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Short Communication

Towards standardizing agitation conditions in the beaker dissolution method

O.I. CORRIGAN and R.F. TIMONEY

Department of Pharmaceutics, School of Pharmacy, Faculty of Science, Trinity College Dublin, 18 Shrewsbury Road, Dublin 4 (Ireland)

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SUMMARY

The beaker dissolution method of Levy and Hayes is being widely used in dissolution studies. In vivo-in vitro correlations obtained using this method seem to be entirely dependent on the agitation intensity employed. However, differences are apparant in the agitation present in published reports using the method. It is suggested that the suitability of the beaker method for universal quality control purposes could more readily be established were authors to quantify the degree of agitation in terms of the operating diffusion layer thickness.

There is increasing interest in the development of in vitro dissolution tests which can be correlated with in vivo absorption rate studies, for use in quality control or in setting official standards. An acceptable procedure should perform reproducibly and closely simulate in vivo dissolution mechanisms (Withey and Bowker, 1972). Levy and Hayes (1960) introduced the beaker method for dissolution determinations on solid dosage forms. The method is one of the simplest and most widely used techniques (Swarbrick, 1970; Hersey, 1969) and has in a recent review (Hersey and Marty, 1975) been recommended as most suitable for universal quality control purposes.

The original method as described by Levy and Hayes utilized a 400 ml beaker and a stirring speed of 59 rpm, and the mild agitation conditions produced are considered comparable to those found in vivo (Levy, 1963). The method has given useful correlations with in vivo absorption (Levy, 1961 and 1964) and the agitation intensity has been found to be critical for such correlations (Levy et al., 1965; Corrigan et al., 1976). Cognisant of the variability in agitation intensity between dissolution methodologies, Levy and Procknal (1964) proposed the rotating disc dissolution method as a means of comparing different procedures. Modifications to the geometry of the beaker method, e.g. alteration of stirrer dimensions, dissolution vessel dimensions and stirring speed, have been introduced by other workers (Bolhuis et al., 1973; Needham et al., 1973; Sawardeker and McShefferty, 1971). The influence of such modifications on hydrodynamic conditions

and hence dissolution rate has also been reported (Underwood and Cadwallader, 1976; Bathe et al., 1975).

Mitchell and Saville (1967) attempted to standardize their beaker method by measuring the dissolution of aspirin from both commercial tablets and compressed discs of the pure drug. The dissolution data obtained using tablets suggest that the agitation conditions being employed were considerably lower than those of Levy and Hayes (1960). Aspirin discs, on the other hand, gave intrinsic dissolution rates varying by as much as 75% depending on the source of the aspirin sample. The rate for the most rapid dissolving sample was 23.7 mg/cm^2/h compared with a value of 24.6 mg/cm^2/h reported by Levy and Procknal (1964). The reasons for the reported differences in the intrinsic dissolution rates of samples of aspirin has been the subject of much debate (Bundgaard, 1974). In our laboratory intrinsic dissolution rate determination on aspirin and salicylic acid gave rates which were greater, by 25% and 22% respectively, than those reported by Levy and Procknal (1964).

The agitation intensity in different beaker dissolution assemblies could, however, be compared from data obtained using a compound with diffusion controlled dissolution and no crystal modification complications, by estimating the diffusion layer thickness h from

$$h = \frac{D\Delta C}{G} \tag{1}$$

where G is the intrinsic dissolution rate, ΔC is the driving force ($\approx$solubility) and D is the diffusion coefficient of the compound. Using salicylic acid data the diffusion layer thickness operative in the apparatus of Levy and Procknal (1964) is approximately 75×10^{-4} cm compared with 62×10^{-4} cm obtained in our laboratory. Hussain (1972) has reported a value for h of 50×10^{-4} cm for the beaker method using a stirring speed of 55 rpm. These results suggest considerable intra-worker variability in apparatus hydrodynamics. Such variations are a function of the efficiency of the stirrer used and the shape and dimensions of the dissolution vessel (Bircumshaw and Riddiford, 1952).

The rate of mass transfer under turbulent conditions in dimensionally similar vessels can be quantitatively expressed by an equation of the form

$$Nu = B(Re)^a(Pr)^{0.33} \tag{2}$$

where Nu, the Nusselt number, equals $Gd/\Delta CD$, Re represents a modified Reynolds number, Nd^2/v, and Pr, the Prandtl number, is v/D, d is the vessel diameter, N the stirring speed, v the kinematic viscosity, B and a are constants (Bircumshaw and Riddiford, 1952). Dissolution rates determined in our laboratories, using beakers of internal diameters 7.21 cm (i.e. 400 ml) and 8.45 cm (i.e. 600 ml), a 5 cm diameter stirrer * and stirring speeds ranging from 20 to 174 rpm were fitted by

$$Nu = 0.532\ Re^{0.61}\ p_r^{0.33} \tag{3}$$

Levich (1962) shows that, under conditions of laminar flow, mass transfer (from a rotat-

* The 5 cm diameter polyethylene stirrer (Nalge Company Inc., Rochester, N.Y.) was kindly supplied by Professor G. Levy, State University of New York, Buffalo.

ing disc or from a plate in a fluid under forced convection) should be dependent on the fluid velocity to the power of 0.5, while as one moves to conditions of turbulent flow the exponent passes to the power of 0.8–0.9. This dependence of the agitation index on the type of fluid flow has been illustrated by Bisaillon and Tawashi (1971). The value of 0.61 obtained in the current work indicates that a low degree of turbulence exists in the fluid at the dissolution surface. Using the beaker method we were able to correlate in vitro dissolution and bioavailability for hydrochlorothiazide capsule formulations at 40 rpm but not at 59 rpm (Corrigan et al., 1976). The diffusion layer thickness calculated at 40 rpm was 89×10^{-4} cm. Levy et al. (1965), in their original studies using aspirin formulations, obtained a quantitative correlation between in vivo and in vitro data at 50 rpm. However, a change of only 20% in stirring rate, to 60 rpm, was sufficient to make the difference between successful correlation and failure. In the absence of intrinsic dissolution data at different stirring speeds in the latter report, quantification of the agitation intensity at which the correlation was obtained is not possible.

In view of the critical dependence of such correlations on agitation intensity and the apparent differences in agitation present in published reports using the beaker method, it would be useful if authors reported the diffusion layer thickness operative at the stirring speed at which correlations were obtained. The value could be estimated from the intrinsic dissolution rate obtained using a standard compound such as benzoic acid or salicylic acid (i.e. a compound with diffusion controlled dissolution). Variation in agitation over the volume of the beaker may still be a problem. However, adoption of the above recommendation should help in comparing dissolution data and deciding on the suitability of the beaker method for universal quality control purposes.

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