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Dissolution rates of sparingly soluble tablets

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The automated dialysis method offers an opportunity for the accurate evaluation of the dissolution rates of sparingly soluble dosage forms. By the analysis of kinetic models, the dissolution rates for disintegrating and non-disintegrating dosage forms may be calculated. The theory is used to examine the effect of additives and compression force on the dissolution rates of sulphathiazole tablets. At the fairly low compression forces used (640–1430 kg) the dissolution rate gradually increases due to penetration of the tablet by the dissolution medium. Polyethylene oxide causes an initial rapid increase in dissolution rate, but the formation of a mucilaginous film results in a constant rate. Using starch, dissolution rate increases rapidly as a result of tablet disintegration. This disintegration is shown to make available less than half the surface area of the original powder. The dissolution rate constant for sulphathiazole under the experimental conditions is $2{\cdot}75 \times 10^{-4}$ cm min^{-1}.

In a previous communication (Barzilay & Hersey, 1968) an automated dialysis method of measuring dissolution profiles of tablets was described. In common with other dialysis methods (Ferrari & Khoury, 1967; Marlowe & Shangraw, 1967; Krogerus, Kristoffersson & Kehela, 1967) dissolution rate is not measured directly. The purpose of this paper is to extend the utility of our method to the measurement of dissociation rates of sparingly soluble medicaments.

Dissolution rate may be expressed theoretically by the Noyes & Whitney (1897) relation

$$\frac{dW}{dt} = KS\,(C_S - C_M) \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where dW/dt is the rate of dissolution, K is the dissolution rate constant, S is the surface area, C_S is the solubility of the drug in the dissolution medium and C_M the concentration of drug in the medium at time t. Providing $C_S \gg C_M$, the above relation simplifies (Parrott, Wurster & Higuchi, 1955; Nelson, 1957) to

$$\frac{dW}{dt} = KSC_S \quad .. \quad .. \quad .. \quad .. \quad (2)$$

Equation (2) is normally used as the basis for dissolution rate determination in which the dissolution process is allowed to proceed in a large volume of solvent. With sparingly soluble drugs, the solubility C_S is low, and build up of concentration in the dissolution medium will have a retarding effect on the dissolution rate (eqn 1). Thus many of the established *in vitro* dissolution rate methods are unable to accurately evaluate the dissolution rate of sparingly soluble drugs (Hersey, 1968).

The absorption of dissolved substances *in vivo* from the gastrointestinal tract is generally quite rapid and consequently in those instances where sparingly soluble

drugs are considered, absorption will depend upon the rate at which dissolution occurs, i.e. the absorption process is dissolution rate-limited. It is among low solubility medicaments that dissolution rate *in vitro* must be evaluated with the greatest care.

A drug dissolving in the gut contents is immediately available for absorption. Hence the concentration of the dissolved drug is kept at a minimum, that is, a natural sink condition exists. Gibaldi & Feldman (1967) have described an *in vitro* dissolution rate method using a sink condition, in which dissolved drug is partitioned into an organic phase. The use of an adsorbent material may also achieve the sink condition (Wurster & Polli, 1961), but may affect the viscosity and considerably retard the dissolution process (Wurster & Polli, 1964).

Dialysis provides a useful alternative to the sink conditions described. The automated dialysis method may, therefore, provide a powerful tool for the evaluation of *in vitro* dissolution rates of sparingly soluble drugs.

EXPERIMENTAL AND RESULTS

The apparatus used and method have previously been described (Barzilay & Hersey, 1968). In most cases the results given there are also used in the present discussion. Further results were obtained for 500 mg sulphathiazole tablets containing 5 and 10% of starch as a disintegrating agent (Fig. 1A) and for 250 mg of sulphathiazole powder (Fig. 1B) over a period of 4 h. For the powder, only half the quantity used in the

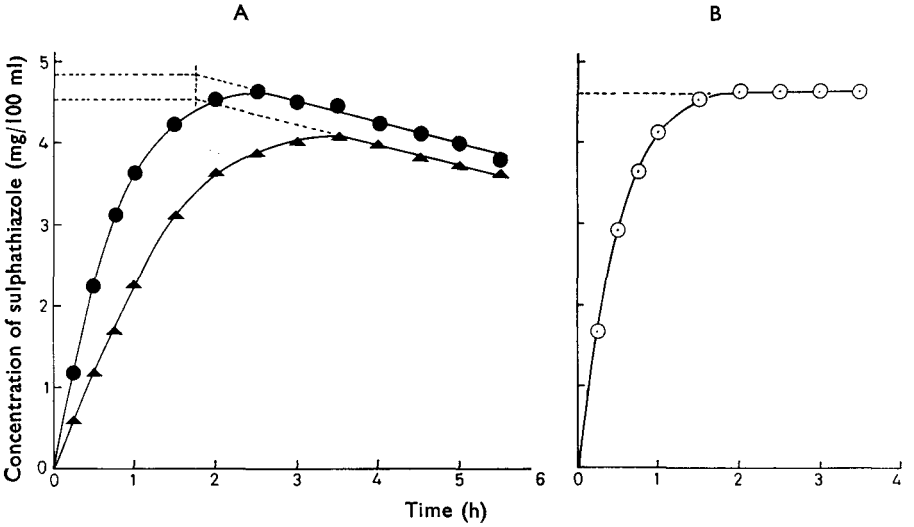

FIG. 1A. Dissolution of sulphathiazole tablets containing maize starch. ● 10% Starch ▲ 5% Starch. B. Dissolution of sulphathiazole powder.

tablets could be examined because of the sensitivity of the assay procedure. The time for disintegration, as measured by standard apparatus (B.P.), for the sulphathiazole tablets containing starch was within 25 s.

The surface area of the sulphathiazole was determined using the Fisher Sub-Sieve Sizer. The value of the surface mean diameter determined at a porosity between 0·45 and 0·60 was 19·4 μm equivalent to a specific surface area of 2000 $cm^2\ g^{-1}$ assuming spherical particles.

The kinetics of the dialysis were examined by placing solutions of 5 and 10 mg of sulphathiazole in the dialysis cell and the concentration measured as previously at suitable time intervals. The results are given in Fig. 2, which shows the dialysis to

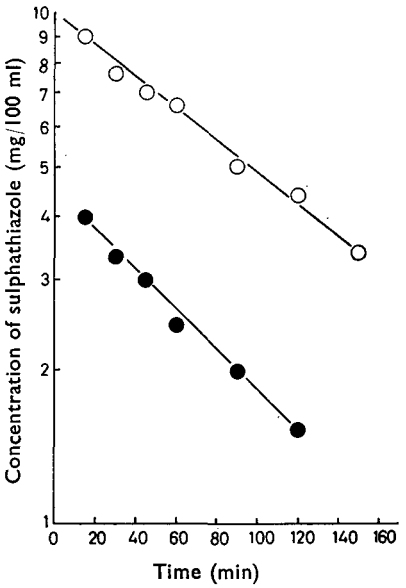

FIG. 2. Dialysis of sulphathiazole through cell membrane. ○ Initial concentration 10 mg/100 ml. ● Initial concentration 5 mg/100 ml.

be of first-order kinetics in the system investigated. The mean value of the dialysis constant (K_2) was calculated to be $3{\cdot}55 \times 10^{-3}$ min^{-1}.

DISCUSSION

In order to evaluate the dissolution rate, it is necessary to examine a kinetic model of the system. For non-disintegrating tablets a suitable kinetic model for the dissolution in the automated dialysis apparatus is given in Fig. 3.

The rate of dissolution of drug from the non-disintegrating tablet is given by the Noyes-Whitney equation (1). When the drug is dissolved it is available for dialysis, hence a sink condition is in operation and the condition $C_S \gg B$ (the concentration in the surrounding medium) may be assumed. Thus equation (1) reduces to

$$\frac{dW}{dt} = K_1 \quad .. \quad .. \quad .. \quad .. \quad .. \quad (3)$$

providing there is negligible change in surface area due to dissolution (see eqn 2).

The rate of dialysis was shown to obey first order kinetics (Fig. 2) due to a second sink condition, whereby solute dialysing is continuously removed and replaced with fresh vehicle. Thus

$$V_B \frac{dB}{dt} = K_1 - V_B K_2 B \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where V_B is the volume of solution of concentration B, surrounding the dissolving tablet.

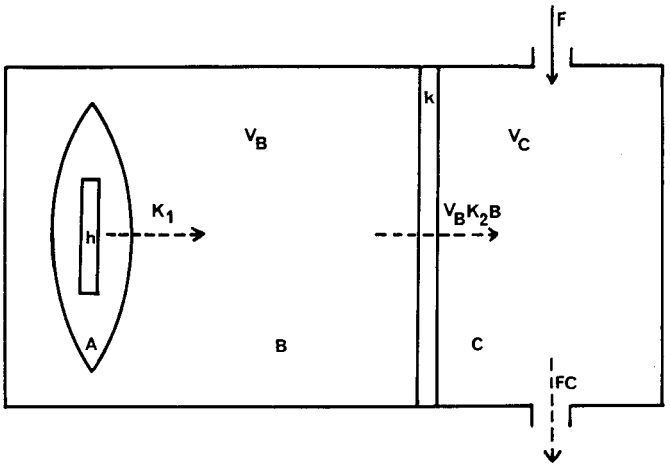

FIG. 3. Proposed kinetic model for the dissolution of non-disintegrating tablets. Drug dissolves from tablet h into the stationary region of saturated solution, A. Drug, K_1, diffuses into the surrounding medium, volume V_B concentration B. Drug, V_BK_2B, dialyses through membrane k, into compartment, volume V_C, concentration C. Diluent is pumped into this compartment at rate F and drug out at rate FC.

The violent agitation occurring on the measuring side of the dialysis membrane ensures a uniform measured solute concentration C at time t. Since F is the flow rate of solution through the measuring cell and also of replacement vehicle into the dialysis cell, the volume V_C of solution outside the dialysis membrane remains constant. Then

$$V_C \cdot \frac{dC}{dt} = V_BK_2B - FC \quad .. \quad .. \quad .. \quad (5)$$

Integration of equation (4) and using the limit $t = 0$, $B = 0$ gives

$$V_BK_2B = K_1(1 - e^{-K_2t}) \quad .. \quad .. \quad .. \quad .. \quad (6)$$

Substitution of equation (6) in equation (5) and using the limit $t = 0$, $C = 0$ gives

$$\frac{C}{K_1} = \frac{K_2V_C(e^{-Ft/V_C} - 1) + F(1 - e^{-K_2t})}{F(F - K_2V_C)} \quad .. \quad .. \quad .. \quad (7)$$

Since all the constants are known, K_1 can be evaluated by substitution of measured values of concentration C at times t, in equation (7). Results of this analysis are shown in Fig. 4. In all cases K_1 is shown to increase with time. For tablets of sulphathiazole compressed at different pressures (Fig. 4A) the increase of K_1 is linear. Comparison of equations (2) and (3),

$$K_1 = KSC_S \quad .. \quad .. \quad .. \quad .. \quad (8)$$

suggests that this is due to a gradual increase in the functional surface area. This may be explained by penetration of the surface of the tablet by the dissolution medium increasing the area available for dissolution. The tablets used in this study were made at pressures between 573 and 1266 kg cm^{-2}, well below those normally used for intrinsic dissolution rate measurements as, for example, by the rotating disc method (Levy & Sahli, 1962). At these low pressures, penetration might be expected to cause a large increase in the surface available for dissolution, although the tablets did not disintegrate during the test.

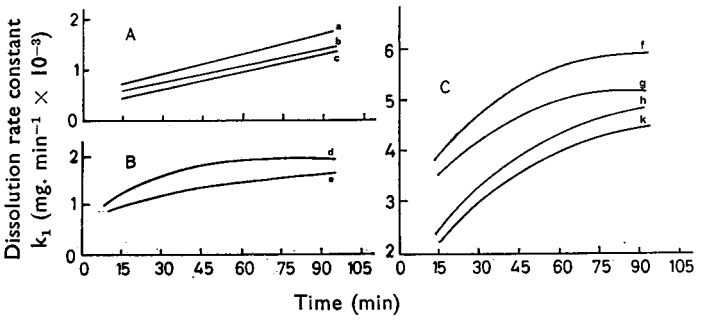

FIG. 4. Effect of time on the dissolution rate constant of 500 mg sulphathiazole tablets. A, compressed at different pressures: applied pressure a, 500 kg cm^{-2}; b, 770 kg cm^{-2}; c, 1090 kg cm^{-2}. B, containing polyethylene oxide: d, 5% Polyox; e, 1% Polyox. Mean applied pressure 790 kg cm^{-2}. C, containing maize starch: f, 10% starch; g, 7·5%; h, 5%; k, 2·5%. Mean applied pressure 660 kg cm^{-2}.

The results using polyethylene oxide (Fig. 4B), especially at the 5% concentration in 500 mg sulphathiazole tablets, indicate an initial rapid increase in the functional surface area, in agreement with the observed splitting of the tablet. This is followed by a much less rapid increase, probably due to the formation of a mucilaginous film around the tablet similar to that observed by Huber, Dale & Christenson (1966). Higher concentrations of polyethylene oxide gave identical results to the 5% concentration. The results for the rapidly disintegrating sulphathiazole tablets containing starch (Fig. 4C) are included for comparison to show the effect of the increasing surface area of sulphathiazole available for dissolution.

If the value of K_1 could have been established as a constant over the period of the investigation, an alternative solution to equation (7) is available. If it is assumed that the dissolution of the sulphathiazole does not effectively alter the surface area of the non-disintegrating dosage form, then at some finite time depending on the flow rate through the dialysis cell, the rate of dialysis and the recipient volume for dialysis

$$C = K_1/F \quad .. \quad .. \quad .. \quad .. \quad .. \quad (9)$$

Since, rearranging equation (7)

$$C = \frac{K_1}{F} + \text{constant}_1\, e^{-Ft/Vc} + \text{constant}_2\, e^{-K_2 t} \quad .. \quad .. \quad (10)$$

then as $t \to \infty$, $C = K_1/F$.

When examining disintegrating dosage forms it is necessary to know the relation between surface area and time for complete evaluation of the kinetic model. The shape of the graph for disintegrating tablets (Fig. 4C) suggests this relation should be exponential in form approaching a limiting value asymptotically. A general relation for this type of curve is given by

$$S = S_o\,(1 - e^{-Qt}) \quad .. \quad .. \quad .. \quad .. \quad (11)$$

where S_o is the surface area at complete disintegration and, for total disintegration, will be equal to the surface area of the original component drug particles assuming no breakdown on compaction, and Q is a rate constant of disintegration. Using equation (11) in the kinetic model (Fig. 3) then

$$\frac{dW}{dt} = KC_S S_o(1 - e^{-Qt}) \quad .. \quad .. \quad .. \quad (12)$$

and $$V_B \cdot \frac{dB}{dt} = KC_S S_o(1 - e^{-Qt}) - K_2 V_B B \quad .. \quad .. \quad .. \quad (13)$$

while $$V_C \cdot \frac{dC}{dt} = K_2 V_B B - FC \quad .. \quad .. \quad .. \quad (5)$$

as before.

Integration of equation (13) using the limits t = 0, B = 0 gives

$$K_2 V_B B = \frac{KC_S S_o}{K_2 - Q}[K_2(1 - e^{-Qt}) - Q(1 - e^{-K_2 t})] \quad .. \quad .. \quad (14)$$

Substitution of equation (14) in equation (5), integrating and using the limits t = 0, C = 0 gives an equation similar in form to equation (10), thus

$$C = \text{constant}_1 + \text{constant}_2\, e^{-tF/V} + \text{constant}_3\, e^{-Qt} + \text{constant}_4\, e^{-K_2 t} \quad .. \quad (15)$$

where

$$\text{constant}_1 = \frac{KC_S S_o}{F} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (16)$$

$$\text{constant}_2 = \frac{-KK_2 C_S S_o Q}{F(F/V_C - Q)\,(F/V_C - K_2)} \quad .. \quad .. \quad (17)$$

$$\text{constant}_3 = \frac{-KK_2 C_S S_o}{V_C(K_2 - Q)\,(F/V_C - Q)} \quad .. \quad .. \quad (18)$$

$$\text{constant}_4 = \frac{-KC_S S_o Q}{V_C(K_2 - Q)\,(F/V_C - K_2)} \quad .. \quad .. \quad (19)$$

Since both Q and K are unknown, even assuming complete disintegration to the the original particle size, S_o, solution of equation (15) cannot be accomplished by simple substitution. Indeed, since this equation is similar to equation (10), a similar technique offers the most practical solution. As t approaches some finite value, depending on the values of K_2, Q and F, then C will approach its asymptotic value, i.e.

$$C = \frac{KC_S S_o}{F} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (20)$$

Examination of Fig. 1B shows that the lag time, T, for attainment of this asymptotic value for the sulphathiazole powder is 105 min due to dialysis and pumping rates chosen (Barzilay & Hersey, 1968). Substitution of the measured concentration 4·6 mg/100 ml at time T in equation (20) using the values for solubility, C_S, 97·7 mg/100 ml and flow rate F of 2·90 ml min^{-1} and specific surface area, S_o, 2000 $cm^2\ g^{-1}$ (i.e. surface area for 250 mg powder = 500 cm^2) gives the dissolution rate constant

$$K = 2{\cdot}75 \times 10^{-4}\ \text{cm min}^{-1}$$

for sulphathiazole under the experimental conditions.

Examination of Fig. 1A shows a lag time, T of 2·5 h for sulphathiazole tablets containing 10% starch and 3·5 h for those containing 5% starch. This difference in lag time between the powder T = 1·75 h and the formulated products (Table 1) may be taken as a measure of the disintegration time under the prevailing agitation conditions in this test. Whereas the pharmacopoeia disintegration test could not distinguish between the two formulated tablets, under the extremely mild 'peristaltic' action in the dialysis cell a long disintegration time is evident.

Using the value of K calculated for the powder, a measure of the degree of disintegration can be obtained from equation (20). Thus in Table 1 it can be seen that

Table 1. *Disintegration of sulphathiazole tablets formulated with starch*

% Starch (maize)	Lag time T	Disintegration time T–T powder	% S_0 at T	% S_0 at T powder
5%	3·5 h	1·75 h	42·2	46·5
10%	2·5 h	0·75 h	47·6	49·7

the calculated surface area available for dissolution subsequent to disintegration is below 50% of that available from a consideration of the original powder compressed. The pressure of 660 kg cm^{-2} used to compact these tablets has evidently caused much bonding, which has not been disrupted by the disintegration mechanism of the starch.

At times in excess of the lag time, a decrease is observed in the measured concentration for the formulated tablets (Fig. 1A) in contrast to the powder (Fig. 1B). Such a decrease may be explained by the reduction in surface area, which accompanies the dissolution process. The discrepancy between the formulated products and the original powder suggests that the compression and disintegration of the formulated tablets has caused a complete change in the particle size distribution. The large reduction in surface area suggests an increased particle size, but the decrease in measured concentration is indicative of a smaller particle size. Such small particles probably formed during compaction rapidly dissolve and cause the significant drop in measured concentration. An alternative reason may be that the starch forms a mucilage surrounding some of the particles and only a few of the particles are therefore available for dissolution. As dissolution proceeds from these few particles the surface area is significantly reduced. In either event the degree of disintegration should be corrected for the amount of dissolution that has occurred in the difference between the lag times for the tablets and powder (T — T powder). Even with this correction, however, the calculated surface area remains below 50% of that based on the original powder.

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