J. Pharm. Pharmac., 1968, **20**, *Suppl.*, 232S–238S Received May 1, 1968

Dissolution rate measurement by an automated dialysis method

R. B. BARZILAY AND J. A. HERSEY

An automated dialysis method for measuring the dissolution profiles of unit dose forms is described. The suitability of the method for the evaluation of these profiles has been demonstrated by an examination of tablets of sulphathiazole prepared under different conditions of pressure and excipient content. The addition of the water soluble resin, polyethylene oxide, has been shown to cause a small increase in the dissolution rates of the tablets.

DISSOLUTION rate tests for tablets and capsules have been developed in an attempt to obtain a more realistic *in vitro* determination of the availability of the drug *in vivo*. The beaker method of Levy & Hayes (1960), although widely used, has the disadvantage of a continually diminishing volume of dissolution fluid and, sometimes, random movement of the tablet under test. Beaker methods also involve a filtration in the sampling technique and where such methods have been automated (Schroeter & Wagner, 1962; Niebergall & Goyan, 1963; Michaels, Greely & others, 1965) continual passage of solution through a filter covered with drug particles may present an erroneous picture of the dissolution process. A constant volume of dissolution medium may be used in a circulatory system, provided dilution is not necessary for analysis of the dissolving drug. The sampling flow rate must also be considered in the continuous method because it may constitute an additional agitation process. Much evidence is available to show that agitation rates affect dissolution profiles. Dialysis techniques have been adopted to overcome the problem of obtaining a representative sample of the dissolution fluid without substantially affecting the fluid volume (Patel & Kostenbauder, 1958; Patel & Foss, 1964). More recently Marlowe & Shangraw (1967) have used a dialysis cell method to examine the release of sodium salicylate from tablet matrices. The disadvantages of their method have been summarized as follows: "The dissolution procedure is not as simple as would be desirable. The manual removal of samples and their assay are time consuming and interruption of rotation of the cell is necessary while samples are withdrawn. Even though the tablet remains immersed in the liquid and removal procedure standardized, there is a chance for a slight distortion in dissolution profile. Obviously an automatic sampler and analyser would be advantageous".

Ferrari & Khoury (1967) developed an automatic technique for use with the Technicon Autoanalyser and attempted to overcome the problem of fine particles passing from the dissolution flask into the dialyser unit by placing a fine plastic screen over the tip of the sampling pipette and introducing air segmentation to prevent fine particles from settling.

Krogerus, Kristoffersson & Kehela (1967) developed a method for dissolution studies involving dialysis, similar to the method which has

From the Department of Pharmaceutics, The School of Pharmacy, University of London, Brunswick Square, London, W.C.1, England.

been developed in this laboratory. Unlike the method of Krogerus & others however, the method described here maintains constant volumes and is fully automatic.

The object of this work was to develop and evaluate a suitable standard technique which could be used to examine dissolution as well as simultaneous disintegration and dissolution. Tablets were prepared at different pressures with and without the addition of starch or polyethylene oxide. The latter substance was chosen for its ability to reduce the onset of turbulence (Giles & Pettit, 1967) and hence its possible use to delay the absorption of drugs.

Experimental

Tablets of sulphathiazole were prepared on an instrumented Lehman tabletting machine. Flat surfaced, 12 mm diameter punches were used and the applied pressure determined as previously described (Shotton & Ganderton, 1960). The die was cleaned and lightly dusted with magnesium stearate before tablet preparation. 500 mg sulphathiazole powder of mean particle size 19·4 μ (Fisher Sub-Sieve Sizer) with the added excipient where indicated was handfilled into the die. Tablets of sulphathiazole alone were prepared at three different pressures. Tablets containing various concentrations of polyethylene oxide (Polyox WSR 301) or maize starch were prepared at 792 kg cm^{-2} or 660 kg cm^{-2} respectively.

Tablet disintegration test equipment readily obtainable in pharmaceutical laboratories was considered to be adaptable for work on dissolution. The only alteration was the replacement of the tablet holder with a cylindrical cell, the walls of which were formed from a dialysis membrane. The membrane was in the form of a tube, Visking Tubing, 32 mm inflated diameter. The lower end of the dialyser cell was formed by inserting a cylindrical Perspex block 13 mm high inside the dialysis tube to provide a tight fit and then clamping this inside a tough, flexible, polythene cap. The upper end of the tubing was held by a thin Perspex ring 12 mm high which could be inserted into the tube and held by a rubber band. This ring contained two holes for suspending the dialyser from the motor unit of the apparatus. The effective area available for dialysis was that supplied by the walls of a cylinder 75 mm high and 32 mm in diameter i.e. 75 cm^2.

For use, 150 ml of distilled water was placed in the outer vessel from which samples were continuously taken at a rate of 2·9 ml/min and replaced with distilled water at an identical rate. The tablet under test was placed inside the dialyser and at the beginning of the experiment 50 ml of distilled water previously equilibrated at 37° was poured into the dialyser and the motor was started.

The dialyser was raised and lowered 30 times a minute. At its highest position it was completely withdrawn from the water and at its lowest position the top of the dialyser remained clear of the water. The temperature of the system was maintained at 37° $\pm$ 1°.

For the purpose of comparison, the method of Ferrari & Khoury (1967)

was adapted for use with the unmodified disintegration apparatus. In place of the dissolution cell an Autoanalyser Dialyser was included in the circuit (Fig. 1B).

METHOD OF ANALYSIS

The method of Werner (1939) was adapted for continuous automatic sampling and assay using the Autoanalyser. This is shown diagrammatically in Fig. 1A. Colour intensity was examined at 460 mμ after passing the reaction stream through double mixing coils for 9 min.

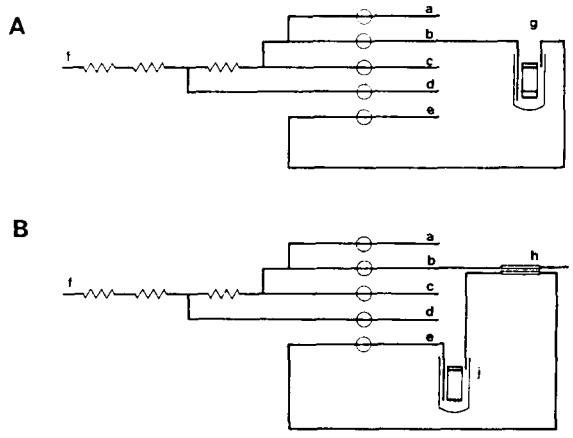

FIG. 1. Diagrammatic representation of the analysis systems. a. Pump tube 0·6 ml/min, air. b. Pump tube 2·9 ml/min, sample. c. Pump tube 2·0 ml/min, distilled water. d. Pump tube 0·1 ml/min, Ehrlich's reagent. e. Pump tube 2·9 ml/min, distilled water. f. to colourimeter, wavelength 460 mμ and recorder. g. Dialysis cell. h. Autoanalyser dialyser. j. Disintegration tube.

The method was chosen after a comparison with the method of Bratton & Marshall (1939) as modified by Wrightman & Holl (1965). The standard deviations of ten results for three sulphathiazole concentrations (1, 5, 10 mg/100 ml) are: 0·0011, 0·0041, 0·0111 for these concentrations by Werner's method and 0·0035, 0·0122 and 0·0334 by Bratton & Marshall's method.

The accuracy and simplicity of Werner's method of analysis has already been pointed out by Andrews & Strauss (1941) when comparing these two methods. In addition, the absorbance of solutions of sulphathiazole over a range of 1 to 20 mg/100 ml was measured for both methods of analysis. Regression lines were plotted and the average variation of absorbance values about the regression lines found were: for Werner's method, 0·0004 (2 exp.) and for Bratton & Marshall's method, 0·0010 (2 exp.). At lower concentrations, the response in Bratton & Marshall's method was non-linear. The passage of small nitrogen bubbles through the flow cell may also constitute an additional source of variation.

Results

The dissolution profile of tablets containing 500 mg of sulphathiazole, compressed at different pressures is shown in Fig. 2. The position of the tablet on the Perspex block at the bottom of the dialyser remained constant in relation to the dialyser itself throughout the experiment. As the tablet remained intact, dissolution could only have occurred from the top surface and from the edge of the tablet. The results indicate a decreasing dissolution rate with increasing applied pressure over the range of pressures used.

In spite of the reduced area available for dialysis much higher dissolution profiles were obtained using the unmodified disintegration apparatus in

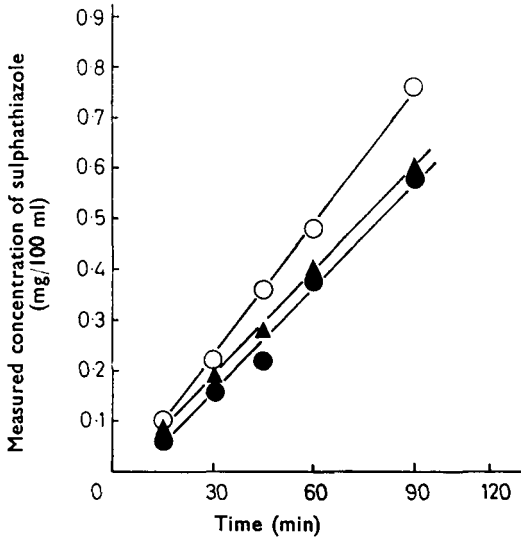

FIG. 2. Dissolution profiles of sulphathiazole tablets prepared at different applied pressures. ○ Applied pressure 500 kg cm^{-2}. ▲ Applied pressure 770 kg cm^{-2}. ● Applied pressure 1090 kg cm^{-2}.

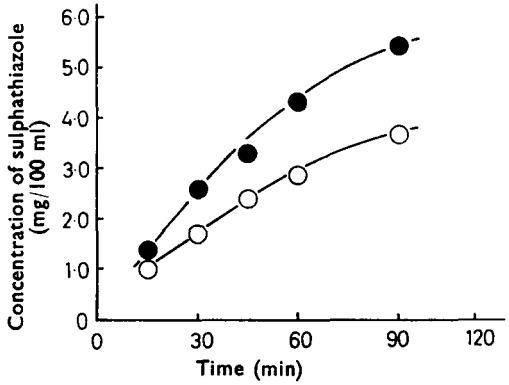

FIG. 3. Dissolution profiles of sulphathiazole tablets prepared at different pressures using the Autoanalyser dialyser system. ● Applied pressure 730 kg cm^{-2}. ○ Applied pressure 1140 kg cm^{-2}.

conjunction with the Autoanalyser dialyser (Fig. 3). This may be explained by the higher agitation intensity experienced by the tablets in the disintegration apparatus and also by the fact that dissolution of drug may occur from the whole of the tablet surface. Once again the tablets did not disintegrate during the period of investigation.

The effects of polyethylene oxide (Polyox WSR 301) and of maize starch on the dissolution profiles of the sulphathiazole tablets (Figs 4 and 5) show that an increasing concentration of either excipient increases the

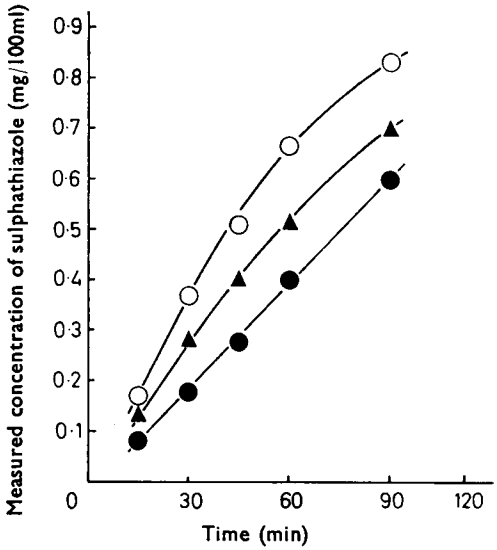

FIG. 4. Effect of polyethylene oxide on the dissolution profile of sulphathiazole tablets. ○ 5% Polyox. ▲ 1% Polyox. ● Sulphathiazole tablets.

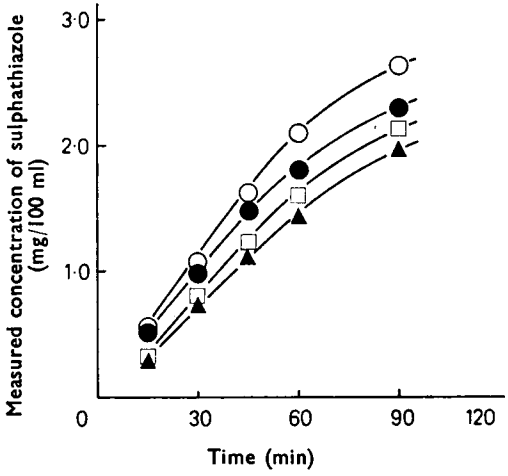

FIG. 5. Effect of starch (maize) on the dissolution profile of sulphathiazole tablets. ○ 10% maize starch. ● 7·5%, □ 5·0%. ▲ 2·5%.

dissolution rate. At low concentrations of polyethylene oxide, the tablets split at right angles to the axis whereas at higher concentrations the tablet became swollen and many fissures were observed. Tablets containing starch disintegrated and increase in the concentration produced a more rapid disintegration. In all cases the results quoted are the mean of two determinations.

Discussion

When adapted for dissolution tests, the British Pharmacopoeia disintegration apparatus has proved satisfactory, mainly because it allows a tablet to dissolve into a constant volume of liquid.

The problem of selecting and standardizing a dissolution test system, with respect to the agitation intensity necessary to provide representative sampling of the solution, has proved to be formidable. Efficient sampling of homogeneous solutions is a prime consideration in these tests, but also, it has been held by Levy (1963) that a certain degree of agitation could represent the conditions prevailing in the stomach. The main object of *in vitro* tests is the attempt to evaluate *in vivo* effects and hence any possible simulation of the latter should be earnestly considered.

Since we used a modified disintegration test apparatus, it was convenient to provide agitation similar to that provided in the official test. The vertical movement of the dialyser at a rate of 30 cycles/min produced suitable turbulence in the recipient fluid and smooth continuous dissolution profiles were obtained. Also, the oscillation of the dialyser produced alternate extensions and relaxations of the membrane when the dialyser was withdrawn from or immersed in the solution.

The dissolution profiles for the tablets made at different pressures indicates a decreased dissolution rate with increasing applied pressure over the range studied. Since the tablets remained intact the area available for dissolution is reduced on increasing the applied pressure by reduction in the tablet porosity. The method of determining dissolution profiles described appears to differentiate adequately between tablets prepared at different pressures. Using the Autoanalyser dialyser, much higher concentrations, indicating higher dissolution rates, were observed, due to the increased agitation of the tablet in the disintegration assembly.

It would be expected that the use of polyethylene oxide to reduce the onset of turbulence would result in an increase in the thickness of the stationary film adjacent to the tablet with an associated decrease in rate of dissolution. In fact, at the concentrations used, the swelling and slightly more hydrophilic nature of the polyethylene oxide appeared to override any retardation effect on dissolution rate and an increased rate was observed. Starch was also used to determine the ability of the apparatus to evaluate differences in dissolution rate of tablets of various disintegration properties. The dissolution rate increased with increasing starch concentration, due to the increased area available for dissolution.

The automated dialysis system is not restricted in use to the Autoanalyzer measuring system. It could, to advantage, be used with any

suitable pumping system and coupled with a recording spectrophotometer using a flow cuvette. In this way a wider range of materials could be examined.

Acknowledgements. We wish to thank the Science Research Council for a grant which permitted the acquisition of the Technicon Autoanalyser and for the financial support of one of us (R.B.B.) which enabled this work to be undertaken. Our thanks are also due to Technicon Instruments Ltd. for the loan of an Autoanalyser Dialyser and to Union Carbide Ltd. for supplying samples of polyethylene oxide.

References

Andrews, M. C. & Strauss, A. F. (1941). *J. Lab. clin. Med.*, **26**, 887–889.
Bratton, A. C. & Marshall, E. K. (1939). *J. biol. Chem.*, **128**, 537–550.
Ferrari, A. & Khoury, A. (1967). Second Conference on "*Automation in Industrial Pharmaceutical Process and Quality Control*". March 15–17. The New York Academy of Sciences.
Giles, W. B. & Pettit, W. T. (1967). *Nature, Lond.*, **216**, 470.
Krogerus, V. E., Kristoffersson, E. R. & Kehela, P. (1967). *Farmaceutiskt Notisbl.*, **76**, 122–125.
Levy, G. (1963). *J. pharm. Sci.*, **52**, 1039–1046.
Levy, G. & Hayes, B. A. (1960). *New Engl. J. Med.*, **262**, 1053–1058.
Marlowe, E. & Shangraw, R. F. (1967). *J. pharm. Sci.*, **56**, 498–504.
Michaels, T. P., Greely, V. J., Holl, W. W. & Sinotte, L. P. (1965). *Ann. N.Y. Acad. Sci.*, **130**, Article 2, 568–574.
Niebergall, P. J. & Goyan, J. E. (1963). *J. pharm. Sci.*, **52**, 29–33.
Patel, N. K. & Foss, N. E., (1964). *Ibid.*, **53**, 94–97.
Patel, N. K. & Kostenbauder, H. B. (1958). *J. Am. pharm. Ass., Sci. Edn.*, **47**, 289–293.
Schroeter, L. C. & Wagner, J. G. (1962). *J. pharm. Sci.*, **51**, 957–962.
Shotton, E. & Ganderton, D. (1960). *J. Pharm. Pharmac.*, **12**, *Suppl.* 87*T*–92*T*.
Werner, A. E. A. (1939). *Lancet*, **1**, 18–20.
Wrightman, K. B. & Holl, W. W. (1965). *Ann. N.Y. Acad. Sci.*, **130**, Article 2, 516–524.