J. Pharm. Pharmac., 1977, **29**, 524–528 *Received February 15, 1977*

The dissolution mechanism in a system undergoing complexation: salicylamide in caffeine solution

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The dissolution rate of compressed salicylamide discs has been measured in water and in caffeine solutions of increasing concentration at 15, 25, 37 and 45° in an apparatus rotating at 48 rev min^{-1} or more. Dissolution rate profiles showed breaks indicative of a shift in the mechanism of dissolution from interfacial towards transport control. The shifts occurred at higher caffeine concentrations on increasing the agitation rate or temperature. The dependencies of dissolution rates on agitation rates typified the intermediate type of dissolution and Arrhenius plots indicated that interfacial and transport processes participated in salicylamide dissolution.

Treatment of dissolution rate as a function of the rates of interfacial and diffusion processes was applied by Wurster & Taylor (1965) to solution of prednisolone tablets on the basis of a theory first proposed by Berthoud (1912). Wurster & Kildsig (1965) distinguished between these two mechanisms in *m*-aminobenzoic acid dissolution by increasing its solubility range by means of complexation, working at a single agitation rate and temperature. From previous studies (Hamlin, Nelson & others, 1962), it is evident that the intensity of agitation is an important factor not only in determining the actual profile of the dissolution process but in revealing which of the two mechanisms is rate-determining in a specific system.

The present work was carried out with the object of investigating some of the factors controlling the dissolution process in systems undergoing complex-formation during dissolution. Since the degree of complex-formation depends on the temperature, agitation rate effects at different temperatures as well as at different saturation solubilities were examined.

MATERIALS AND METHODS

Materials. Salicylamide (Sigma), recrystallized benzoic acid and caffeine (Merck) were of NF grade and had the literature m.ps.

Dissolution rate studies

The salicylamide was compressed into tablets in a KBr die (Research and Industrial Instruments Co.) using a high-pressure laboratory press. The tablets were cylindrical with diameter 13·1 mm, thickness 2·9 mm, weight 493 mg ± 1·5%, and hardness 7 kg (measured by means of an Erweka hardness tester). Drug release from the tablets was determined, using the rotating compartmentalized dissolution apparatus described by Simmons, Frechette & others (1972) modified by use of a Perspex screen in place of the metal screen with the original mesh. The experiments were carried out in a covered beaker using 1 litre of dissolution medium at 15, 25, 37 or 45° in a constant temperature bath (±0·5°). The dissolution medium was water or caffeine solution in increasing concentrations. The basket was rotated at the selected rev min^{-1} (±3%) by means of a constant rate adjustable stirrer (Fisher Stedi-Speed Stirrer). Two tablets, accurately weighed, were used in each experiment placed horizontally in opposite compartments. The caffeine concentration in the dissolution medium was checked spectrophotometrically before each experiment. Samples of 5 ml were withdrawn at 15 min intervals and replaced by equal volumes of dissolution medium at the same temperature; 1 ml from each sample was added to 5 ml modified Trinder reagent (Donbrow, Touitou & Ben-Shalom, 1976) and the concentration was measured spectrophotometrically at 525 nm. For benzoic acid, the same procedure was used except for the omission of caffeine, and the concentration was determined spectrophotometrically at 230 nm in 0·01 N HCl.

A cumulative correction was made in determining the total amount dissolved in the dissolution medium using the equation:

$$C_n = C_{n_1} + \frac{5}{1000} \sum_{s=1}^{s=n-1} C_p \quad \ldots \quad (1)$$

* Correspondence.

where C_n = corrected concentration of nth sampling, C_{n_1} = measured concentration, C_p = measured concentration of preceeding samples.

The tablets maintained a constant shape throughout the test time and the Hixson-Crowell equation (Hixson & Crowell, 1931) was applied to the dissolution data.

The cube root weight *vs* time plots were linear throughout all experiments and were reproducible to within 2 to 3%. The rates of dissolution were obtained from the slopes of these lines.

RESULTS AND DISCUSSION

Influence of solubility of salicylamide on dissolution rate

The presence of caffeine in solution increased the salicylamide dissolution rate compared with that in water. This is attributable to the solubility increase of salicylamide caused by complexation with caffeine in aqueous solution. The stability constants for the complexes at 15, 25, 37 and 45° and the phase diagrams obtained by the solubility method have recently been determined (Donbrow & others, 1976). The resulting total salicylamide concentration termed the apparent solubility, C_a, is the sum of its solubility in water A_o, and the concentration of complex present [CS], assuming 1:1 interaction. Apparent solubility in each dissolution medium at a given temperature was calculated*. Influence of the increase in apparent solubility C_a of salicylamide on the dissolution rates at two temperatures (25 and 37°) and at two different rates of agitation (48 and 90 rev min^{-1}) can be seen from Fig. 1. In three of the curves there is a sharp break, probably indicating a change in the mechanism controlling dissolution. Had the process been purely diffusional, a single straight line would have been expected for each set of conditions, hence it is possible that an interfacial process is involved. Dissolution rate may be controlled by either of these two processes, as in other heterogeneous reactions (Bircumshaw & Riddiford, 1952). When the rate is controlled by both, the reaction is of the intermediate type (Van Name & Hill, 1916), for which case two velocity constants are involved, k_c, the rate constant for the interfacial process, and k_t, the transport rate constant. The interfacial reaction supplying an intermediate concentration C_i at the interface from which the transport process begins can be expressed by:

$$-\frac{dW}{dt} = Sk_c (C_s - C_i) \quad .. \quad .. \quad (2)$$

where S is the surface area at time t and C_s is the saturation concentration. If the rate is determined by the interfacial reaction, steady-state conditions exist for C_i and it remains constant. Transport from the interface follows Fick's law* which gives:

$$-\frac{dW}{dt} = Sk_t (C_i - C) \quad .. \quad .. \quad (3)$$

where C is the concentration in the bulk solution. In the steady state, under zero sink conditions, the observed velocity constant k_1 will be given by:

$$-\frac{1}{S} \cdot \frac{dW}{dt} = k_1 C_s \quad .. \quad .. \quad (4)$$

where $$k_1 = k_c k_t/(k_c + k_t) \quad .. \quad .. \quad (5)$$

Observed rates of the intermediate type may change in value in accordance with equation (5) under the influence of three major factors influencing k_c and/or k_t: (a) temperature, (b) agitation conditions, (c) concentration of substrate in the dissolution medium. The change in total substrate concentration resulting from complexation may thus influence not only the actual rate of dissolution but also the mechanism.

If in the dissolution of the salicylamide system both transport and interfacial processes are involved, the observed velocity constant k_1 should be in accord with equation (5). Dissolution rate dependence on solubility is predicted by means of equation (2) for interfacial control and equation (4) for transport control (where $k_1 = k_t$). From Fig. 1 it is evident that the second branch at 25° and 48 rev min^{-1} conforms with the direct proportionality predicted by equation (4) and extrapolation to zero dissolution rate gives an intercept value of C_s close to zero ($-2{\cdot}5 \times 10^{-3}$ M). Considering the first branch, extrapolation to zero dissolution rate gives the value of C_i ($7{\cdot}0 \times 10^{-3}$ M) on the basis of

* C_a = (S1) X + A_o, where X is the caffeine concentration in the dissolution medium and S1 is the slope of the initial linear region of the phase diagrams. This treatment assumes rapid attainment of equilibrium in the complexation reaction compared with the rate of transportation of salicylamide from the surface, and maintenance of salicylamide saturation at the surface.

* The stationary layer theory has been used in the present work rather than a diffusive-convective equation. Although the hydrodynamics of the rotating apparatus used here are not known, experimental evidence based on dissolution rate dependence on agitation rate and D indicates that the unstirred layer model describes the behaviour more closely than a convection model such as that of Shah & Nelson (1975). These data will be described elsewhere (Donbrow & Touitou, to be published).

equation (2) which enables solution of the equation for k_c in accordance with interfacial control of the process. For the other experimental conditions, extrapolations to zero dissolution rate gave higher intercept values of C_s, which indicated that the control does not accord with equation (4). It is presumed that in these systems the observed k_1 values were not determined by one dominant rate constant but that both k_c and k_t had a large influence; k values are estimated later. The low correlation coefficient (0·965) obtained for the single regression line at 25° and 90 rev min^{-1} may indicate that experimental conditions were not favourable for clearly distinguishing a shift in rate control.

Estimation of apparent interfacial and transport velocity constants

Rearrangement of equation (5) gives

$$1/k_c = 1/k_1 - 1/k_t \quad .. \quad .. \quad (6)$$

The apparent rate constants, k_1, were obtained from the slopes of the second branches of the plots of dissolution rate *vs* solubility (Fig. 1 and eqn (4)). The theoretical transport velocity constants, k_t, were estimated by means of equation (7) in which D is the diffusion coefficient of the salicylamide in the medium and h is the effective diffusion layer thickness:

$$k_t = D/h \quad .. \quad .. \quad (7)$$

D values obtained using the Stokes-Einstein equation* (Flynn, Yalkowsky & Roseman, 1974) were $1{\cdot}06 \times 10^{-5}$ and $1{\cdot}42 \times 10^{-5}$ for salicylamide in water at 25° and 37° respectively. Values of h were estimated using benzoic acid as a model solute known to undergo dissolution by a diffusion mechanism (Prakongpan, Higuchi & others, 1976). Its calculated D value and experimentally measured rates were inserted in the Nernst equation. The h values varied with rev min^{-1} (Table 1) as expected (Collett, Rees & Dickinson, 1972). Substitution of values of k_1 and k_t in equation (6) gave k_c and the estimated values are included in Table 1.

Effect of agitation intensity on dissolution rate

It is evident that at 25° and 48 rev min^{-1} $k_c \gg k_t$, hence $k_1 \rightarrow k_t$ and the dissolution is essentially transport-controlled over the second branch. However, at 37° at both agitation rates, k_c and k_t are of the same order, hence k_1 is not purely diffusional, which accounts for the non-zero extrapolation value and the failure to observe the direct proportion of equation (4). At 90 rev min^{-1}, the increased importance of the chemical process is reflected in the greater k_t/k_c ratio, which signifies that increase of agitation rate at a given temperature favours interfacial control. This is indicated in Fig. 1 by the ratio of the concentration range over which there is interfacial control to that over which there is transport control. The ratio increases with rev min^{-1} markedly at 37°, while at 25° the transport branch vanishes altogether. Agitation rate-induced shift to interfacial control is to be expected if the heterogenous reaction is of the intermediate type (Bircumshaw & Riddiford, 1952). Agitation increases the rate of the transport process in accordance with equation (7) by reducing the thickness of the diffusion layer. When $k_t \gg k_c$, k_1 approaches k_c (eqn 5) and this shifts the observed rate towards that of the chemically-controlled reaction.

Table 1. *Velocity constants estimated for the transport branches in Fig. 1.* k values: cm min^{-1} × 10^2.

Temp. °C	rev min^{-1}	h, cm × 10^3	k_1	k_c	k_t
25	48	1·75	3·71	∞	3·70
37	48	1·73	2·46	4·84	5·00
37	90	0·81	4·18	6·90	10·50

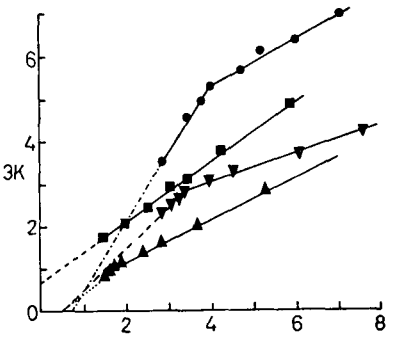

FIG. 1. Salicylamide dissolution rate profiles: influence of solubility, agitation rate and temperature. ▼—37°, 48 rev min^{-1}, ●—37°, 90 rev min^{-1}, ▲—25°, 48 rev min^{-1}, ■—25°, 90 rev min^{-1}. Ordinate—Dissolution rate, 3 K (g cm^{-2} min^{-1} × 10^4). Abscissa—Salicylamide solubility (M × 10^2).

The influence of agitation intensity as a means of confirming the rate-determining step is presented in Table 2 which gives the slope values of log-log

* For salicylamide, this equation gives $D = 3{\cdot}17 \times 10^{-10}\ T/\eta$ cm^2 s^{-1} where η is the viscosity of the solvent and T is the absolute temperature. With the small mol wt differences of the species involved, errors in using a single D value were negligible.

Table 2. *Slopes of log-log plots of the dissolution rate vs rev min^{-1} (rev min^{-1} range 48–280).*

Temperature °C	Salicylamide solubility M × 10^2	Slope
25	1·50	0·39
	3·71	0·66
37	1·90	0·57
	5·52	0·89

plots of the dissolution rate *vs* rev min^{-1}. Linearity up to 180 rev min^{-1} with a slope above 0·5 was in fact observed at solubilities of 5·52 × 10^{-2} M salicylamide at 37° and 3·71 × 10^{-2} M at 25°, both of which were high enough at the respective temperatures for the process to be mainly transport controlled. Further evidence for the interfacial control at lower solubilities was afforded by the slope values for salicylamide dissolution in water, which were below 0·4 at 25° and close to 0·5 at 37° (Table 2). The high slope values are suggestive of some turbulence in the system which would also account for the upward deviation of the last points at 280 rev min^{-1} (Levich, 1962; Bisaillon & Tawashi, 1971; Fee, Grant & Newton, 1976).

Effect of temperature on dissolution rate of salicylamide in caffeine solutions

For the caffeine-salicylamide system, the experimental energy of activation will be a composite of the interfacial and transport energies of activation, E_c and E_t respectively. In the case in which $E_c > E_t$, k_1 is controlled by the interfacial reaction at low temperatures and the transport process at the higher temperatures (Bircumshaw & Riddiford, 1929).

From Fig. 1, we can see that at constant rev min^{-1} and a selected solubility of salicylamide, temperature variation altered the observed dissolution rate. Arrhenius plots of log k_1 *vs* 1/T (Fig. 2) at 48 rev min^{-1} for salicylamide in 0·49 M caffeine solution including additional data measured at 15 and 45° (Table 3) curved at the lowest temperatures instead of giving the expected linear relation for transport control. The changing slope again indicates that the process is not purely transport controlled. A straight line Arrhenius plot (Fig. 2) was obtained using theoretical k_t values calculated by means of equation (7) using the estimated D values with h values obtained from the benzoic acid dissolution experiments. From the slope of this line, which lay close to the experimental plot, the transport activation

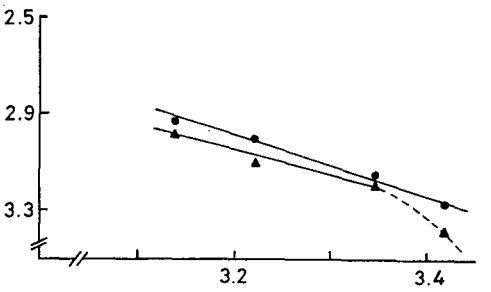

FIG. 2. Arrhenius plots of experimental (▲) and theoretical (●) dissolution rate velocity constants. Ordinate—log k_1, Abscissa 1/T (°K^{-1} × 10^3).

energy was calculated to be 5·88 k cal mol^{-1} (24 kJ mol^{-1}) for this system, which accords with the value expected for a transport-controlled process (2·8–6·5 k cal mol^{-1}, 12–26 kJ mol^{-1}) (Mitchell & Saville, 1969), a high value tending to occur under turbulent conditions (Bisaillon & Tawashi, 1971).

It may be concluded that the presence of complexant raises the dissolution rate and that the dissolution of salicylamide in water and in low concentration caffeine solutions is controlled by the rate of the interfacial reaction. Only with higher complexant concentration is there a shift towards transport control. The concentration at which the shift becomes apparent is a function of temperature

Table 3. *Dissolution rates of salicylamide in caffeine solutions at 48 rev min^{-1}, 15° and 45°.*

	Caffeine concn M × 10^3	Ka* g$^{1/3}$ min^{-1} × 10^4	Diss. rate g cm^{-3} min^{-1} × 10^4	Salicylamide solubility M × 10^3
15°	0	1·14	0·55	1·05
	49·0	2·18	1·06	3·18
45°	0	7·46	3·62	4·28
	49·0	12·80	6·18	7·29

* Slopes of the lines obtained by plotting $W_0^{1/3}$—$W^{1/3}$ *vs* time.

and rate of agitation. The dissolution rate will consequently not be related to the solubility of the salicylamide in the water as predicted by equations for transport-controlled dissolution. It is possible that similar interfacially-controlled dissolution may be the cause of deviations reported periodically in the literature (Nogami, Nagai & Ito, 1966). This may be an important factor in limiting the rate of dissolution and hence the bioavailability of such compounds.

Acknowledgements

The authors thank Mrs Dalia Gilhar for technical assistance and the family of the late Mr Jack Bogush of London, for the presentation of a Unicam SP1800 Recording Spectrophotometer used in this work.

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