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Dissolution kinetics of three component non-disintegrating compacts: theophylline, benzoic acid and salicylamide

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Abstract

The dissolution characteristics of three component compacts containing theophylline, benzoic acid and salicylamide were investigated over a wide range of compositions, the dissolution profiles of all three components being monitored. Benzoic acid and theophylline interacted to form a soluble complex with an apparent binding constant of 37.1 l/mol. Reasonable agreement between individual component steady state dissolution rates and those predicted by a three component diffusion controlled dissolution model, with two components interacting to form soluble complexes, was obtained. Benzoic acid rates tended to be higher than predicted in the absence of salicylamide while theophylline dissolution tended to be lower than predicted. Plateaus in the theoretical profiles for salicylamide rate versus composition reflected the absence of complex formation by this component and its lower intrinsic dissolution rate, which resulted in it forming the surface layer over a wider composition range.

Keywords: Benzoic acid; Dissolution mechanisms; Multi-component compacts; Salicylamide; Theophylline

1. Introduction

Many pharmaceutical solid dosage forms are multi-component compacts, yet few detailed studies have been conducted aimed at predicting drug dissolution of each component from such systems. The theoretical basis for predicting polyphase mixture dissolution was first outlined by Higuchi et al. (1965) and concentrated on two component non-interacting and interacting systems. The steady state dissolution rates from constant surface area compacts of each component were diffusion controlled, release being dependent on the

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solubilities, diffusion coefficients and proportions of the two components as well as the mass transfer resistances due to an aqueous boundary layer (h) and porous surface layer (s) present. In essence this work showed that, in the steady state, the dissolution rate of the surface component controlled the dissolution rate of the more rapidly receding component. Good agreement between the theoretical predictions and experimental results was obtained. These findings have been corroborated in a number of subsequent studies (Shah and Parrott, 1976; Corrigan and Stanley, 1981; Carmichael et al., 1981; Parrott et al., 1983; O'Reilly and Corrigan, 1995). Carmichael et al. (1981) investigated the dissolution of two and three component spheres and compared the experimental and theoretical sphere weights after 2 h and the average flux of each dissolving component at 2 h. They reported reasonable qualitative agreement with the theoretical predictions, however in some cases actual average dissolution rates were systematically four times greater than the theoretical predictions. Subsequently (Simpson and Parrott, 1983) developed the equations to predict the steady state dissolution rates of each component from three component non-interacting compacts and data using spheres gave reasonable agreement with theory (Simpson and Parrott, 1983; Parrott et al., 1983). The use of spheres of decreasing surface area and possibly also decreasing h, in the later studies, complicated interpretation of the results.

The objective of this work was to systematically investigate the steady state dissolution rates of two and three component compacts containing theophylline, benzoic acid and salicylamide using the constant surface area static disc dissolution methodology thus enabling a better comparison of the experimental dissolution results with theory. As theophylline and benzoic acid formed a soluble complex in solution, equations are presented to predict the dissolution rate per unit surface area of each component from three component compacts where two components interact to form such a soluble complex.

2. Theory

The dissolution of each individual pure component is considered to be diffusion controlled. Hence according to the Nernst–Brunner film theory the dissolution rate per unit surface area (G) of a pure component (n) under sink conditions is given by:

$$G_n = D_n C_{sn}/h \quad (1)$$

where D_n is the diffusivity, C_{sn} is the solubility

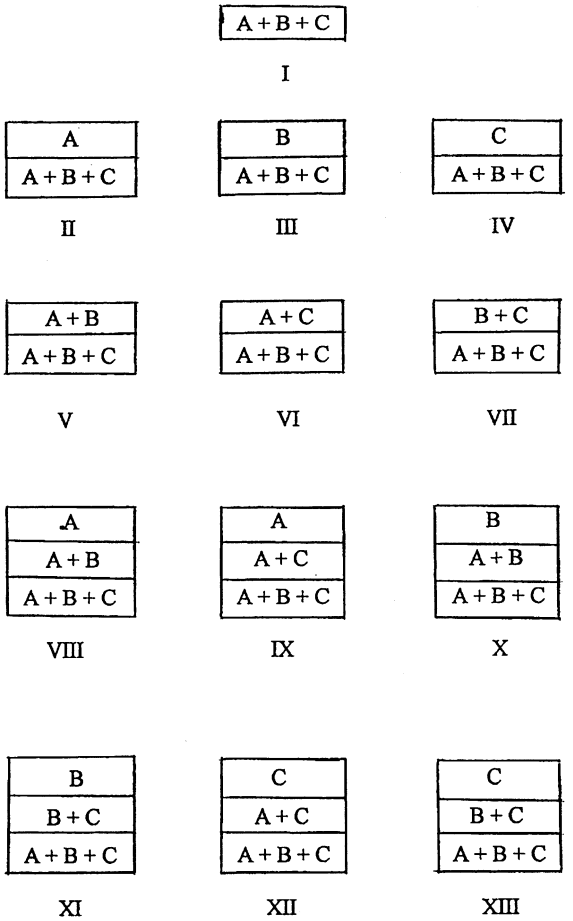

Fig. 1. The 13 different dissolution interface compositions possible for a three component dissolving solid at steady state (dissolution occurring from the upper surface only). I represents the critical mixture case where the three component boundaries recede at the same rate, II–VII two of the components recede at the same rate and VIII–XIII all three component boundaries recede at different rates.

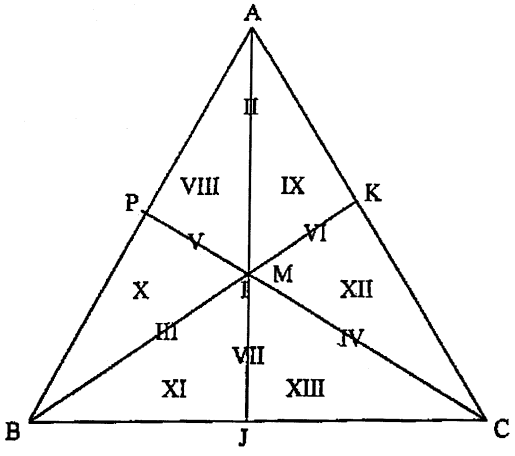

Fig. 2. Theoretical phase composition diagram for a non-interacting three component mixture of components having equal solubilities and diffusion coefficients showing the regions corresponding to the 13 dissolution behaviours represented by Roman numerals.

of component n and h is the diffusion layer thickness.

In compacts having more than one component extra resistances to dissolution may develop for some components present due to recession of the component from the solid surface exposed to the dissolution medium. With the dissolution of three component systems, if one assumes a Nernst–Brunner film theory, there are 13 different dissolution behaviors possible at steady state (Fig. 1).

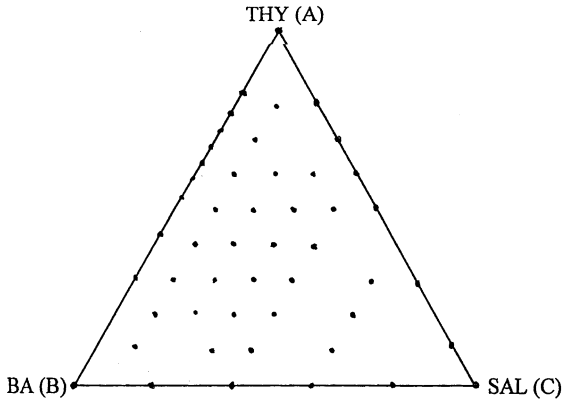

Fig. 3. Composition diagram for three component theophylline [TH(A)] benzoic Acid [BA(B)] and salicylamide [SAL(C)] mixed compacts showing the compositions of systems studied as solid circles.

Fig. 2 shows the compositions corresponding to the 13 dissolution behaviors cited for three hypothetical non-interacting components which have equal solubilities and diffusion coefficients. Each corner of the triangle represents a compact composed of a single component, and the three straight lines joining the corners of the triangle represent the two component compositions. The lines AB, BC and AC represent two component mixtures of A and B, B and C and A and C respectively. The intercept of any three lines parallel to one of these lines AB, BC and AC represents the composition of a particular three component system.

The points P, K and J represent the critical compositions for the two component systems AB, AC and BC, respectfully. The point M where the lines AJ, BK and CP intersect represents the composition where the three components will recede together at the surface (case I). Points along the lines MP, MJ and MK represent the compositions where two components recede together at the surface (cases V–VII). Cases II–IV are represented by points along the lines AM, BM and

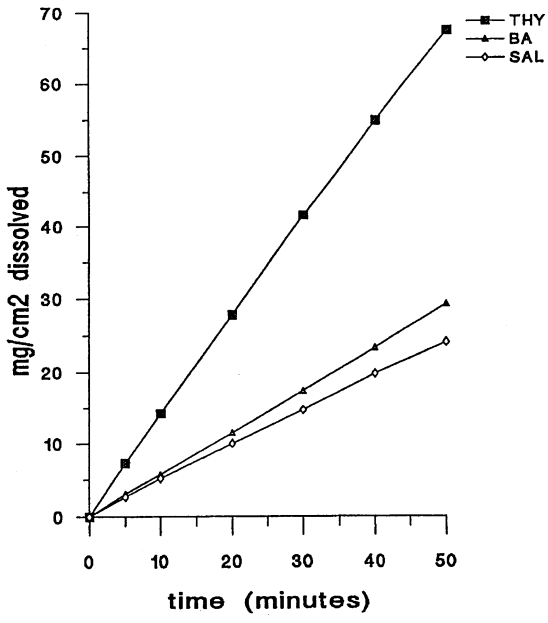

Fig. 4. Dissolution profiles of single component compacts containing theophylline, benzoic acid and salicylamide in an isotonic pH 2 medium at 37°C.

Table 1
Solubilities, intrinsic dissolution rates and diffusion coefficients at 37°C of theophylline, benzoic acid and salicylamide

Compound	Solubility (mg/ml)	Dissolution rate (mg/cm^2 per min)	Diffusivity (cm^2/min $\times 10^{-4}$)
Theophylline	13.4	1.359	6.47
Benzoic acid	5.21	0.583	7.14[a]
Salicylamide	4.58	0.478	6.72[a]

[a] From Ref. Simpson and Parrott (1983).

CM. All other compositions are represented by the areas enclosed within these lines (Fig. 2).

When components A and B form a soluble complex in solution, the lines AJ and BK will be curved. However AJ, BK and CP will still intersect at the point M corresponding to case I dissolution behavior.

In case I dissolution behavior (critical mixture composition), the three components A,B,C, coexist at the solid–liquid interface. For non-interacting systems this behavior occurs at the unique composition where

$$N_A/N_B = D_A C_{SA}/D_B C_{SB} \quad (2)$$

$$N_A/N_C = D_A C_{SA}/D_C C_{SC} \quad (3)$$

It follows from Eqs. (2) and (3) that

$$N_B/N_C = D_B C_{SB}/D_C C_{SC} \quad (4)$$

where N_A, N_B and N_C are the mass fractions of the components.

In cases II–IV one of the components forms the surface layer, the other two component interfaces receding at the same rate. In case VIII, component C dissolves faster than A and B, and the dissolving boundary of component C recedes into the solid. Component B dissolves faster from the solid surface than component A, such that the dissolving boundary of component B recedes within the solid leaving a surface layer of component A. Case VIII dissolution behavior occurs under the conditions that

$$N_A/N_B > D_A C_{SA}/D_B C_{SB} \quad (5)$$

$$N_A/N_C > D_A C_{SA}/D_C C_{SC} \quad (6)$$

$$N_B/N_C > D_B C_{SB}/D_C C_{SC} \quad (7)$$

The other dissolution behaviours may be explained in an analogous manner.

Theoretical predictions of steady state dissolution rates (G) for a three component system containing two interacting components (A and B) were obtained by combining the two component non-interacting model of Higuchi et al. (1965) with their two component interacting model as follows:

$$G_A = (D_A C_{SA} + D_{AB} K C_{SA} C_{SB})/h \quad (8)$$

$$G_B = (D_B C_{SB} + D_{AB} K C_{SA} C_{SB})/h \quad (9)$$

$$G_C = D_C C_{SC}/h \quad (10)$$

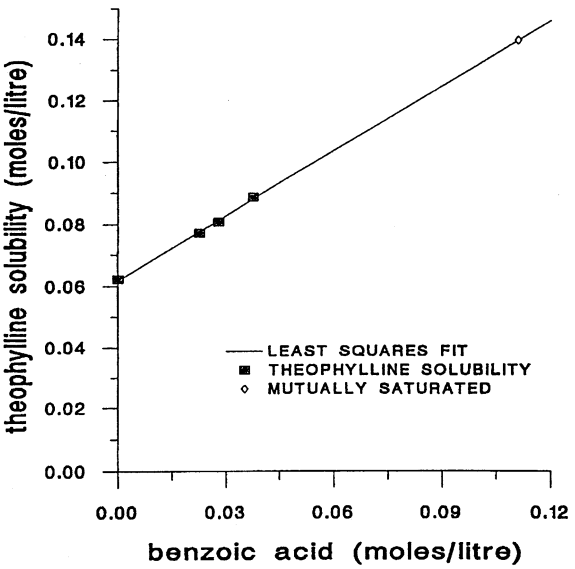

Fig. 5. The phase solubility profile of theophylline in increasing concentrations of benzoic acid in an isotonic pH 2 medium at 37°C.

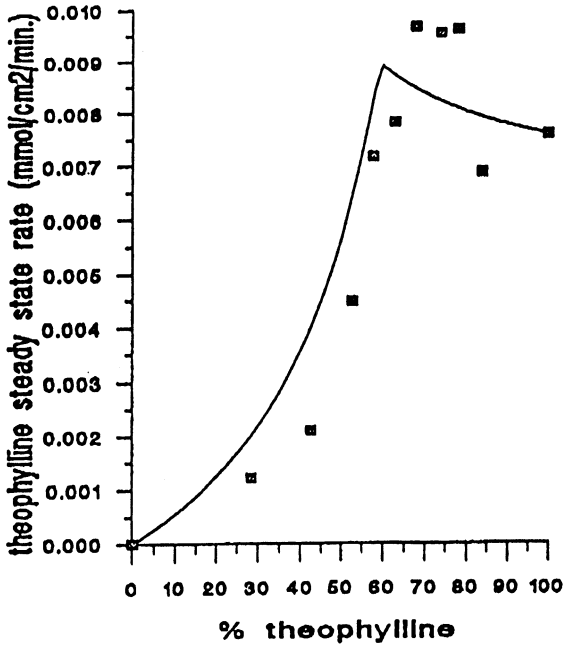

Fig. 6. Predicted and observed relationship between theophylline dissolution rate and composition for two component theophylline–benzoic acid compacts dissolving in isotonic pH 2 medium at 37°C.

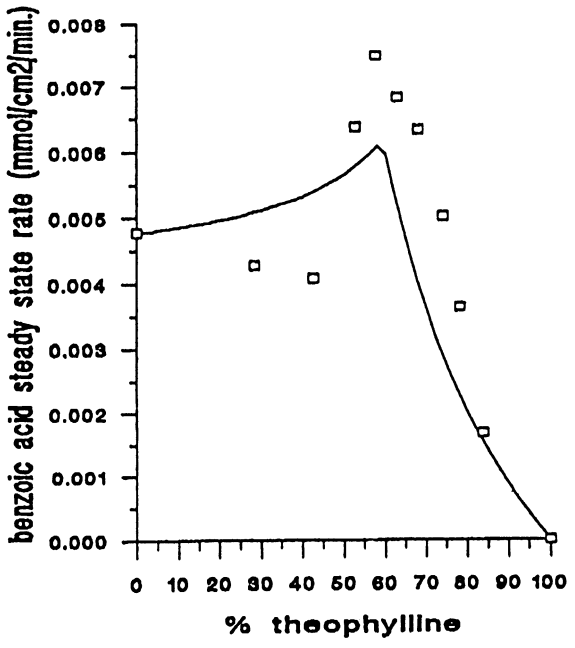

Fig. 7. Predicted and observed relationship between benzoic acid dissolution rate and composition for two component theophylline–benzoic acid compacts dissolving in isotonic pH 2 medium at 37°C.

where K is the binding constant for the complex A–B. When A and B dissolve at the same rate but C dissolves faster than either component, the dissolution rate of component C may then be expressed as

$$G_C = G_A N_C/N_A = G_B N_C/N_B \tag{11}$$

Component C dissolves faster than both A and B, and B dissolves faster than A (case VIII) when

$$\frac{N_A}{N_B} > \frac{D_A C_{SA} + D_{AB} K C_{SA} C_{SB}}{D_B C_{SB} + D_{AB} K C_{SA} C_{SB}} \tag{12}$$

$$\frac{N_A}{N_C} > \frac{\dfrac{D_A C_{SA}}{1 - \dfrac{N_B}{N_A}\left(\dfrac{D_{AB} K C_{SA} C_{SB}}{D_B C_{SB} + D_{AB} K C_{SA} C_{SB}}\right)}}{D_C C_{SC}} \tag{13}$$

$$\frac{N_B}{N_C} > \frac{\dfrac{D_A C_{SA}}{\dfrac{N_B}{N_A}\dfrac{D_{AB} K C_{SA} C_{SB}}{D_B C_{SB} + D_{AB} K C_{SA} C_{SB}}}}{D_C C_{SC}} \tag{14}$$

The dissolution rates of the three components are then given by

$$G_A = \frac{\dfrac{D_A C_{SA}}{1 - \dfrac{N_B}{N_A}\left(\dfrac{D_{AB} K C_{SA} C_{SB}}{D_B C_{SB} + D_{AB} K C_{SA} C_{SB}}\right)}}{h} \tag{15}$$

Table 2
Parameters used to simulate the change in dissolution rates with composition of compacts composed of theophylline (A), benzoic acid (B) and salicylamide (C)

$D_A = 6.47 \times 10^{-4}$ cm^2/min
$D_B = 7.14 \times 10^{-4}$ cm^2/min
$D_C = 6.72 \times 10^{-4}$ cm^2/min
$D_{AB} = 7.56 \times 10^{-5}$ cm^2/min
$C_{SA} = 0.0744$ M
$C_{SB} = 0.0426$ M
$C_{SC} = 0.0334$ M
$K = 37.1$ l/mol
$h = 63.8 \times 10^{-4}$ cm

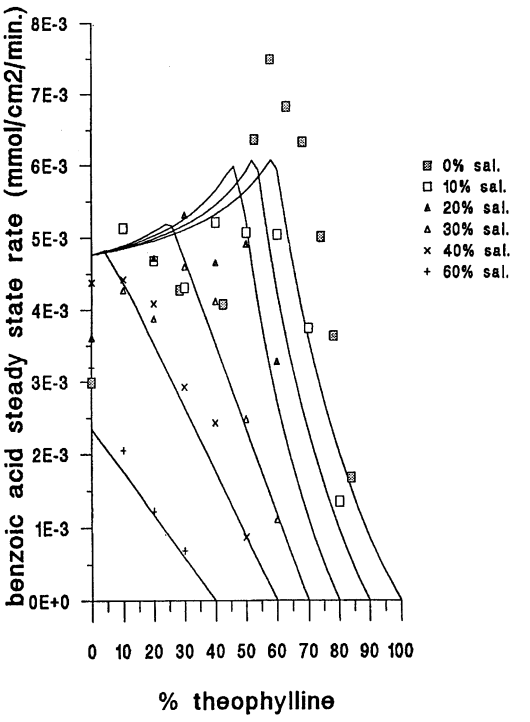

Fig. 8. Comparison of the observed steady state dissolution rates of benzoic acid from a series of three component theophylline/benzoic acid/salicylamide discs containing a constant percentage of salicylamide with those predicted by theory (Eqs. 9, 16 and 22; see text).

$$G_B = \frac{\dfrac{D_A C_{SA}}{\dfrac{N_A}{N_B} - \dfrac{D_{AB} K C_{SA} C_{SB}}{D_B C_{SB} + D_{AB} K C_{SA} C_{SB}}}}{h} \tag{16}$$

$$G_C = \frac{N_C}{N_A} G_A \tag{17}$$

Component C forms the surface layer (case XII or XIII) under the following conditions

$$\frac{N_C}{N_A} > \frac{\dfrac{D_C C_{SC}}{D_A C_{SA}}}{1 - \dfrac{N_B}{N_A}\left(\dfrac{D_{AB} K C_{SA} C_{SB}}{D_B C_{SB} + D_{AB} K C_{SA} C_{SB}}\right)} \tag{18}$$

and

$$\frac{N_C}{N_B} > \frac{\dfrac{D_C C_{SC}}{D_B C_{SB}}}{1 - \dfrac{N_A}{N_B}\left(\dfrac{D_{AB} K C_{SA} C_{SB}}{D_A C_{SA} + D_{AB} K C_{SA} C_{SB}}\right)} \tag{19}$$

The dissolution rates of the components are then given by

$$G_C = D_C C_{SC}/h \tag{20}$$

$$G_A = \frac{N_A}{N_C} G_C \tag{21}$$

$$G_B = \frac{N_B}{N_C} G_C \tag{22}$$

The dissolution rates for the other cases may be developed by the same reasoning.

The compositions of the two component systems studied in the current work are represented by the solid circles along the lines AB, BC and AC (Fig. 3). The compositions of the three component systems chosen for investigation are represented by the solid circles within the triangle.

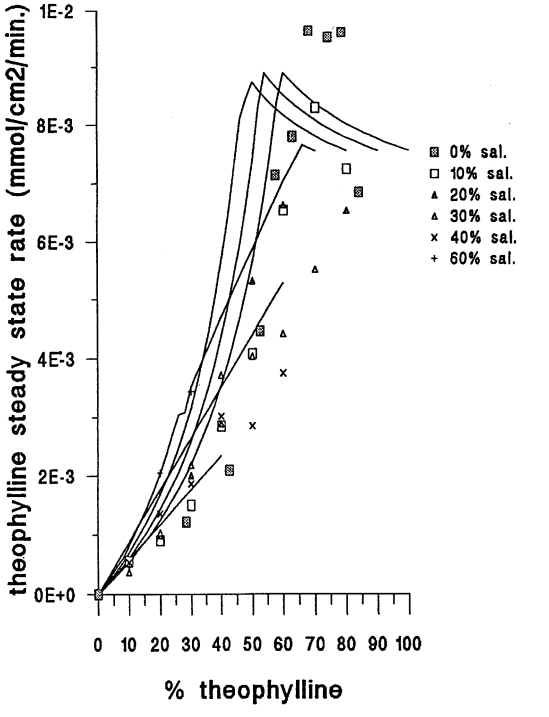

Fig. 9. Comparison of the observed steady state dissolution rates of theophylline from a series of three component theophylline/benzoic acid/salicylamide discs containing a constant percentage of salicylamide with those predicted by theory (Eqs. 8, 15 and 21; see text).

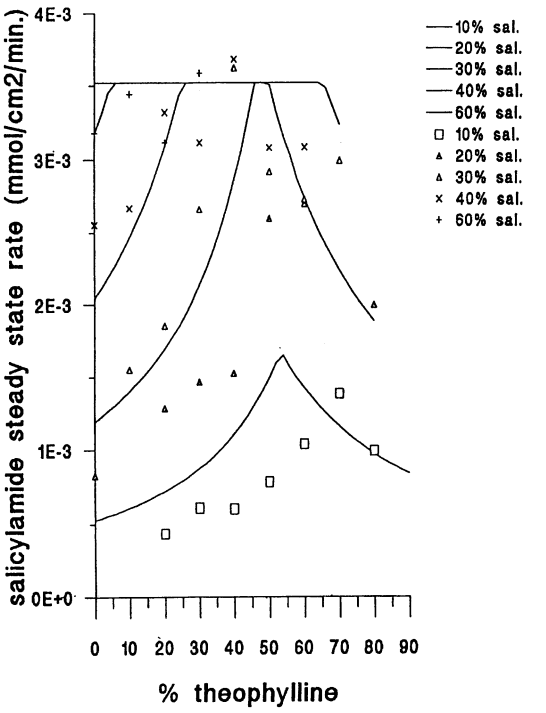

Fig. 10. Comparison of the observed steady state dissolution rates of salicylamide from a series of three component theophylline/benzoic acid/salicylamide discs containing a constant percentage of salicylamide with those predicted by theory (Eqs 10, 17 and 20; see text).

3. Experimental

3.1. Preparation of compacts

Physical mixtures for compression were prepared from powders, ground to sub 125 μm size, prior to compression. For multicomponent discs, the constituents in the required proportions were mechanically mixed for 15 min using an agate pestle and mortar to ensure intimate mixing of the powders. The powder, 200–230 mg, was then weighed out and compressed in a Perkin-Elmer hydraulic press using a 13 mm punch and die set under a pressure of 7000 kg/cm^2. The discs were then mounted with paraffin wax between glass cover slips of diameter 19 mm so that a single surface was subsequently exposed to the dissolution medium.

4. Dissolution studies

Dissolution testing was carried out on compressed discs using the static disk method as previously outlined (Corrigan and Timoney, 1975). The dissolution medium used was an isotonic HCl solution of pH 2, adjusted to isotonicity with NaCl. This pH was chosen to avoid the complications introduced by ionization of dissolving components. Studies were conducted at a stirring speed of 60 rpm in 500 ml at 37°C.

The dissolution runs were carried out using a VanKel Vanderkamp VK 6000 dissolution tester. At specific time intervals, samples of 3 ml were removed and were diluted if necessary with dissolution medium prior to assaying by UV spectroscopy. Sink conditions prevailed throughout the dissolution runs. All dissolution profiles presented are the mean of at least two determinations.

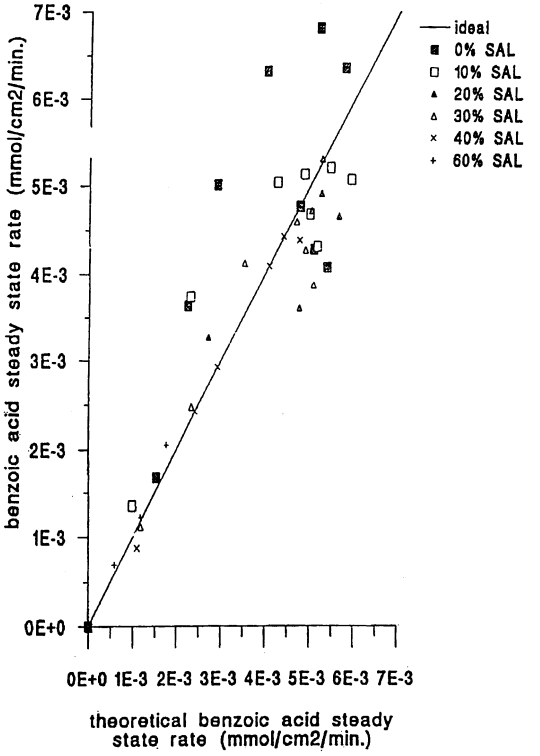

Fig. 11. Comparison of the observed steady state dissolution rates of benzoic acid from theophylline/benzoic acid/salicylamide mixed discs with that predicted by theory.

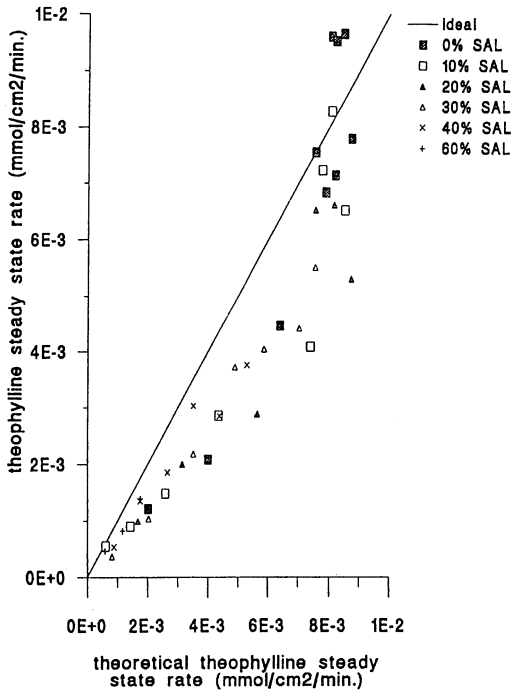

Fig. 12. Comparison of the observed steady state dissolution rates of theophylline from theophylline/benzoic acid/salicylamide mixed discs with that predicted by theory.

5. Solubility studies

A sealed vial method, similar to that described by Hamlin et al. (1965), Ramtoola and Corrigan (1987), was used to determine the saturation solubilities of benzoic acid, theophylline and salicylamide at 37°C. After 48 h samples were filtered through 0.45 μm filters, the aliquot of the filtrate suitably diluted was assayed by UV spectroscopy. The pH of the saturated solution was also recorded.

The binding constant for complex formation in solution between two interacting components was determined by the overhead stirrer solubility method (Corrigan and Stanley, 1981). Solutions of the various concentrations of the complexing agent, equilibrated at 37°C were added to conical flasks immersed in a water bath at 37°C. An excess of the substrate in the solid state was then added to the flask and the contents stirred at 150 rpm using a glass stirrer. After 2 h, a 5 ml sample was removed from the flask and immediately filtered through 0.45 μm membrane filters and assayed by UV spectroscopy.

6. Analytical methods

All samples were assayed spectrophotometrically on a Hewlett Packard 8452A Diode Array Spectrophotometer. For the dissolution of single component discs, the absorbance of the appropriately diluted sample of dissolution medium was measured at the wavelength of maximum absorption, of the substance. The calibration curve of each substance exhibited a Beers' Law relationship in the concentration range used.

For the dissolution of multi-component discs, analysis was effected by the use of simultaneous equations (Simpson and Parrott, 1983). Thus, the concentration of each component was obtained by UV absorbance at three selected wavelengths and converted to amount dissolved. The addi-

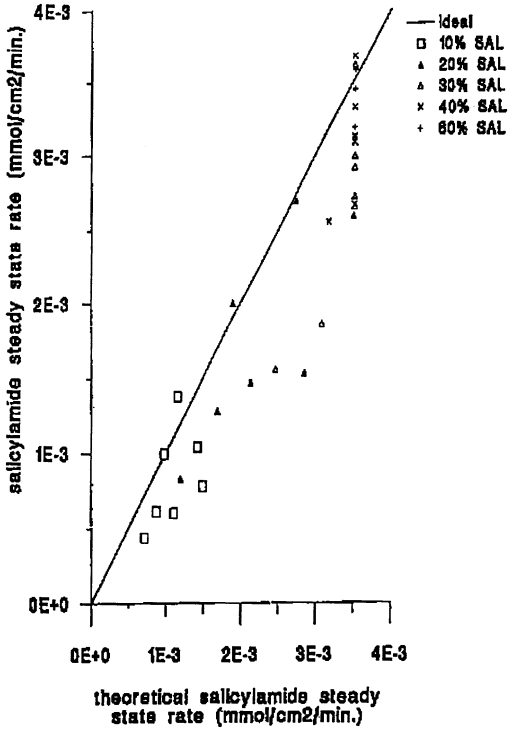

Fig. 13. Comparison of the observed steady state dissolution rates of salicylamide from theophylline/benzoic acid/salicylamide mixed discs with that predicted by theory.

tivity of the absorbances at the chosen wavelengths for each system were tested using mixed solutions of known concentrations of the components.

7. Results and discussion

7.1. One and two component compact dissolution

The dissolution profiles of benzoic acid, theophylline and salicylamide from single component discs were linear (Fig. 4) theophylline having the highest and salicylamide the lowest intrinsic dissolution rates. The diffusion layer thickness was estimated from the benzoic acid data to be 63.8×10^{-4} cm. The intrinsic dissolution rates (G), solubilities at pH 2 and diffusion coefficients (37°) are summarized in Table 1.

Solubility and dissolution studies of salicylamide–benzoic acid and salicylamide–theophylline systems gave phase solubility and dissolution results consistent with the diffusion controlled model for non-interacting components (Higuchi et al., 1965). In contrast benzoic acid was found to interact to form a soluble complex with theophylline (Fig. 5), the complex formed having an apparent binding constant of 37.1 l/mol assuming a 1:1 complex. The dissolution data for these two components was therefore fitted to the two component interacting model equations of Higuchi et al. (1965). The fit obtained for theophylline (Fig. 6) and benzoic acid (Fig. 7) using a DAB of 7.56×10^{-5} cm^2/min was reasonable. Dissolution rates of benzoic acid however tended to be higher than predicted when the theophylline content was greater than 50%. During dissolution, disc surfaces tended to develop an undulating, rather than retain a perfectly flat, dissolution surface which may explain the higher than predicted rates. Slightly positive curvatures were evident in some dissolution profiles also consistent with some disintegration of the disc surface leading to a higher than expected limiting dissolution rate. Positive curvatures in dissolution profiles of two component compacts in reactive media have been reported previously (Healy and Corrigan, 1996).

7.2. Dissolution of three component compacts

Theoretical limiting dissolution rates of a series of theophylline/benzoic acid/salicylamide mixed discs, each series containing a constant percentage of salicylamide, were calculated using the parameters (A-theophylline, B-benzoic acid, C-salicylamide) listed in Table 2 and Eqs. (1)–(22).

The steady state predictions of the change in rates with composition for each component, benzoic acid, theophylline and salicylamide, are compared to the observed rates in Figs. 8–10, repectively. In the case of theophylline/benzoic acid systems, the highest steady state dissolution rates for these two components occurs at a higher content of theophylline than predicted. The peaks in the rate versus composition profiles, observed for benzoic acid (Fig. 8) and theophylline (Fig. 9), reflect complex formation between these two components. The peak dissolution rates of theophylline and benzoic acid from the three component systems containing 10 and 20% salicylamide are less than for the two component theophylline/benzoic acid systems, although theory predicts equal rates. For all series, the dissolution rate of theophylline does not increase as much as predicted with increasing theophylline content.

The steady state dissolution rates of salicylamide from most compositions are less than predicted by theory (Fig. 10). Best agreement with theory is apparent with compositions where salicylamide is expected to form the surface layer controlling dissolution.

The observed steady state dissolution rates of the components from three component benzoic acid/theophylline/salicylamide discs are plotted against the rates predicted from theory in Figs. 11–13.

With the exception of the two component theophylline/benzoic acid systems, the agreement of the observed steady state dissolution rates of benzoic acid with theory is satisfactory (Fig. 11). The agreement appears to be best for compositions where benzoic acid is not expected to form the surface layer.

The observed dissolution rates of theophylline from theophylline/benzoic acid/salicylamide com-

pacts are systematically less than theory (Fig. 12).

Observed and predicted rates for salicylamide are shown in Fig. 13. The plateau in the theoretical profile reflects the absence of complex formation by this component and salicylamide's lower intrinsic dissolution rate which results in it forming the surface layer over a wider composition range. The dissolution rates of salicylamide from most theophylline/benzoic acid/salicylamide compacts were less than predicted (Fig. 13).

The lower than predicted rates for salicylamide, particularly when it is the surface layer and hence rate controlling, should retard dissolution of the other components the effect being most evident in the case of the most rapidly dissolving compound.

Flaking of the surface component would be expected to increase the dissolution rate of each component and this was particularly evident in the two component theophylline–benzoic acid systems.

Examination of the benzoic acid rates in (Fig. 11) show that benzoic acid dissolution rate is highly susceptible to changes in the proportion of both theophylline and salicylamide. As the theophylline content is reduced the enhancement due to complexation is reduced. The dissolution rates of theophylline on the other hand, while sensitive to benzoic acid content, are much less sensitive to salicylamide content reflecting the similarity in the solubility and diffusivity of benzoic acid and salicylamide. However rates are systematically lower than predicted at the lower salicylamide disc contents and when the theophylline content is also low.

The experimental results are in reasonable agreement with theory. The deviations observed could be related to the ability of theophylline to form a hydrate (Shefter and Higuchi, 1963; Morris and Rodrigues-Hornedo, 1993). Were this to occur during dissolution it might explain the lower than expected dissolution rates for theophylline. It could also contribute to the tendency towards disintegration particularly evident in the two component systems with benzoic acid. However the linearity of the dissolution profile of pure theophylline (Fig. 4) does not indicate that the conversion is particularly rapid under the conditions of the study.

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