The dissolution of aspirin and aspirin tablets*

A. G. MITCHELL** AND DOROTHY J. SAVILLE

An attempt has been made to standardize the "beaker" method of measuring *in vitro* dissolution rates of tablets against published data for aspirin. An unexpected problem arose when it was found that samples of commercial aspirin have different intrinsic dissolution rates. The form of aspirin used in tablet manufacture is likely therefore to be of significance from the viewpoint of *in vivo* dissolution and drug availability.

FOR many drugs, dissolution is the rate-limiting factor in their absorption from the gastrointestinal tract. It has become increasingly apparent that the standards for a pharmaceutical product should include some measure of the availability of the drug and simple, convenient *in vitro* methods, previously correlated with *in vivo* studies are required for adequate quality control. Levy, Leonards & Procknal (1965) have said that the development of *in vitro* dissolution rate tests capable of reflecting absorption rate in man is one of the most important tasks in biopharmaceutics. The difficulties involved in the design and operation of such a test have been discussed by Morrison & Campbell (1965).

Aspirin is rapidly absorbed and is therefore a convenient drug to use in the design of an *in vitro* dissolution test. Levy has made an extensive study of the dissolution of aspirin and aspirin tablets using a "beaker" method (Levy & Hayes, 1960; Levy & Hollister, 1964). Excellent correlation was found between *in vitro* dissolution rates and *in vivo* absorption rates determined from measurements of plasma salicylate (Levy, 1961; Levy & Hollister, 1964; Levy & others, 1965). It is probable that the beaker method will prove satisfactory as a standard method of testing for drug availability. To establish this, however, further work is necessary using other drugs.

Dissolution rates determined by the beaker method depend on the dimensions of the stirrer and beaker, and on the stirring rate. It would be theoretically possible to duplicate the apparatus and the conditions used by Levy, but a more reliable approach would be to determine the stirring rate giving conditions of agitation equivalent to those used by Levy. Having established these conditions, the apparatus should be suitable, in principle, for evaluating the dissolution behaviour of other tablets.

We describe an attempt to "standardize" the beaker method against published data for aspirin, as a preliminary step to its application to other tablets. However, it became apparent that the intrinsic dissolution rate depended on the crystalline form of aspirin used.

From the Pharmacy Department, University of Sydney, Australia.

Experimental

Aspirin.   Aspirin is available in a number of grades and crystalline forms.   Some of these are suitable for tablet compression without preliminary treatment (British patent 810,050, U.S. patent 2,890,240).

Preliminary examination of samples of commercial aspirin showed them to have marked differences in intrinsic dissolution rate.   The purity of each sample was established spectrophotometrically using recrystallized aspirin as a standard.   Two samples showing the maximum difference in intrinsic dissolution rate were selected for more detailed investigation. These are designated form I* and form II**.

Aspirin tablets.   Five brands of plain aspirin tablets were examined.

MEASUREMENT OF INTRINSIC DISSOLUTION RATE

(i) *"Beaker"* method (Levy & Procknal, 1964).   Discs of 400 mg and 1·3 cm diameter were prepared by compression of finely ground aspirin at about 5,000 kg/cm^2 in a potassium bromide punch-die assembly. Each disc was mounted on a microscope cover slip with a suitable water-insoluble adhesive such as flexible collodion or hard paraffin, so that only one face remained exposed.

(ii) *"Rotating disc"* method.   About 300 mg finely ground aspirin was compressed at about 3,500 kg/cm^2 in a compression punch and die assembly constructed according to the specifications of Wood, Syarto & Letterman (1965).   The assembly was then used as the rotating disc holder at 430 rev/min.

Intrinsic dissolution rates were independent of pressure over the compression range 2,000 to 13,000 kg/cm^2.   The intrinsic dissolution rate was also independent of the particle size of aspirin used in preparing the compressed discs.†   Hence no attempt was made to standardize the particle size although normally each sample was ground in an agate mortar before compression.   At least two replicate determinations were made and the results averaged.   The reproducibility was within ±2% for form I and ±3% for form II.

Dissolution of tablets.   The dissolution behaviour of aspirin tablets was investigated using the "beaker" method of Levy & Hayes (1960) with the modifications described by Levy & Hollister (1964).   On completion of each dissolution experiment the remaining aspirin was dissolved to enable calculation of the percentage of drug dissolved.   Up to 7 replicates were made on each brand of tablet and the results were averaged.

All dissolution experiments were at 37° in 0·1N hydrochloric acid. 5 ml samples were withdrawn at suitable intervals, by pipette, using a glass-wool filter when necessary.   The samples were diluted appropriately with 0·1N hydrochloric acid and analyzed spectrophotometrically at 278 and 305 mμ for aspirin and salicylic acid respectively.   The total amount of aspirin dissolved was calculated using simultaneous equations (Willard, Merritt & Dean, 1958).

* Aspirin No. 3 special.   ** Asagran 4D (Monsanto, Chemicals, Australia).

† Micronized aspirin, sample J, supplied by Nicholas Pty. Ltd. showed the same intrinsic dissolution rate as the same material not subjected to the micronizing process (Table 1).

Results and discussion

Intrinsic dissolution rates were calculated from the slope of the dissolution curve as shown in Fig. 1, and the surface area of the compressed disc of aspirin.
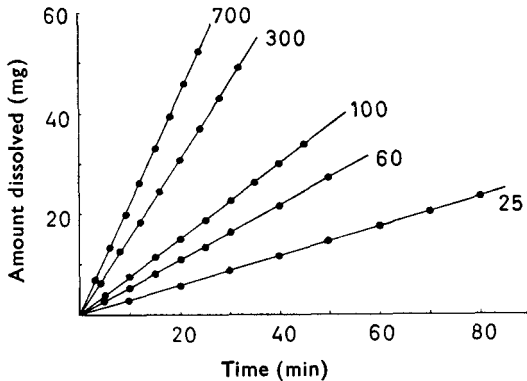

FIG. 1. The dissolution of aspirin at various stirring rates (rpm). Beaker method using compressed discs (diameter 1·3 cm) of aspirin (form I) in 0·1N HCl at 37°.

Levich (through Cooper & Kingery, 1962) derived an equation, relating intrinsic dissolution rate, DR, and rotation rate, RR. Levy & Procknal (1964) expressed this in the form

$$\log DR = a \log RR + C \qquad .. \qquad .. \qquad (1)$$

where a and C are constants.

Fig. 2 shows the intrinsic dissolution rates of aspirin form I and II, plotted as a function of stirring rate over the range 25–700 rev/min. If the dissolution process is purely transport controlled the plot of log DR
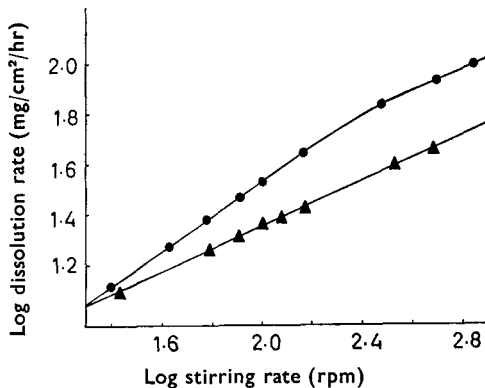

FIG. 2. Variation of intrinsic dissolution rate of aspirin with stirring rate. Beaker method using compressed discs of aspirin: form I, ●; form II, ▲; in 0·1N HCl at 37°.

versus log RR should be a straight line where the slope, a, is approximately 0·5 (Riddiford & Bircumshaw, 1952). If there is a change in control with RR the plot is non-linear with a maximum slope <0·5 (Bircumshaw & Riddiford, 1952). In the present work the dissolution of form II appears to be transport controlled since a = 0·45. Form I, however, shows a non-linear plot with a maximum slope of 0·65 which indicates that some additional process is involved. Work is continuing on this point. At high stirring rates the DR of form I is 75% greater than that of form II. The difference becomes smaller as the stirring rate is reduced and disappears at about 20 rev/min.

Using the beaker method at 59 rev/min, Levy & Procknal (1964) found that DR for aspirin was 24·6 mg/cm^2/hr. On the assumption that Levy used form I the rate of stirring necessary to produce the same DR is 62 rev/min.

The dissolution of several commercial aspirin tablets was followed at 62 rev/min, and the results are shown in Fig. 3. Differences are apparent between the behaviour of the different brands, particularly between
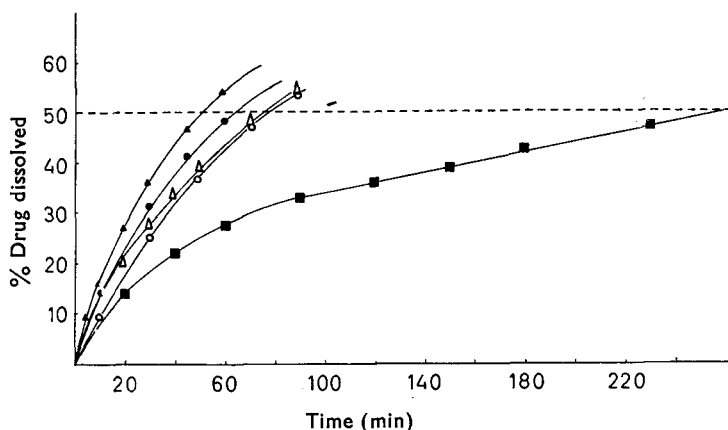

FIG. 3. *In vitro* dissolution of commercial aspirin tablets, P ▲, Q ●, R △, S ○, T ■. Beaker method at 62 rpm in 0·1N HCl at 37°.

brand T and the remaining brands. In each instance, however, dissolution is rapid at first and then decreases in a non-exponential manner. Dissolution behaviour was compared on the basis of the time required for 50% of the aspirin to dissolve, t50%. Values of t50% range from 51 to 267 min and are much longer than times reported by Levy & Hayes (1960). The discrepancy suggests that either there is a marked difference between the tablets tested by Levy and those tested in the present work, or a rotation rate of 62 rev/min does not provide conditions of agitation equivalent to those used by Levy. The variation of t50% with stirring rate for two of the brands of aspirin tablets shown in Fig. 4 emphasizes the importance of the correct choice of stirring rate.
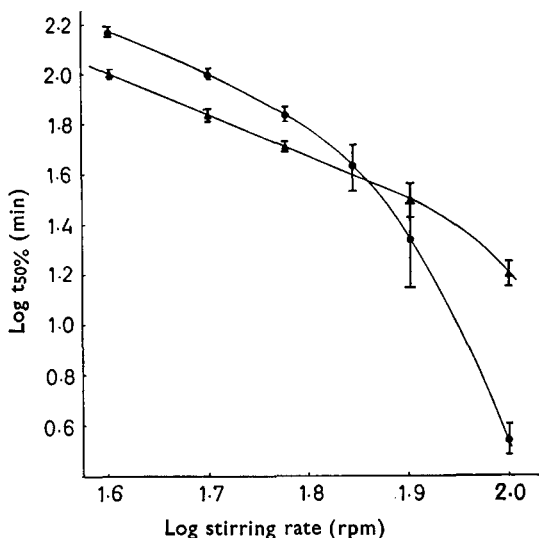
FIG. 4. Variation of *in vitro* dissolution half-lives, t50% of aspirin tablets P ▲, and Q ●, with stirring rate. Beaker method using 0·1N HCl at 37°. Vertical bars show ± 1 s.d.

If we assume that Levy used form II, then from Fig. 2 the stirring rate necessary to produce DR equal to 24·6 mg/cm²/hr is 120 rev/min. This stirring rate would bring the values of t50% for tablets closer to the values reported by Levy & Hayes but one of the conditions of the test is that the disintegrated tablet must remain as an aggregate on the bottom of the beaker. At 120 rev/min in our apparatus, particles of the disintegrated tablet circulate in the dissolution medium.

It is probable that the aspirin used by Levy was not the same as either form I or form II. Intrinsic dissolution rates depend on the conditions of agitation and it is difficult therefore to make comparisons with other published data. However, Wood & others (1965) have determined a value for aspirin using a rotating disc method. Values of DR were therefore measured using the dissolution apparatus of Wood. The results are shown in Table 1. The intrinsic dissolution rate of form I

TABLE 1. INTRINSIC DISSOLUTION RATES OF COMMERCIAL ASPIRIN. ROTATING DISC METHOD IN 0·1N HCL AT 37°

Aspirin sample	Intrinsic dissolution rate (mg/cm²/min)
Wood, Syarto & Letterman (1965)	1·75
B (form I), C and G	1·75
J (before and after micronizing)	1·70
D	1·54
H	1·54
E	1·25
A (form II)	0·995

agrees with the value reported by Wood, and is 75% greater than form II in agreement with the results found using the beaker method at high stirring rates. The intrinsic dissolution rates of a number of the other aspirin samples tested lie between the values found for form I and form II and are included in Table 1.

Variations in intrinsic dissolution rate of crystalline aspirin make it difficult to standardize the beaker method against published data. Moreover it is apparent that the dissolution rate, or t50%, of compressed aspirin tablets will depend not only on the formulation and factors such as particle size but also on the form of aspirin used. The effect on dissolution rate of differences in polymorphic form has been studied by Hamlin, Nelson & others (1962), Levy & Procknal (1964), Wurster & Taylor (1965) and Higuchi, Bernado & Mehta (1967). Preliminary crystallographic studies on aspirin, however, indicate that the differences in intrinsic dissolution rate are not a result of polymorphism.

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