A simplified dissolution rate apparatus

The rate at which the active ingredient of a solid dosage form dissolves into the fluid of the gastrointestinal tract may be the rate-determining step in the absorption sequence of the drug. This dissolution rate may show little correlation to the disintegration time of the formulation (Schroeter, Tingstad & others, 1962). These and other authors (Parrott, Wurster & Higuchi, 1955; Levy, 1961; Finholt, 1966) have suggested that a dissolution rate test should supplement the present official disintigration standards. Numerous methods have been devised to measure *in vitro* dissolution rates and have been reviewed by Hersey (1969). Several of these proposals referred to specialized techniques designed to determine intrinsic dissolution rates, others were concerned with one particular application or were unsuitable for evaluating commercial dosage forms. Many have disadvantages including, non-uniformity of agitation around the dose form, non-sink conditions, or over complexity of design which introduces other variable factors such as transport across membranes.

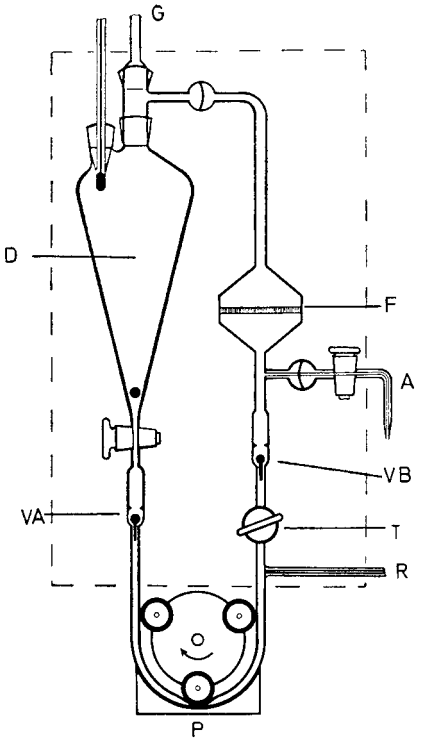

FIG. 1. Diagram of apparatus. For description see text.

The apparatus described here (Fig. 1) is designed to be simple whilst remaining versatile. Chapman, Crisafio & Campbell (1954) and Morrison & Campbell (1965) have pointed out that *in vitro* methods cannot simulate all the conditions encountered *in vivo*, hence only *in vivo* conditions which are easily contrived and reproducible have been included in the method. Agitation is provided by the flow of liquid in the apparatus which is maintained by a peristaltic pump (P) forcing liquid along a short length of lubricated nylon tubing. Except for this short length of tubing the rest of the apparatus is constructed entirely of borosilicate glass. The flow rate can be adjusted by altering the diameter of the tubing used or the speed of the rotor. Fluid leaving the pump passes through a one way valve (VA) to eliminate any back surge due to the peristaltic action. The resultant flow is a series of forward pulses with no

mixing of solutions once they have passed the sample under test in the dissolution vessel (D). The fluid enters this vessel, a standard 250 ml separating funnel, by lifting a simple glass ball valve which prevents any heavier particles from dropping out of the vessel at low pump rates. This valve and the narrow bore of the tap preceding it give rise to a small area of turbulence above the valve, the extent of which depends upon the pumping rate. Tablets, capsules or powders can thus be given any desired constant agitation by controlling the flow rate.

Above the turbulent region the flow is laminar with little mixing and therefore the actual amount of sample dissolving in the agitation zone at any given time is obtained by analysing the fluid leaving the dissolution vessel. X-ray studies have shown (Levy; 1963; Steinberg, Frey & others, 1965) that agitation in the stomach is usually very gentle with wide variations between subjects. These conditions can be reproduced in the apparatus by using very low flow rates or filling the base of the vessel with glass spheres which raise the sample into a zone of gentler laminar flow. The shape of the funnel causes the flow rate to decrease with height above the agitation zone and tests with solutions of dyes have indicated that no dead spots of static fluid are created i.e. it ascends as a perfectly horizontal plane. It can be argued that different sized particles will be subjected to a varying velocity of dissolution medium past them as smaller particles are carried up the vessel. Where this is thought to be significant the effect may be minimized by the inclusion of several large glass beads into the bottom of the dissolution vessel so that all particles, whether large or small, are retained in a region of more uniform fluid velocity.

Because of the very low velocity at the top of the vessel most drug particles are retained at lower levels and only very fine or light particles such as starch grains are carried over on to the glass sinter (F). In practice any drug particles leaving the vessel are so small that they dissolve completely before reaching the sinter or within a very short time after settling on it and do not affect the bulk dissolution rate significantly. However, to measure the degree of blocking of this filter a pressure gauge may be attached to the top of the dissolution vessel at G. Below the filter samples are removed for batchwise or on-stream analysis along capillary line (A). Replacement dissolution fluid is automatically drawn into the system from a reservoir (not shown), via the inlet tube R, by the pump, to compensate for the outflow. If the sampling rate equals the pump rate the ideal situation of a perfect sink is established with fresh fluid continually bathing the sample. As this situation is approached a one way valve VB prevents any tendency for fresh fluid to flow back and dilute the sampling line. For perfect sink conditions with rapidly absorbed drugs, the tap T is closed. The whole apparatus and the compensating reservoir, except the pump are immersed in a water bath (indicated by the broken line) maintained at 37·5°.

Fig. 2 shows typical concentration versus time histograms for the dissolution in water of three different commercial batches of 300 mg acetylsalicylic acid tablets B.P., the pumping rate being 50 ml/min. Histograms A1 and A2 are derived from one batch and give identical high initial concentration peaks which are characteristic of rapidly dissolving tablets. The rate of continuous sampling for histogram A1 was 13 ml/min, while that for histogram A2 was 10 ml/min. This resulted in a more rapid decrease in concentration with time in the former profile. Histogram B1 was from a different source but had the same B.P. disintegration time as tablets used for A1 and A2. The initial peak, however, was much lower and more delayed, indicating a slower dissolution rate. Histogram B2 represents a batch of tablets that disintegrated very slowly and the concentration profile illustrates the extremely slow release of drug under these circumstances. Continuous recording of concentration at point A provides a smooth concentration versus time plot, which is more desirable but requires more sophisticated analytical instrumentation.

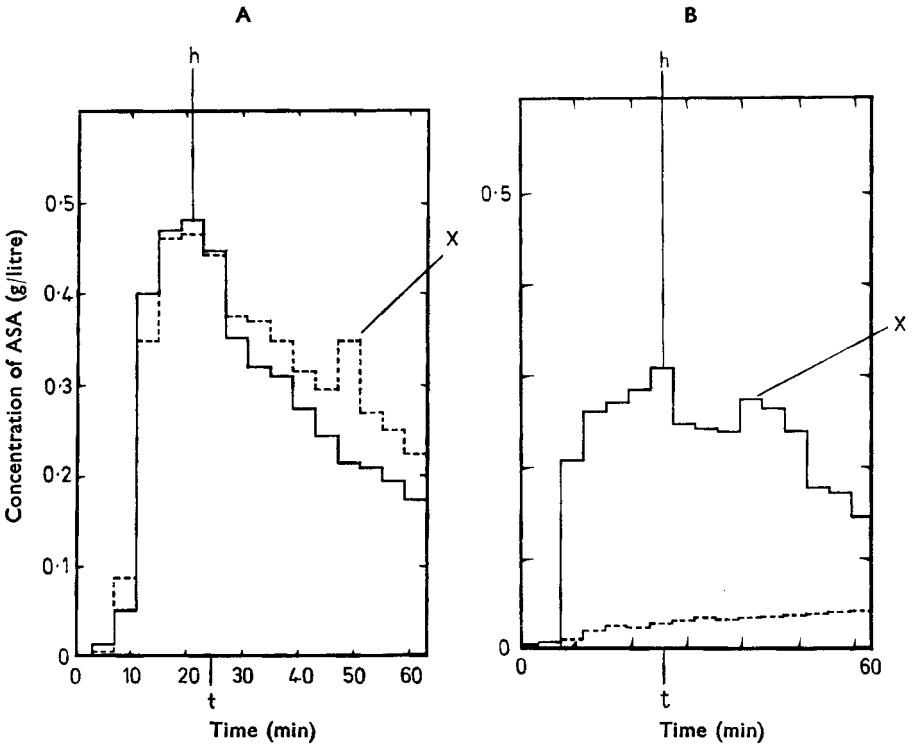

FIG. 2. Concentration versus time histograms of three batches of acetylsalicyclic acid tablets B.P. A1(—) sampled at 13 ml/min; A2(- - -), same batch sampled at 10 ml/min; B1(—), second batch with same B.P. disintegration time as A1 and A2 sampled at 13 ml/min; B2(- - -), from a batch of slow disintegrating tablets sampled at 13 ml/min.

It is tentatively suggested that a combination of the height of the concentration peak "h" together with the time "t" at which it occurs and possibly the time to reach some minimal residual concentration, might provide the numerical criteria necessary to characterize and compare solid dosage forms, although more work is necessary to establish their relative significance. The effect of only partial sink conditions can be clearly seen in histograms A2 and B1 where recycling causes the subsidiary peaks at X. Detailed studies of the variable parameters of the apparatus, different solid dosage forms and *in vivo* correlation are now proceeding.

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