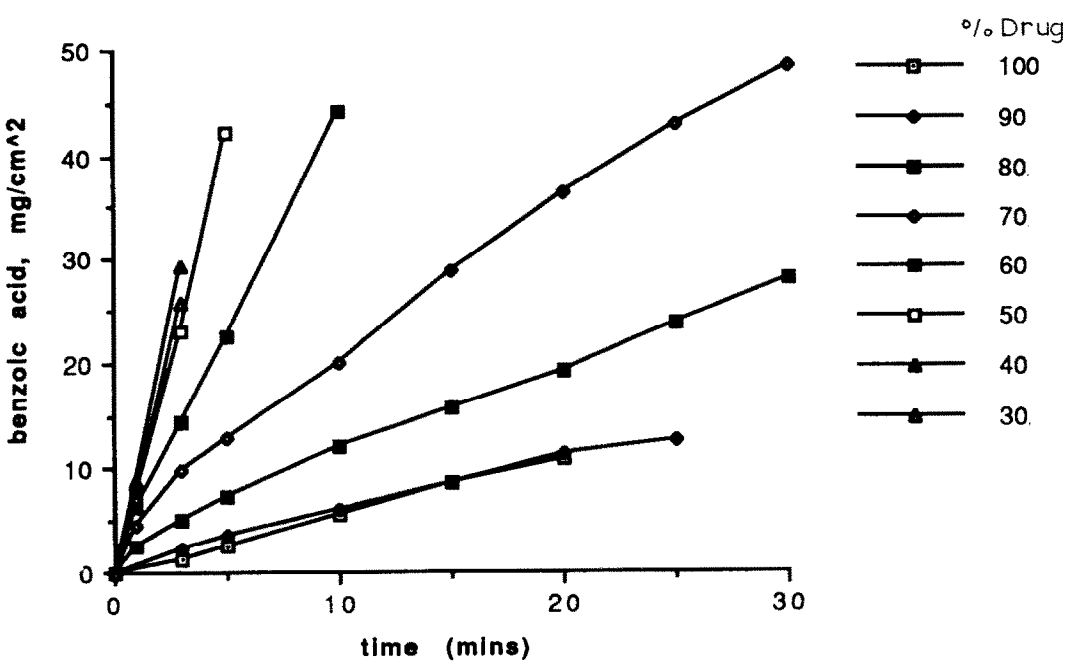


Fig. 1. Dissolution profiles in saline of benzoic acid from mixtures of benzoic acid and Tris.

tended towards that of pure benzoic acid, in keeping with the theory of dissolution from polyphase mixtures (Higuchi et al., 1965). In each medium, rates increased with increasing Tris content to a maximum at a Tris content of 60% and then declined. The more soluble component (Tris) dissolves more rapidly and, for weight fractions up to the critical mixture ratio, a surface layer of benzoic acid is expected from theory to control dissolution. X-ray diffraction patterns of discs following dissolution were consistent with this prediction. Limiting dissolution rates of benzoic acid obtained in each medium are plotted vs Tris content in Fig. 2. A maximum in the rate vs composition curve was seen at the 40 : 60 drug : excipient ratio in each medium (Fig. 2). The intrinsic dissolution rates of pure benzoic acid in saline (pH 5.9), and in 0.1 M HCl were of similar magnitude being 0.443 and 0.437 mg cm^{-2} min^{-1}, respectively. This is consistent with the strong self-buffering action of benzoic acid on the diffusion layer (Mooney et al., 1981). The latter authors showed that the pH at the surface of a pure benzoic acid disc changes little for pH bulk values in the range 3–11 in unbuffered media.

When the dissolution rates were determined in saline the inclusion of Tris in the disc was shown to increase the dissolution rate, to a maximum enhancement of 22-fold at the 60% weight fraction (Fig. 2). Thus, the basic excipient, Tris, increased the surface pH, overcoming the self-buffering effect of benzoic acid.

The intrinsic dissolution rate of pure benzoic acid in phosphate buffer was greater than that in saline or 0.01 M HCl. The presence of the buffer salts together with the OH^- in the bulk medium (total base) caused increased ionization of benzoic acid at the disc surface, the subsequent diffusion of benzoate, together with the undissociated benzoic acid, into the bulk medium accounting for the increased dissolution rate. With increasing Tris content, the rate increased to a maximum, again at the 60 : 40 benzoic acid : Tris ratio, the maximum degree of enhancement being 8-fold. The dissolution rate decreased at the 70 and 80% weight fractions of Tris despite the continued increase in the bulk pH as determined at the end of the dissolution run. This decrease in dissolution rate is a consequence of the low content of benzoic acid in the disc. The maximum absolute enhancement in dissolution rate was therefore obtained in saline (9.8 mg cm^{-2} min^{-1}) and the lowest in 0.1 M HCl (6.5 mg cm^{-2} min^{-1}). The maximum relative enhancement in rate achieved

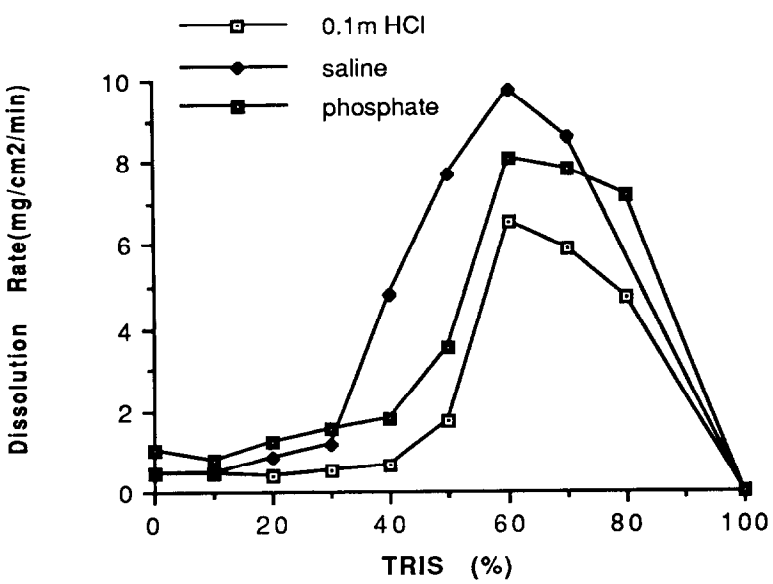
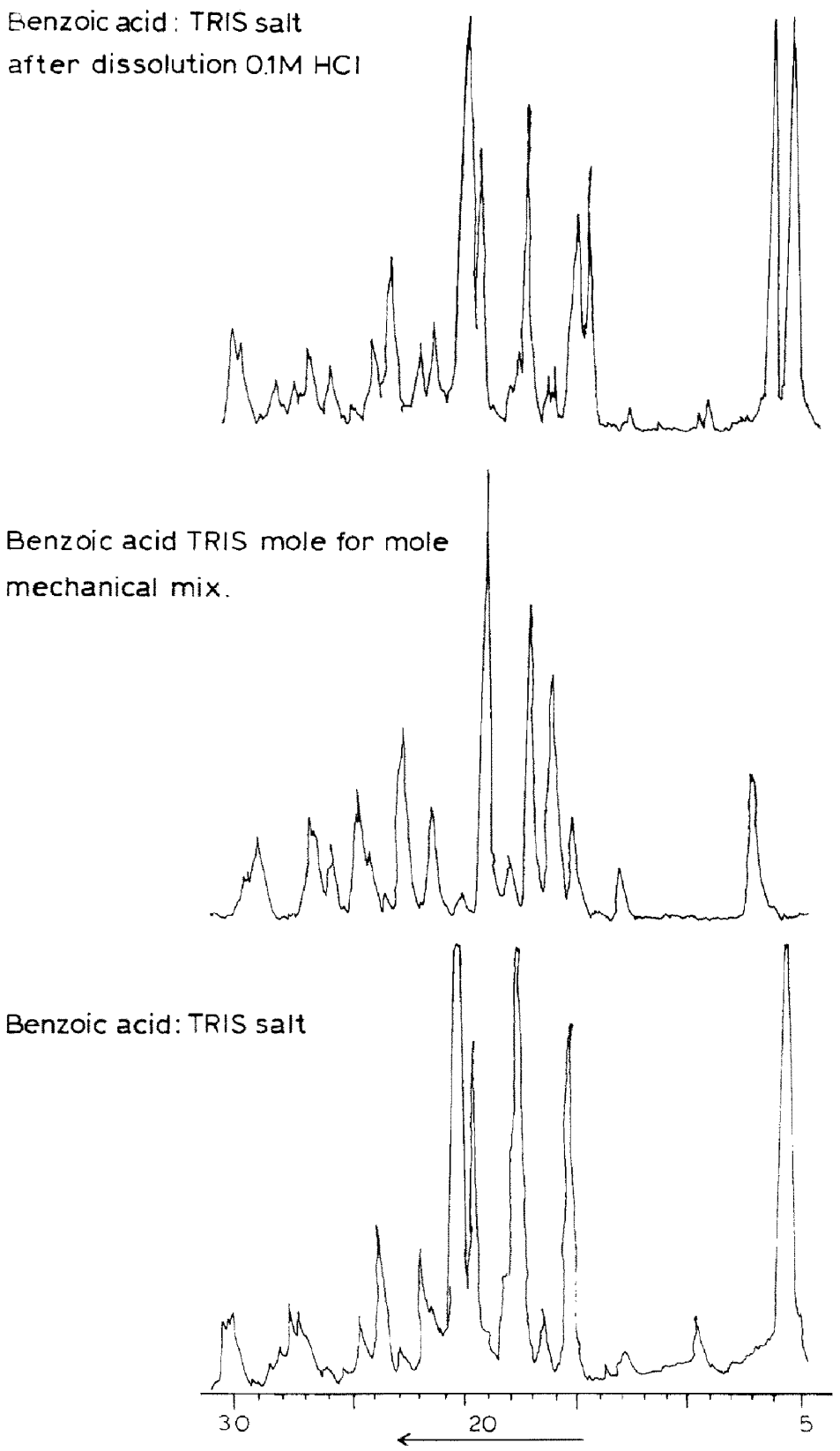


Fig. 2. Limiting dissolution rates for benzoic acid from mixtures with Tris in 0.1 M HCl, saline and phosphate buffer.


Benzoic acid : TRIS salt
after dissolution 0.1M HCl
Benzoic acid TRIS mole for mole
mechanical mix.
Benzoic acid: TRIS salt
30
20
5

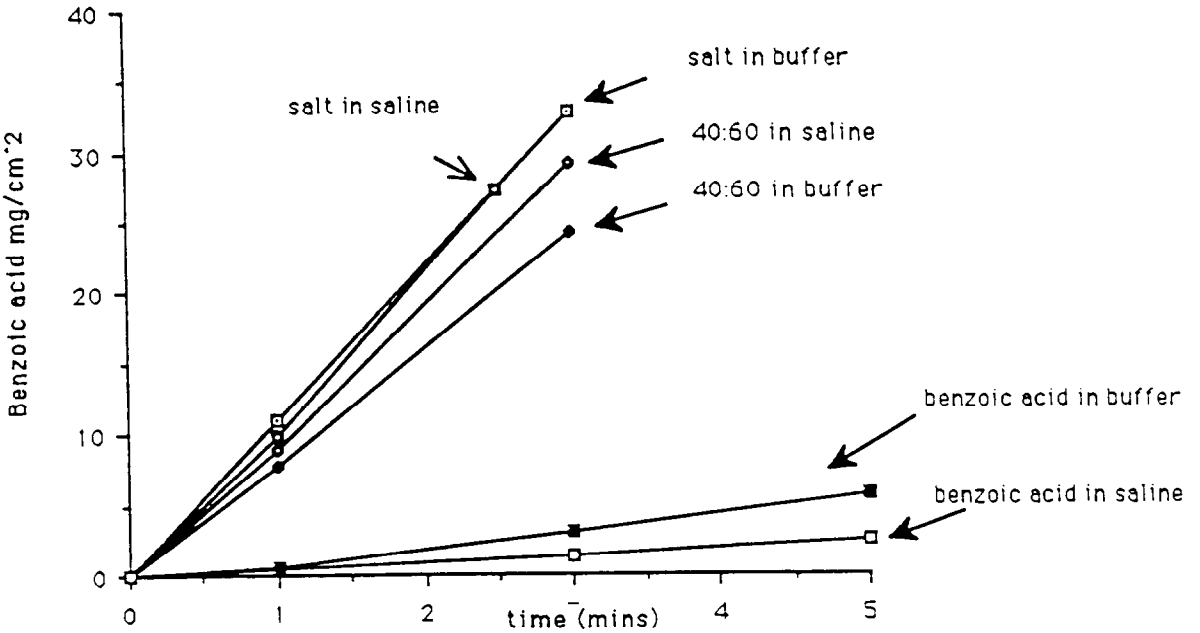


Fig. 4. Dissolution profiles of the salt of benzoic acid and Tris in buffer and saline compared to the dissolution of the 40:60 mechanical mixture and that of pure benzoic acid.

by the inclusion of Tris was also observed in saline (22-fold). However, the lowest relative enhancement was obtained in phosphate buffer, reflecting the higher dissolution rate of pure benzoic acid in this medium. The results of these studies showed that the peak in dissolution rate always occurred at a weight fraction of Tris near, but above, the 1:1 salt-forming ratio.

A salt of benzoic acid and Tris was therefore prepared. The salt formed had a molar ratio of 1:1. The XRD pattern of the salt (Fig. 3) differed from that of a simple mechanical mixture as did DSC scans. Dissolution of the salt in 0.1 M HCl was erratic, resulting in flaking of the disc. XRD of the surface of the disc, after dissolution, showed the presence of undissociated benzoic acid and its salt at the surface. Thus, it seems that the salt was reverting to the free acid form during dissolution as the Tris diffused into the bulk solution. This is consistent with the findings of Serajuddin and Jarowski (1985), who showed that at pH values below the pK_a, the salt of a weak acid prefers to revert to the free acid.

The dissolution profiles for the salt are compared to those of mixtures in Fig. 4. The dissolution rate of the salt in phosphate buffer and in saline was greater than the maximum dissolution rates of mixtures of the salt-forming components. The rate for the salt may be somewhat overestimated because of the flaking mentioned above. Interestingly, it is evident that the mixtures containing a high weight fraction of basic excipient can achieve dissolution rate enhancements of the same order of magnitude as the salt.

Ageing experiments on mixtures of benzoic acid and Tris demonstrated that salt formation in the solid phase had not occurred before dissolution testing was carried out on the disc, no XRD or DSC changes being observed over a period of at least 14 days.

Fig. 3. X-ray diffraction patterns of the salt of benzoic acid and Tris, before and after dissolution in 0.1 M HCl and of the mechanical mixture.

Solubility studies

The effect of Tris concentration on the solubility of benzoic acid in phosphate buffer and in 0.1

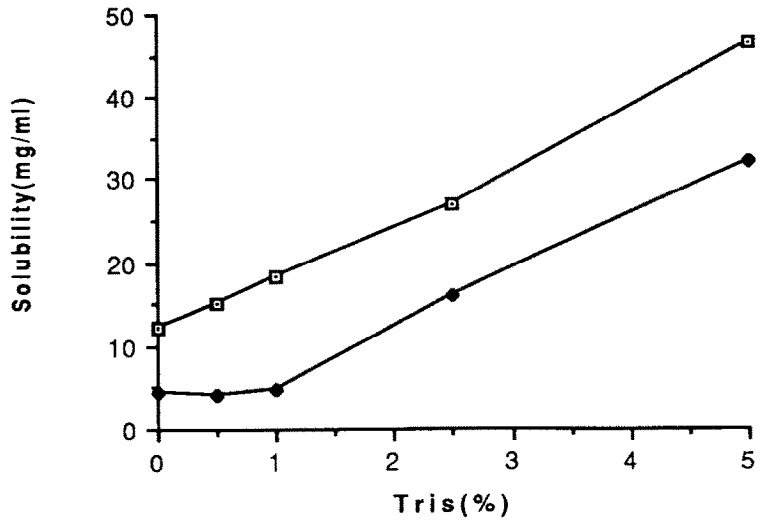


Fig. 5. Effect of Tris on the solubility of benzoic acid in phosphate buffer (⊡ ——— ⊡) and 0.1 M HCl (♦ ——— ♦).

M HCl was determined. The solubility of benzoic acid increased linearly with increasing Tris concentration in phosphate buffer (Fig. 5). There was an initial nonlinearity in the solubility profile in 0.1 M HCl possibly due to consumption of Tris as a result of HCl from the medium forming Tris-HCl, with little change in bulk pH of the starting medium. The increase in solubility of benzoic

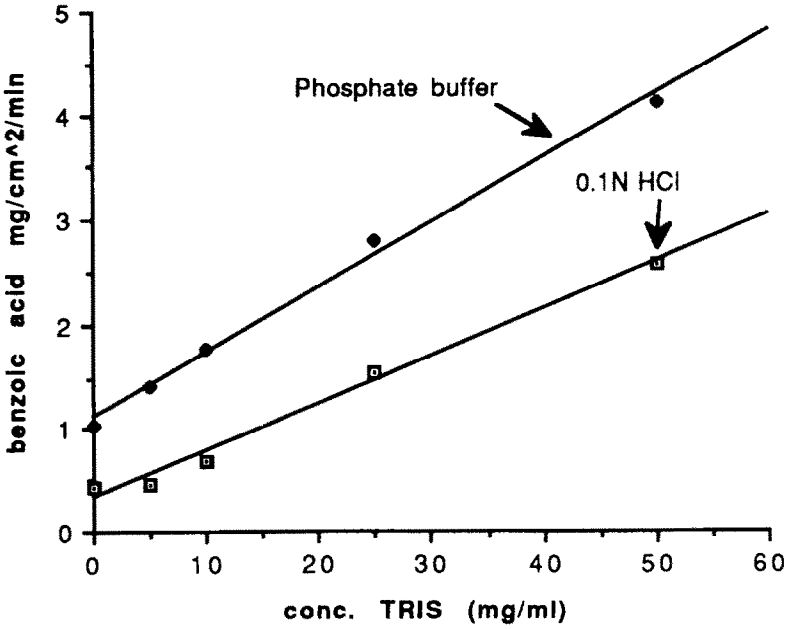


Fig. 6. Plot of the dissolution rate of benzoic acid vs concentration of Tris in the bulk medium.

acid became linear for concentrations of Tris greater than approx. 0.1 M (i.e., 1% Tris in the bulk solution) (Fig. 5). The pK_a of benzoic acid was determined from the plot of solubility vs $1/[H^+]$. A value of 4.11 was obtained which is in good agreement with the literature value of 4.19. The solubility of the salt in water was measured (gravimetric method) and found to be 310 mg/ml.

Plots of benzoic acid dissolution rate (mg cm^{-2} min^{-1}) vs solubility (mg ml^{-1}) in acid and in buffer yielded slopes of 0.0757 and 0.0892, respectively. The slope of these plots gives an estimate of D/h for the system. Using a value of $h = 62 \times 10^{-4}$ cm, previously determined, values of D (cm^2 min^{-1}) of 4.69×10^{-4} and 5.53×10^{-4}, respectively, were obtained. Literature values are 3.97×10^{-4} (Stokes-Einstein) and 5.76×10^{-4} (Mooney et al., 1981).

Assuming that Tris is the only basic species present and that the Tris diffusing to the surface is consumed in reaction with benzoic acid (i.e., [base] surface is zero) then:

$$\text{rate} = (D_{HA}/h)C_s + (D_{Tris}/h)C_{Tris} \quad (1)$$

Then a plot of dissolution rate of benzoic acid vs bulk concentration of Tris will be linear with an intercept of $(D_{HA}/h)C_s$ and a slope of (D_{Tris}/h), where C_{Tris} is the bulk concentration of Tris. Plots of experimental rates vs C_{Tris} in acid and in phosphate buffer are shown in Fig. 6. The plots are roughly parallel, the difference in the intercepts accounting for the contribution of the phosphate buffer salts in increasing the dissolution rate. The data obtained from dissolution studies in 0.1 M HCl exhibited a sharper peak in rate than that obtained in phosphate buffer (Fig. 2). Therefore, an attempt was made to fit these data to the interacting model of Higuchi et al. (1965). Thus, it was assumed that benzoic acid and Tris reacted at the disc surface forming a salt, which then diffused into the bulk solution. The diffusivity of the salt was assumed to be that of the free acid, and k, the binding constant, was estimated using a simplex least-squares procedure. The model predicted a degree of enhancement of 40-fold at the critical mixture ratio estimated to be between the 60 and 70% weight fraction of Tris. A sharp peak in the rate vs composition profile was also predicted in contrast to the broad plateau observed experimentally. Thus, poor correlation with this model was obtained. The two-component non-interacting model was therefore modified to account for the solubility-enhancing effect of the basic component Tris, on benzoic acid solubility at the disc surface. The equation employed to estimate the limiting rate of the surface component, i.e. benzoic acid (G_{ba}) was:

$$G_{ba} = D_{ba} \cdot C_{bas(h=0)}/h \quad (2)$$

where G_{ba} is the dissolution rate per unit surface area, D_{ba} denotes the diffusion coefficient, $C_{bas(h=0)}$ is the solubility at the interface and h is the diffusion layer thickness. The limiting rate of the receding component Tris (G_t) was obtained from:

$$G_t = G_{ba} \cdot N_t/N_{ba} \quad (3)$$

where N_t/N_{ba} represent the relative proportions of the two phases in the disc. The recession of Tris (t) from the surface leads to an alteration in the surface solubility of benzoic acid. This change was accounted for iteratively by estimating the surface concentration of the receding phase (Tris) $C_{t(h=0)}$ from:

$$C_{t(h=0)} = G_{ba} \cdot h \cdot N_t/(D_t \cdot N_{ba}) \quad (4)$$

and then recalculating the benzoic acid solubility at the surface from the relationship between benzoic acid solubility and Tris concentration. This approach was previously used successfully to predict the dissolution rates of acid mixtures (Ramtoola and Corrigan, 1987). Thus, the linear relationship between the solubility of benzoic acid and Tris concentration was incorporated into the non-interacting model of Higuchi et al. (1965). Furthermore, it was assumed that the solubility of benzoic acid will increase only to that of the Tris salt. The predicted profile for drug dissolution in phosphate buffer, using this modified model, shows an increase in dissolution rate to a maximum at the 60% weight fraction of the Tris, consistent with the experimental findings. There

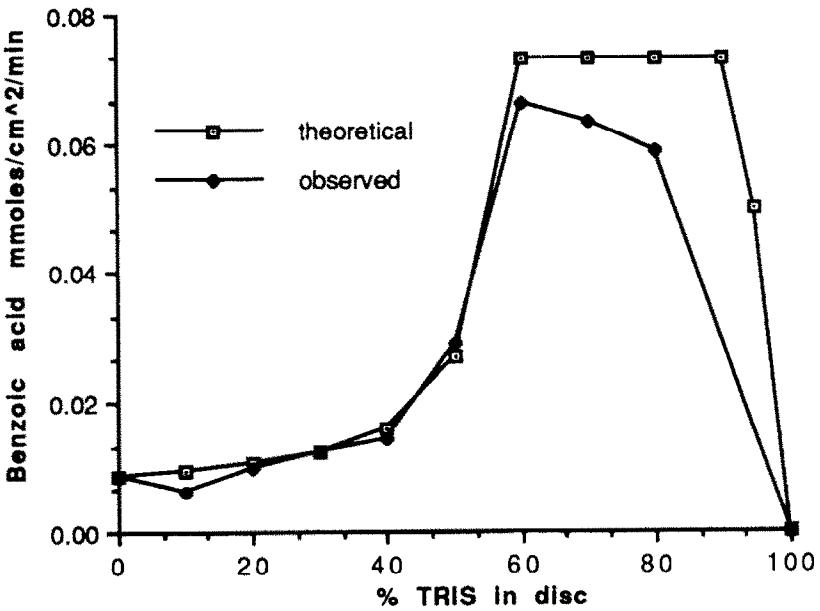


Fig. 7. Comparison of benzoic acid dissolution rates in phosphate buffer predicted by the two-component (linear solubility) model with the observed results.

is then a plateau in rate predicted, when the components enter into solution as the salt. The rate decreases when the critical mixture ratio, estimated to be 91.11% Tris, has been exceeded. The 'linear solubility' model prediction, together with experimental data (limiting rates in phosphate buffer), is illustrated in Fig. 7. The observed data are in reasonable agreement with the model. The rates, however, form a broad peak rather than a plateau as predicted by the modified model. The solubility of the salt was determined from the dissolution rate of the salt in phosphate buffer (since $G = (D/h)C_s$ and D for the salt is assumed to be that of the free acid). This yielded a value of 117 mg/ml which gives a predicted increase in G_{ba} of 7.86-fold. The value obtained experimentally was 7.76.

The dissolution data obtained in 0.1 M HCl correlated to a lesser extent with the modified model. In this case, the model predicted a maximum at the 65% weight fraction of Tris, in contrast to that observed of 60%. The poor correlation at low weight fractions of Tris was due to the non-linearity in the benzoic acid solubility profile in Tris. A 13.11-fold maximum increase in dissolution rate was predicted. This prediction compared favourably with the observed increase of 15.2. Serajuddin and Jarowski (1985) reported the formation of supersaturated solutions of salt in and around the molar ratio, when the salt-forming components are combined. Such a phenomenon may be occurring at the 40:60 ratio giving rise to dissolution rates higher than those predicted by the model.

In conclusion, modification of the two-component model to take account of solubility changes at the solid-liquid interface, arising from the more rapid dissolution of one component from the surface, gives a reasonable prediction of the composition vs dissolution profiles of acid-base mixtures such as benzoic acid and Tris, provided the solubility of the salt is set as the upper limit of solubility.

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