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COMMUNICATIONS

An automated dissolution apparatus for non-disintegrating pellets and granules

M. P. RAMSEY, J. M. NEWTON*, G. G. SHAW, *Department of Pharmacy, University of Nottingham, Nottingham NG7 2RD, *Department of Pharmacy, Chelsea College, Manresa Road, London SW3 6LX, U.K.*

Dissolution testing of dosage forms has become a recognized method for assessing the effects of formulation on drug release and as a routine quality control procedure for controlled release preparations.

Numerous dissolution methods have been reported (Hersey & Marty 1975) including the rotating bottle systems of Wruble (1930) and Souder & Ellenbogen (1958). Such systems ensure that the flow of dissolution medium across the surface of the solid is streamlined and reproducible, conditions which Wood (1967) suggests are essential requirements for dissolution tests. In the rotating bottle systems, flow is controlled by the solid falling through the medium rather than by external agitation. However, the systems described in the literature suffer from the disadvantages of requiring intermittent sampling and providing a limited volume. The former causes interruption of rotation and hence of the dissolution process and the latter may not provide sink conditions which are necessary for reproducibility (Groves & Alkan 1975).

An automated dissolution apparatus based on the rotating bottle has been developed to follow the release of drug substances from pellets and granules, especially sustained-release products which do not disintegrate but release their drug by erosion or diffusion. The equipment consists of a glass chamber through which dissolution medium is pumped for analysis. The chamber itself consists of a Pyrex heavy walled tube with hemispherical ends 150 mm in length and 25 mm in outer diameter. The internal volume of the tube is 50 ml. Fused centrally into the side of this tube is a sidearm terminating in a screwthread joint (Quickfit, Corning Ltd, Stone, Staffs) suitable for 7 mm (outer diameter) glass tubing. A glass lip is formed on the inner surface of the fused union (Fig. 1). Two lengths of 2 mm diameter polyvinyl chloride (PVC) tubing (Portex Ltd, Hythe, Kent) protrude from either end of a length of 7 mm diameter Pyrex glass tubing bent at a right angle with the length of the longer arm being sufficient to allow clearance of the surface of a constant temperature water bath. At the end of the shorter length of tubing a silicone rubber seal is made around the PVC tubes terminating in a rubber 'O'-ring.

With the apparatus set up, the shorter arm of the right angled tube is secured in the screwthread joint through a Teflon washer and silicone rubber ring with the 'O'-ring forming a liquid-tight mobile seal on the lip at the tube-sidearm boundary. This system effectively seals the dissolution chamber whilst providing a means of rotation, continuous sampling, and isolation from the water bath fluid. The chamber is rotated at a controlled speed about the short arm of the right angled tube (which forms a horizontal axis) on a brass bearing which is immersed in the water bath and is driven from outside the bath by a timing belt system (Fenner (Power Transmission) Ltd, Marfleet, Hull) from an electric motor. With this motion, a 'tumbling' action is achieved with the pellets repeatedly falling through the dissolution medium. The rate of rotation can be varied by changing the pulleys on the drive and motor shafts.

Solution to be sampled is pulled through a short length of the PVC tubing penetrating the dissolution chamber with the second, longer length of tubing

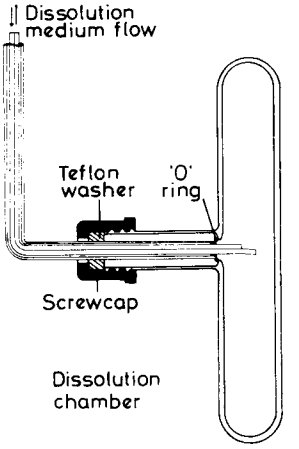

FIG. 1. Dissolution chamber of automated dissolution apparatus.

* Correspondence.

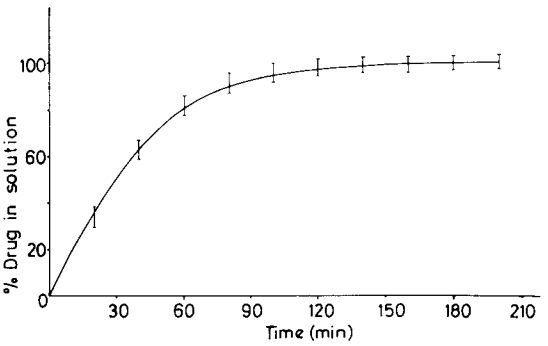

FIG. 2. Dissolution of imipramine-containing spheres in 'closed mode' operation of automated dissolution apparatus. Error bars represent standard deviation of four replicate tests.

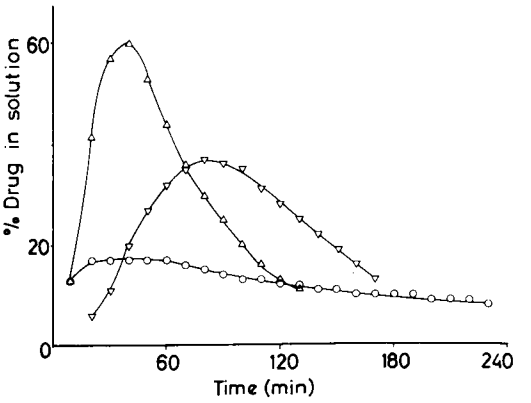

FIG. 3. Dissolution of imipramine-containing spheres in 'open mode' operation of automated dissolution apparatus. Rapidly dissolving pellet △; slowly dissolving pellet ▽ and non-dissolving porous pellet ○.

allowing replacement of the removed medium. The system may be operated in a 'closed mode' with dissolution medium flowing through a spectrophotometer and back into the chamber or in an 'open mode' where fresh preheated solvent replaces that removed and may thus allow maintenance of sink conditions.

In the 'open mode' the sample may be analysed by a continuous flow method or as collected fractions which allows dilution of solutions too highly concentrated before analysis. Both methods have been reported previously for continuous systems (Eide 1973; Borst & Wald 1972).

Tests using pellets containing methylene blue dye showed that mixing of the contents within the chamber provided by the pellets themselves is sufficient to maintain homogeneity of the sample. However, 'open mode' dissolution of fast dissolving concentrated pellets may require additional mixing during the dilution phase after dissolution is completed in order to give more uniform dilution and improved reproducibility. This can be achieved with the addition of a small number of non-dissolving inert pellets (such as glass beads) to the system.

Release data from four replicate samples of imipramine-containing spheres was used to construct Fig. 2 which shows a typical 'closed mode' release curve. The dissolution profiles of three formulations of imipramine; a rapidly dissolving pellet, a slowly dissolving pellet and a non-dissolving porous pellet; in the open mode apparatus are shown in Fig. 3. When total drug release has been achieved, the logarithm of the drug concentration in solution is directly related to time, indicating simple dilution of the contents.

The system described constitutes a versatile dissolution procedure which easily accommodates the testing of non-disintegrating pellets and granules under variable but reproducible conditions which may be used to investigate the release mechanisms of drugs from various dosage forms and to simulate in vivo kinetics.

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