J. Pharm. Pharmac., 1972, **24**, 345–351 *November* 30, 1971

Agitation of the solvent in tablet dissolution studies—a flow visualization technique

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A flow visualization technique has been used to compare flow patterns in several kinds of dissolution apparatus in wide use. The technique readily reveals undesirable characteristics and provides a rational basis for judging empirically developed dissolution apparatus. Some undesirable mixing and flow characteristics were seen in all the methods examined. The U.S.P. apparatus appeared the most promising.

The dissolution rate of a solid dosage form often governs the rate at which active ingredients pass from the gastrointestinal tract into the blood. Thus, the measurement of a parameter related to the rate of dissolution of a solid dosage form has been suggested as a meaningful indication of physiological availability (Oser, Melnick & Hochburg, 1945; Parrott, Wurster & Higuchi, 1955; Wagner, 1961) An example is the fraction of the amount declared on the label dissolved within a given time (National Formulary, 1970).

For a valid test procedure, it is essential that the apparatus should perform reproducibly and closely simulate *in vivo* dissolution mechanisms (Withey & Mainville, 1968). By starting with a simple apparatus and adding restrictive features, such as baffles, baskets or vanes, a range of designs can be achieved. Hixson & Crowell (1931) have classified the various methods of agitation, to promote dissolution.

We have examined dissolution in six types of apparatus in which agitation is accomplished by using a free rotational motion and a pulsating motion. These are: (1) Stationary basket (SB), (2) Food and Drug Directorate disintegration apparatus (FDD), (3) United States Pharmacopeia disintegration apparatus (USP), (4) Levy beaker (LB), (5) Resin kettle (RK), (6) Rotating basket (RB). Details are given by Withey (1971).

Several authors (Hixson & Crowell, 1931; Levy, Leonards & Procknal, 1965; Wurster & Taylor, 1965) have derived empirical relations between dissolution rates and agitation intensity although a number of inherent variables can influence such relations and this restricts the application of a generalized law. It seems reasonable to expect a relatively simple relation between the dissolution rate and agitation intensity where the latter is achieved by the same method (e.g. a rotating impeller, or a reciprocating perforated plunger). No inter-apparatus comparisons of agitation intensity have been made where agitation has been accomplished by different methods. A flow visualization technique that illustrates the nature of the agitation in specific regions of the dissolution medium is now described and the flow characteristics of each method discussed.

METHODS

The photographic technique adopted was similar to that used to illustrate flow patterns around airfoil sections or ship propellers in water tunnels (Clutter, Smith & Brazier, 1959; McEachern & Bowker, 1960). The principle is based on the photographic recording of the tracks of light reflecting particles. If the light source which is used to illuminate the particles is pulsed, then the track of a particle is revealed as a series of particle images (dots or streaks). The length of a particle track is proportional to the velocity of the particle and the exposure time while the number of images per track is proportional to the exposure time and the frequency of the illuminating source (for example, a lamp frequency of 120 Hz and an exposure time of 1/15 or 1/8 s will give eight or fifteen images per particle).

The experimental arrangement is illustrated (for the Levy beaker dissolution apparatus) in Fig. 1. To obtain optimum photographs exposure time, water velocity,

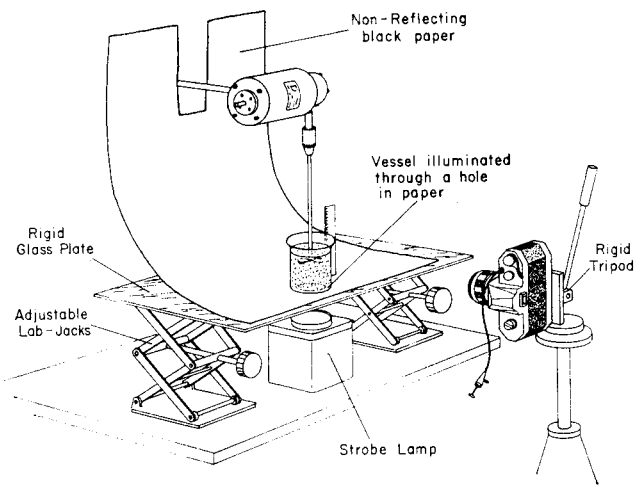

FIG. 1. Typical apparatus arrangement.

film type, developer, developing time, particle type, particle size, particle concentration, aperture, and the light source frequency must be considered. Adequate rather than optimum conditions were obtained by us.

Equipment

An Asahi Pentax S.2 camera (Asahi Optical Co. Ltd., Japan) with a 55 mm lens was used with apertures varying from f 2·0 to f 22 and exposure times from 1/2 to 1/500 s. Kodak Tri-X film (A.S.A. 400) was used.

A Strobotac electronic tachometer and motion analyser (General Radio Company, West Concord, Massachusetts, U.S.A.) was used as a light source in a completely darkened room. The frequency of light pulses from this instrument was checked by means of a dual beam cathode ray oscilloscope

The reflecting particles used for high resolution photographs were of aluminium powder, with a particle size ranging from 5 to 50 μm diameter; polystyrene beads of 100 μm diameter and specific gravity 1·06 were also used for improved clarity.

Because they have a specific gravity close to unity their settling rate was very slow, so that they followed fluid motion closely.

Among the different types of dissolution apparatus, apparatus variables, such as the rotation rate of propellers, solvent volume and geometric arrangement of the components were fixed. The apparatus we used were either based on original descriptions in the literature or are in use extensively in Food and Drug Directorate laboratories.

RESULTS AND DISCUSSION

Since the mechanism of dissolution should remain the same the dissolution test should be substantially independent of the specific gravity of the dosage form, as widely different formulations of the same drug may have to be compared. Dimensional analysis and model techniques, commonly employed in fluid mechanics, have been suggested as a means of studying the performance and effectiveness of geometrically similar agitation systems (Hixson & Baum, 1941). The devices which are considered in this paper, being geometrically dissimilar, cannot be studied by using these techniques. They have been developed empirically and this study has indicated some inherent deficiencies in these devices.

A factor affecting both fluid flow and particle movement, is the effect of fluid viscosity. The effect of viscosity is to restrict fluid movement relative to all surfaces with which it is in contact. Thus agitators, baffles, baskets, container walls and even the surfaces of immersed test objects will be "coated" with a boundary layer of fluid. As a consequence, viscosity factors can cause complex flow fields even for simple geometric configurations.

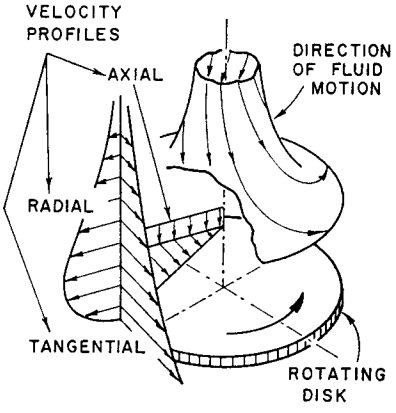

FIG. 2. Flow near rotating disc.

Consider a rotating disc immersed in a fluid which is at rest. In the absence of viscosity the fluid would remain stationary but as a consequence of viscosity the induced flow field (Fig. 2) is complex. Forces due to viscosity cause a circumferential flow with a resulting component centrifugal force which induces radial flow and consequently axial flow. The system becomes more complicated if the effects of container walls are included.

A rotating propeller, such as is used in the Levy beaker or resin kettle apparatus, introduces the additional complication of stagnation points within the fluid in a container. In this case, stagnation points occur where a flow normal to the container

surface is arrested in the process of being redirected parallel to the surface, with two undesirable effects. First, the radial velocity outside the boundary layer (i.e. where viscosity effects are negligible) is position-dependent. Secondly, there is a boundary layer near the wall of the containing vessel where the velocity of the fluid is greatly attenuated by the wall. These two flow factors have a more serious effect for solid dosage forms with specific gravity greater than unity. Small particles at regions of stagnation and within the boundary layer reduce the mechanism of the dissolution process to one of simple diffusion. In the main body of the solution, large and small particles will dissolve by a dissolution mechanism which involves both diffusion and facilitated (by the movement of solvent) transport.

Different flow characteristics are observed in system such as the F.D.D. and U.S.P. equipment, where the substrate is moved through the solvent by means of six axially oscillating cylinders with screened ends. If the fluid motion, near a wall which is oscillating in the plane of its surface, is considered it can be seen from Fig. 3 that the effect of the wall decreases rapidly as the distance from the wall increases, and there is a region of fluid adjacent to the wall which moves with it (Schlichting, 1960).

In an apparatus using such baskets, particles near the cylinder walls are subjected

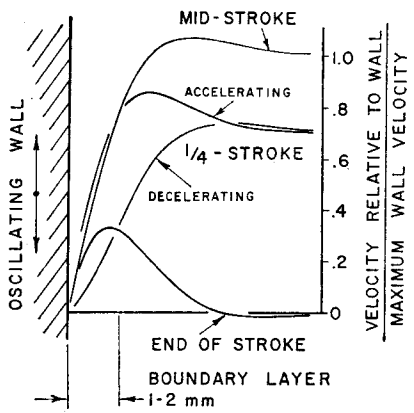

FIG. 3. Velocity profiles near an oscillating wall.

to flows of reduced velocity compared with those near the centre. Eventually, all particles reduce to a size which permits them to pass through the mesh which covers the bottom end of the moving cylinder whereupon they settle or rise to an undisturbed area. This situation is somewhat more complex than those previously considered in that the flow field is time-dependent.

Having considered the flows in some simple arrangements it is now possible to examine the results of the flow visualization technique applied to the dissolution methods which are considered in this report. The devices, 1, 4 and 5, have a common feature in that agitation is provided by the rotation of a simple propeller or T-shaped paddle. The motion of the polystyrene beads, revealed a central core of vortical fluid, surrounded by a slower-moving region (Fig. 4A). The effects of the propellers were not visually different from the T-shaped paddle. This is because, in the absence of baffles, the drag effect of the propeller accumulates, while the thrusting effect is

reduced as the fluid acquires rotational velocity. A consequence of this motion was noted by Levy & Hayes (1960) who observed that when tablets of acetylsalicylic acid disintegrated the powder either collected to form a mound in the centre of the beaker bottom or settled around its periphery. Levy arbitrarily rejected dissolution data when the disintegrated tablet components collected at the periphery. There the solvent agitation is at a minimum and consequently dissolution in this region is slow. Even if the propellers were rotated faster, the boundary layer and stagnation regions would still exist. In this respect the stationary basket apparatus has an advantage in that the test objects are restrained in a specific part of the flow field where solute concentrations cannot accumulate and agitation remains fairly constant. However, as dissolution proceeds, particles will sift through the screen and settle to the bottom, losing any such advantage.

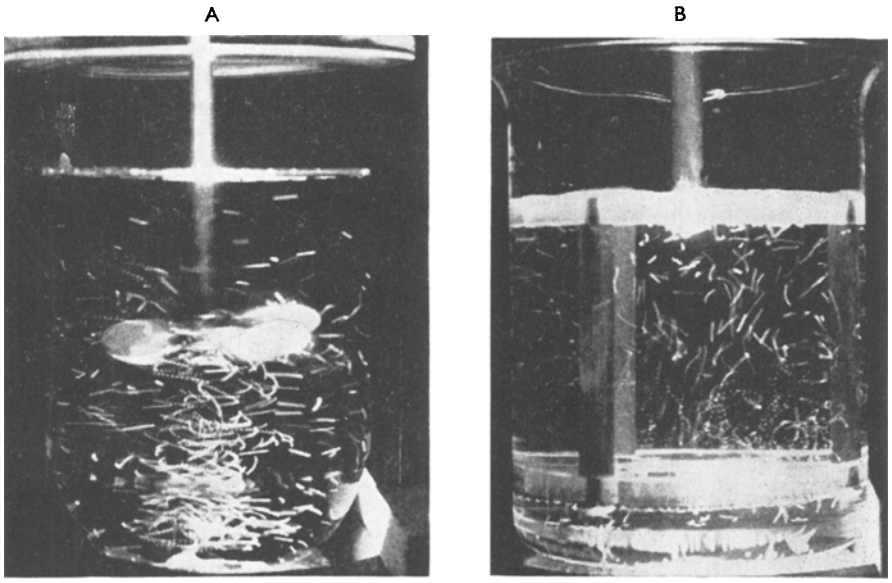

FIG. 4A. Flow pattern for resin kettle apparatus. Note central stable core. Strobe lamp frequency: 2100 flashes/min, aperture and exposure time: f 4·0, ¼ s.

B. Flow pattern for U.S.P. apparatus. Strobe lamp frequency: 2700 flashes/min, aperture and exposure time: f 4·0, ¼ s.

As might be anticipated from the analogy of the rotating plate, the rotating basket, while a simple device, causes a complex non-uniform flow pattern. The photograph in Fig. 5A shows the vortex flow which is built up from the end plates of the basket over a period of 90 s, at the end of which the fluid near the surface of the dissolution medium is still barely moving and layers with little mixing can be seen at the bottom of the containing vessel and in the plane of the basket. Particulate matter, on escape through the mesh of the basket, will tend to settle in the stagnant regions near the container bottom or on the surface of the liquid and not contribute to the dissolution process in a regular manner. In the plane of rotation of the basket, flow is primarily radial. There is little vertical mixing, creating, in effect, upper and lower cells with a resulting vertical solute concentration gradient which depends on the specific gravity of the solution (Fig. 5B).

There is a superficial resemblance between the U.S.P. and the F.D.D. apparatus in that solid dosage formulations are constrained within an open-ended cylindrical cage which is then stroked axially through the fluid. However, there are some significant differences between them. There is a large leakage path around the oscillating framework, the F.D.D. arrangement that tends to create a region of low mixing at the periphery of the bottom of the test beaker. Hence, any particles that migrate to this region accumulate there interfering with the dissolution process. In addition, this leakage path allows most of the test medium to flow around the test chambers instead of through them, which is not an effective way of dispersing the more concentrated solution from the test chamber throughout the solvent.

By contrast, the U.S.P. arrangement with a relatively small radial clearance, causes a more rapid flow through the clearance, thus reducing the influence of the stagnation region at the bottom periphery. The more uniform mixing (Fig. 4B) occurred throughout the stroke, making this apparatus appear the most promising of any so far discussed, as far as reproducibility and uniformity of mixing are concerned.

In fact, as noted previously (Withey, 1971) these superior characteristics of the U.S.P. apparatus were apparent when a reproducible substrate of NaCl was used

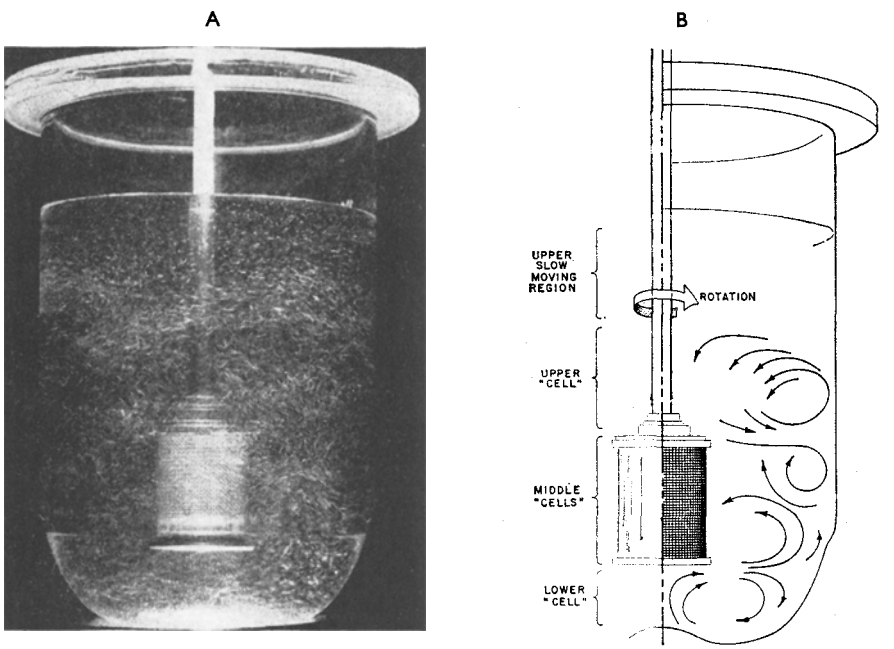

FIG. 5. A. Flow in rotating basket apparatus, 90 s after rotation commenced. Strobe lamp frequency: 600 flashes/min, aperture and exposure time: f 4·0, ½ s. B. Diagrammatic representation of conditions in the apparatus.

since the dissolution kinetics obeyed the expected "cube root law" and there was good repeatability. However, all particles eventually reduce to a size which permits passage through the screen mesh at the bottom end of the test cylinder, whereupon they tend to settle in an undisturbed area. For example, during trials with soft elastic capsules containing chloramphenicol, the oil-base contents accumulated on the bottom of the containing vessel, placing this dosage form at an unjustifiable disadvantage (Withey & Mainville, 1968).

A complete hydrodynamic analysis of diverse dissolution apparatuses can hardly be considered practical, particularly in the presence of viscous effects.

Conclusions

Dimensional analysis and model techniques are not useful in comparing such geometrically dissimilar systems. However, a simple flow visualization technique such as that described in this paper will readily reveal undesirable characteristics and provide a relatively rational basis for judging any empirically developed dissolution apparatus. The application of this flow visualization technique has revealed some undesirable mixing and flow characteristics within the agitated solvent in all the methods examined. It is suggested that these techniques could be used to assess the characteristics of future dissolution equipment design.

Acknowledgements

It is a pleasure to acknowledge the assistance of Mr. F. Bryce, who took some of the photographs used in this study. Thanks are also due to Mr. R. J. Templin and Mr. G. A. Dobrodzicki of the Low Speed Aerodynamics Laboratory, National Research Council, Ottawa, for their assistance in the early stages of this work.

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