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The dissolution of commercial aspirin

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Two samples of commercial aspirin showing a difference in intrinsic dissolution rate have been studied. Crystallographic examination and solubility determinations failed to reveal any difference between them. The effects of agitation and temperature on intrinsic dissolution rates showed that the samples had different thermodynamic activities and, depending on the conditions, the metastable form was capable of rapid reversion to a more stable form.

Tawashi (1968), has reported the existence of two polymorphic forms of aspirin, one of which dissolves 50% faster than the other. Differences in dissolution rate have been observed between samples of commercial aspirin (Mitchell & Saville, 1967). The two samples showing the greatest difference in dissolution rate have been examined further. These are designated form A† and form B‡.

Factors affecting the dissolution of solids have been reviewed by Bircumshaw & Riddiford (1952) and more recently by Wurster & Taylor (1965a) who paid particular attention to the pharmaceutical literature. Higuchi (1967) has discussed the use of physical models to describe dissolution rate mechanisms.

EXPERIMENTAL

Measurement of dissolution rate. Dissolution rates in 0·1 N hydrochloric acid were measured using the beaker method of Levy & Procknal (1964) and the rotating disc method of Wood, Syarto & Letterman (1965). Samples were removed at suitable time intervals and assayed for aspirin and salicylic acid as described by Mitchell & Saville (1967). At least two replicate determinations were made and the results averaged. Reproducibility varied with the method, the form of aspirin and the experimental conditions of agitation and temperature but was normally within $\pm$ 4%. Using the conditions of Wood & others, the intrinsic dissolution rates of form A and form B were 0·995 and 1·75 mg/cm^{2}min^{-1} respectively.

Determination of solubility. Excess aspirin was equilibrated with 0·1 N hydrochloric acid by rapid stirring in a water-jacketed beaker maintained at the appropriate temperature. Samples were removed using a pipette fitted with a filter-stick, diluted immediately with 0·1 N hydrochloric acid and assayed for aspirin and salicylic acid.

RESULTS AND DISCUSSION

Representative dissolution curves are shown in Fig. 1A and B. Form B behaves as expected but with form A the linear dissolution curve is preceded by a steeper non-linear portion which occurs at all rotation rates and temperatures using both the beaker and rotating disc methods. Intrinsic dissolution rates per unit area were calculated from the slopes of the straight lines for form B and the linear part of the curve for form A.

† Asagran 4D ‡ Aspirin No. 3 special; both from Monsanto Chemicals, Australia

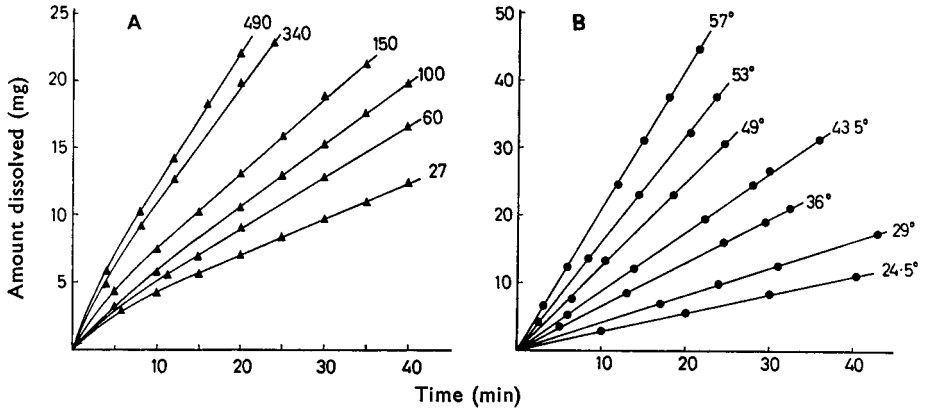

FIG. 1A. Dissolution curves of form A aspirin. Beaker method using compressed discs (diameter 1·3 cm) at various stirring rates (rev/min) in 0·1N HCl at 37°.

B. Dissolution curves of form B aspirin. Rotating disc method at various temperatures in 0·1N HCl at 150 rev/min.

Examination of the discs of aspirin after a dissolution experiment showed that much pitting had occurred in discs of form A but not in discs of form B.

Crystallographic examination. Polarized light microscopy showed that both forms A and B belonged to the monoclinic system. In view of the differences in dissolution rate the samples were examined for polymorphism by X-ray diffraction powder patterns, infrared spectra (Nujol mull) and attenuated total reflectance of infrared. These methods failed to reveal any difference between forms A and B. It is possible however, that one or both forms may be a mixture of polymorphs and that the initial rapid dissolution and pitting of form A is due to the presence of a small amount of a more rapidly dissolving form such as B.

Effect of agitation on dissolution rate. An increase in agitation intensity (rate of stirring or velocity of the dissolution medium across the surface of the dissolving substance) will increase the dissolution rate of a system in which the transport of solute molecules from the solid-solution interface is wholly or partially the rate-determining step. If the rate-determining step is the rate of the interfacial reaction, the overall dissolution rate will be independent of agitation.

The influence of agitation on the transport process is a result of its effect on the thickness of the diffusion layer. Levich (1942) calculated that for a disc rotating in a volume where wall effects are minimal, the thickness of the diffusion layer, "h", should be related to the angular velocity of the disc, "w", by the expression

$$h = 1{\cdot}612\ D^{\frac{1}{3}}v^{\frac{1}{6}}w^{-\frac{1}{2}} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where D is the solute molecule diffusion coefficient and v the viscosity. Therefore, for laminar flow

$$k_t \propto w^{\frac{1}{2}} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (2)$$

where k_t, the rate constant for the transport process, $= D/h$. For other types of stirring

$$k_t \propto w^a \quad .. \quad .. \quad .. \quad .. \quad .. \quad (3)$$

where the value of a, which lies between 0 and 1, depends on the type of agitation (laminar or turbulent), the geometrics of the stirrer and vessel and the position of the stirrer with respect to the dissolving substance (Bircumshaw & Riddiford 1952).

Levy & Procknal (1964) have expressed the relation between the dissolution rate, DR, and the rotation rate RR, according to the general equation

$$DR = K(RR)^{a'} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where K is a constant and a' depends on the nature of the dissolution control as well as the experimental conditions. For transport controlled dissolution using the beaker or rotating disc methods under conditions of laminar flow, $a = a'$. When plotted as log DR against log RR a straight line of slope approximately 0·5 has been taken as evidence that dissolution is transport controlled. Dissolution under total interfacial control is independent of agitation and the expected slope is zero. If both transport and interfacial processes are of the same order of magnitude however, the overall rate will be a function of both processes and the observed rate constant, k_{obs}, is related to k_t and the rate constant for the interfacial reaction, k_i, by

$$k_{obs} = \frac{k_i\, k_t}{k_i + k_t} \text{ (Wurster \& Taylor, 1965b)} \quad .. \quad .. \quad (5)$$

Using equation 5 it can be shown that an increase in interfacial control with rotation rate will produce a non-linear plot of log k_{obs} (or log DR) against log RR with a maximum slope of 0·5 ($k_i \gg k_t$) decreasing to zero when dissolution is under total interfacial control ($k_i < k_t$). Dissolution can be under 15% interfacial control (85% transport control) however, before the slope of the log DR against log RR curve changes significantly from 0·5, i.e. to $< 0{\cdot}45$. Moreover the change in slope is very gradual and in studies which cover a limited range of rotation rates the slope will appear to be linear.

The effect of agitation on the dissolution rate of aspirin has been reported previously (Mitchell & Saville, 1967). For convenience, results using the beaker method plotted as log DR against log RR are given in Fig. 2A. The results for form A fall on a straight line of slope 0·45. Form A also shows a slope of approximately 0·45 at two different temperatures using the rotating disc method, Fig. 2B. As discussed above such a plot may indicate that the dissolution process is under partial interfacial control.

The log DR against log RR profile for form B, Fig. 2A, is unusual. A change in the relative dissolution rates of polymorphs with variation in agitation has been reported

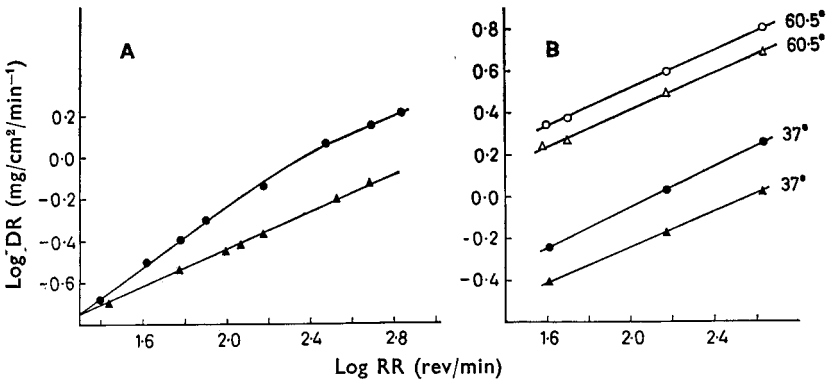

FIG. 2A. Variation of intrinsic dissolution rate with stirring rate. Beaker method using compressed discs of aspirin in 0·1N HCl at 37°. Form A, ▲; form B, ●.

B. Variation of intrinsic dissolution rate with rotation rate. Rotating disc method in 0·1N HCl. Form A, ▲; form B, ●.

previously for methylprednisolone (Hamlin, Nelson & others, 1962; Levy & Procknal, 1964) and in this case the dissolution rate of the metastable form approaches that of the stable form with increase in agitation intensity. From Fig. 2A, however, it can be seen that at an estimated rotation rate of about 20 rev/min the dissolution rates of forms A and B are the same but with increase in rotation rate up to about 300 rev/min the dissolution rate of form B increases relatively faster than A. The slope of the curve is 0·65 whereas under the experimental conditions used, the maximum slope for transport or mixed transport-interfacially controlled dissolution should be about 0·5. Above 300 rev/min the slope of the curve changes to 0·45 and the relative dissolution rate of form B is about 75% faster than form A. At rotation rates less than about 300 rev/min it is evident that some process additional to the normal interfacial and transport processes is involved.

Solubility of aspirin. On the basis of the dissolution behaviour it seems reasonable to suggest that the two forms have different thermodynamic activities. The solubilities of form A and form B are the same at each temperature studied, however, and at no time during solubility determinations on either form did the concentration of aspirin in solution rise above the equilibrium solubility as reported, for example, with metastable crystalline forms of prednisone (Wurster & Taylor, 1965b). Hence if the differences in dissolution rate are due to a difference in thermodynamic activity, it follows that one form must be reverting rapidly to the other during the solubility determination. Solubility data reported by Edwards (1951) for aspirin are shown in the van't Hoff type plot, Fig. 3, together with additional data obtained in this work. As expected from thermodynamic considerations the curve is linear only at lower temperatures (Moelwyn-Hughes, 1961).

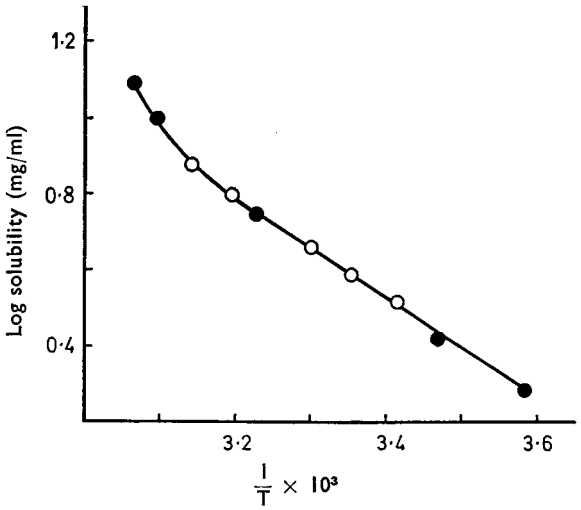

FIG. 3. Solubility of aspirin as a function of temperature. Edwards (1951) in 0·1N H_2SO_4, ○; this work in 0·1N HCl, ●.

Effect of temperature on dissolution rate. An increase in temperature will increase the rates of both the interfacial reaction and transport processes (Bircumshaw & Riddiford, 1952). For a transport controlled dissolution process the dependence of k_t on temperature can be expressed by the Arrhenius equation

$$k_t = Z_t e^{-Et/RT} \quad .. \quad .. \quad .. \quad .. \quad (6)$$

where k_t is given by the ratio of the dissolution rate, DR, and solubility, C_s, provided the experimental conditions are such that the concentration of dissolved solute is negligible compared with C_s. Hence for a transport controlled process a plot of log DR/C_s against 1/T should be linear where the slope of the line is related to the activation energy of the transport process, E_t. E_t changes only slightly with agitation intensity so that plots of log DR/C_s against 1/T at different rotation rates should have approximately the same slope.

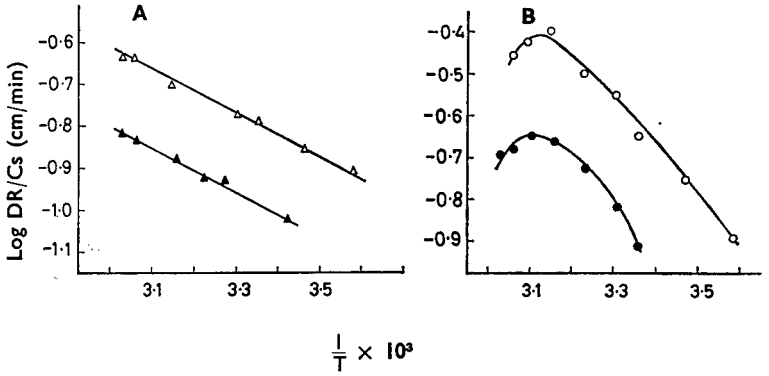

FIG. 4A. Dependence of log DR/C_s, form A, on temperature. ▲ 150 rev/min; △ 430 rev/min in 0·1N HCl, rotating disc method.

B. Dependence of log DR/C_s, form B, on temperature. ● 150 rev/min; ○ 430 rev/min in 0·1N HCl, rotating disc method.

Log DR/C_s against 1/T curves for aspirin forms A and B are plotted in Fig. 4A, B respectively. The activation energy of form A calculated from the slope of the line is 2·4 kcal/mole which is slightly below the range of 2·8–6·5 kcal/mole expected for a transport controlled process (Bircumshaw & Riddiford, 1952). The curves for form B are unusual and show a maxima at 50°. A change in slope indicates a shift in dissolution control but a change in sign is thereoretically impossible. It is concluded therefore that the true solubility of form B is greater than the equilibrium solubility, C_s, used in plotting Fig. 4B, and that forms A and B are thermodynamically different species of aspirin.

Dissolution rate and crystal reversion. Higuchi, Bernardo & Mehta (1967) have developed a model for the dissolution of a mixture of two polymorphs. The theory also provides a qualitative explanation of the "anomalous" effect of agitation intensity on the dissolution of the metastable polymorph of methylprednisolone first reported by Hamlin & others (1962). During the dissolution of the metastable form it is suggested that a layer of the stable form crystallizes at the solid-solution interface. After a time-lag the effect on the dissolution curve is the same as dissolution from a mixture of the two forms. With increase in agitation intensity the thickness of the diffusion layer, *h*, decreases and the dissolution rate quickly approaches that of the pure stable form. The theory requires the assumption that the reversion rate of the metastable form is neither very rapid nor very slow.

The dissolution of aspirin differs from the model proposed for methylprednisolone in several respects. The effects of agitation and temperature on the dissolution of

form B indicate that it is a metastable form, but no time-lag is apparent in the dissolution curves (Fig. 2 and Fig. 1 of Mitchell & Saville, 1967). The results for form A suggest that it is a stable form which contains a small amount of a less stable form. The intercepts of the steady-state dissolution curves on the ordinate (Fig. 1A) are not related to the agitation intensities (and therefore to the diffusion layer thickness, h), however, as required by the model of Higuchi. Finally the dissolution rates of forms A and B appear to be the same at low agitation intensities using the beaker method, but diverge with increase in stirring rate (Fig. 2A) whereas with methylprednisolone polymorphs the dissolution rates differ at low agitation intensities and approach each other as the agitation rate is increased (Levy & Procknal, 1964).

At low stirring rates and in the presence of excess solid, as in the solubility determinations, it is apparent that form B undergoes rapid reversion to a more stable form. The effect of the increase in rotation rate on the dissolution rate of form B suggests an inverse relation between rate of reversion and agitation intensity. Thus the dissolution rate approaches that expected of a more soluble form and gives rise to the unusually high value of 0·65 for the slope of the log DR against log RR curve (Fig. 2A). The change in slope from 0·65 to approximately 0·45 at stirring rates greater than about 300 rev/min indicates that the rate of reversion has reached a minimum limiting value and that dissolution is taking place as if from the more soluble form. The slope of log DR against log RR for form B using the rotating disc method shows no change with rotation rate and is approximately the same as form A (Fig. 2B). From the values of dissolution rate it is apparent, for a given rotation rate, that agitation intensities using the rotating disc method are much greater than for the beaker method, e.g. 150 rev/min rotating disc method $\equiv$ 400 rev/min beaker method. It is likely therefore that minimal reversion occurs with the rotating disc method under the given experimental conditions.

According to the Noyes-Whitney law the ratio of dissolution rates should correspond to the solubility ratio (Hamlin, Northam & Wagner, 1965). Hence, using the difference in dissolution rates found at high rotation rates, it can be postulated that the true solubility of form B at 37° is approximately 75% greater than form A and therefore the interfacial concentration, C_i, is greater than the equilibrium solubility, C_s. During the dissolution of form B the diffusion layer will be supersaturated with respect to a more stable form and polymorphic reversion may occur simultaneously with dissolution. From a consideration of the factors controlling crystal growth it is possible to offer a qualitative explanation for the dependence of reversion rate on agitation intensity. Crystal growth rates are highly dependent on the degree of supersaturation (Taylor & Wurster, 1965). The degree of supersaturation at the solid-solution interface of a metastable crystal undergoing dissolution is given by C_i/C_s where $C_i > C_s$. For a mixed transport-interfacial dissolution process the results of Wurster & Taylor (1965b) show that C_i decreases with increase in agitation intensity. It is suggested therefore that the corresponding reduction in the degree of supersaturation is responsible for the decrease in reversion rate.

A comparison of our results with those of Tawashi (1968) reveals another problem. The more stable of the two forms of aspirin recrystallized by Tawashi was very similar to commercial aspirin U.S.P. We have found that most commercial samples are similar to form B which by comparison with form A must be metastable. It is possible that both forms of aspirin recrystallized by Tawashi are metastable polymorphs and that another more stable form exists.

An important conclusion from a practical viewpoint is that a study of intrinsic rates may be more useful in selecting a suitable drug sample than techniques such as infrared and X-ray diffraction since these will probably fail to distinguish between samples containing different mixtures of polymorphs.

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