The evaluation of a column-type dissolution apparatus

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An improved column-type dissolution apparatus is described. The column of the apparatus is built from standard screw-cap connected 'Sovirel' glass tubes which should enable inter-apparatus variability to be reduced. The main problem with this type of device is the build up of back pressure as fragments from the disintegrating solid dosage form progressively block the filtration system, itself necessary to stop the solution process and present the solution for analysis. A simple type of light-activated switch is therefore used which works across the indicator float of a flow meter to drive a motor connected to a needle valve. As the float falls the motor is switched on to open the valve and increase the flow rate until the float rises again and causes the motor to switch off. Observation on the dissolution characteristic of dyed lactose tablets and the injection of dye solutions into the flowing stream of liquid around tablets showed that there was back-flow of solution at Reynolds Numbers below 10 but visible instability of flow at Re>100. Over a range of flow rates between Re 10–70 the mass of drug released at a given time was a direct function of flow rate for a film coated product but an inverse function for a sugar coated tablet. The results are discussed in relation to the main problems which can be experienced with a column-type dissolution apparatus.

Although the need to establish the dissolution behaviour of the drug solid dosaged forms has long been recognized, the variety of suggested methods (e.g. Hersey, 1969) would indicate that there is less agreement on the requirements for such methods, including the design of the apparatus and operating conditions.

The only dissolution method to gain official recognition to date is the rotating basket device described in the United States Pharmacopeia XVIII but this has been criticized (Beyer & Smith, 1970; Shah & Moore, 1970; Withey, 1971).

Langenbucher (1969) discussed the problem and suggested that the column-type of apparatus had advantages since it was possible to control both the flow rate and the mass transfer conditions with some precision. He suggested a simple device in which the product under test is continually bathed in a stream of fresh solvent flowing under streamline conditions, and he provided a means of calculating dissolution parameters obtained when using this apparatus. Although dimensions are described, we did not find it easy to reproduce this apparatus. In addition, Lerk & Zuurman (1970) found that the use of a pulsating pump as described by Langenbucher produced unacceptable fluctuations in flow rate which to some extent could be overcome by the use of a centrifugal pump.

Tingstad and his co-workers (Tingstad & Riegelman, 1970; Tingstad, Gropper & others, 1972, 1973; Tingstad, Dudzinski & others 1973) designed and evaluated a similar device based on standard components supplied by a firm of membrane filter manufacturers. These authors incorporated a filter in their unit to enable the effluent

to be continually monitered by a flow-through spectrophotometer but reported that the flow rate through the apparatus had to be continually adjusted by hand (Tingstad & Riegelman, 1970) owing to progressive blockage of the filter by the product disintegrating under test.

During our own investigation of the properties of coated oxytetracycline tablets (Groves, 1973) it seemed that there were undoubted attractions in using the column method provided the apparatus could be standardized in some manner and the problem of filter blockage either overcome or compensated for by some means or another.

MATERIALS AND METHODS

In general a column-type dissolution apparatus consists of a column or tube through which liquid is passed or pumped after heating to an appropriate temperature. The liquid containing the solute must then be clarified and analysed. The apparatus will therefore usually incorporate ancilliary attachments such as reservoirs, valves, flow-measuring devices and some means of supporting the solid dosage form under test (Fig. 1). It seemed to us that the main problem to be overcome in any design would
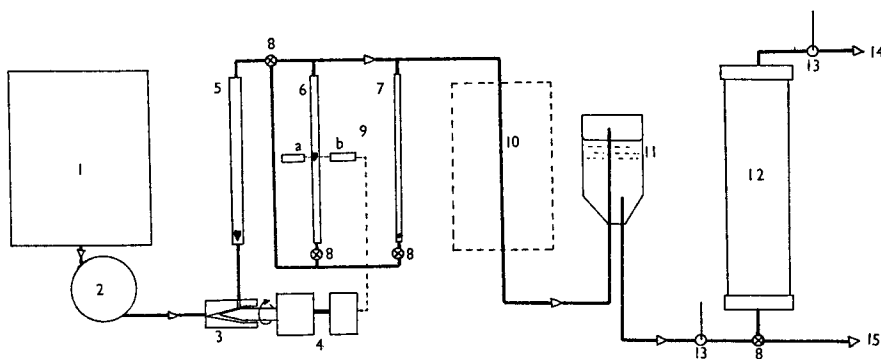

Fig. 1. Flow diagram for column dissolution apparatus. 1–20 litre aspirator as liquid reservoir. 2–Charles Austin Model C25 centrifugal pump. 3–needle valve fitted to Rotameter tube. 4–motor unit to drive needle valve. 5,6,7–rotameter flow meters. 8–valves. 9–light activated switch, a–b across flow meter float. 10–heat exchanger. 11–pressure fluctuation vessel. 12–dissolution column. 13–thermometers. 14–outlet to fraction collector. 15–outlet to column drain.

be uniformity of dimensions, to allow reproducibility of flow conditions in replicated equipment, and the slowing down of the flow rate as the filtration unit experiences progressive blockage. The column and its connections were therefore constructed from Sovirel (V. A. Howe Ltd.) screw assemblies (details in Fig. 2), using wherever possible standard tubing.

Inlet and tablet support. This is a Sovirel connecting tube 18 mm internal diameter and, for convenience, cut to a length of 80 mm. The cut end is polished and closed with a 72 mesh stainless steel gauze using epoxy resin cement. In the centre of the gauze is fixed, also with epoxy resin cement, the end of the longest arm of a cross made by forging two unequal lengths of gold-palladium wire (0·5 mm dia.), the centre of the cross being 18 mm from the surface of the gauze.
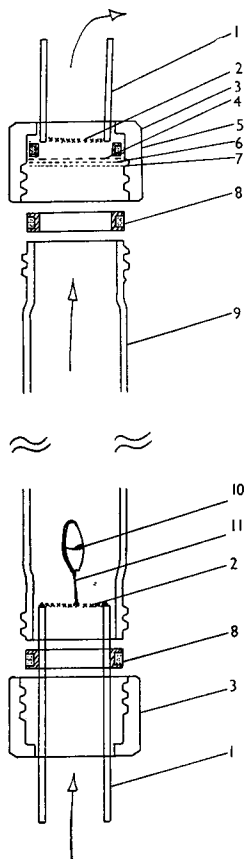
FIG. 2. Dissolution column. 1–Sovirel (V. A. Howe Ltd.) connecting tube, No. 4. 703–02. 2–72 mesh stainless steel gauze. 3–Sovirel sliding connecting sleeve, No. 4. 701–43. 4–Sovirel Teflon-faced silicon rubber sealing ring 4.701–245. 5–cellulose paper, Whatman, No. 540. 6–1·0 μm microfibre glass paper, Whatman, type GF/C. 7–1·5 μm microfibre glass paper, Whatman, type GF/B. 8–Sovirel Teflon-faced silicon rubber sealing ring 4·701–03. 9–Sovirel connecting tube, No. 4. 703–30. 10–tablet, held 1 inlet tube diameter above surface of gauze. 11–gold-palladium wire cross.

Main column. The inlet tube is held concentrically inside a standard length Sovirel double ended connecting tube, internal diameter 28 mm, by a sliding connecting sleeve and a Teflon-faced silicon rubber sealing ring.

Filter unit and outlet. The outlet is similar to the inlet and is also closed with 72 mesh stainless steel gauze. The filtration system consists of 24 mm circles cut from, in sequence, 1·5 μm microfibre glass paper, 1·0 μm microfibre glass paper and cellulose paper, and sandwiched between two Teflon-faced silicon rubber rings. This whole unit can be held securely inside the connecting sleeve, with the metal gauze at the end of the outlet tube butting onto the filter surface and holding it in position.

Automatic flowrate control. The problem of maintaining a constant flow rate through the apparatus can be overcome by constant manual control of the regulating valve. However, a simple light-activated switch was designed to monitor the position of the float in the flow meters and operate the needle valve with a suitable motor.

This device is shown in Fig. 3 and consists of a light bulb set opposite a photo-conductive diode. Using magnetic clamps on the metal faceboard of the flow meter support, the light and detector can be straddled across any desired position of a flow tube so that the float in the tube will block off sufficient of the light to keep the reed relay switch open. As the flow rate decreases the float sinks and the increase in received light is sufficient to activate the relay, bringing the motor into circuit. By rotating the needle valve the flow rate is increased until the float rises and once again causes the switch to open and stop the motor. Manual adjustment of the needle valve is allowed for by appropriate directional switches and speed controls.
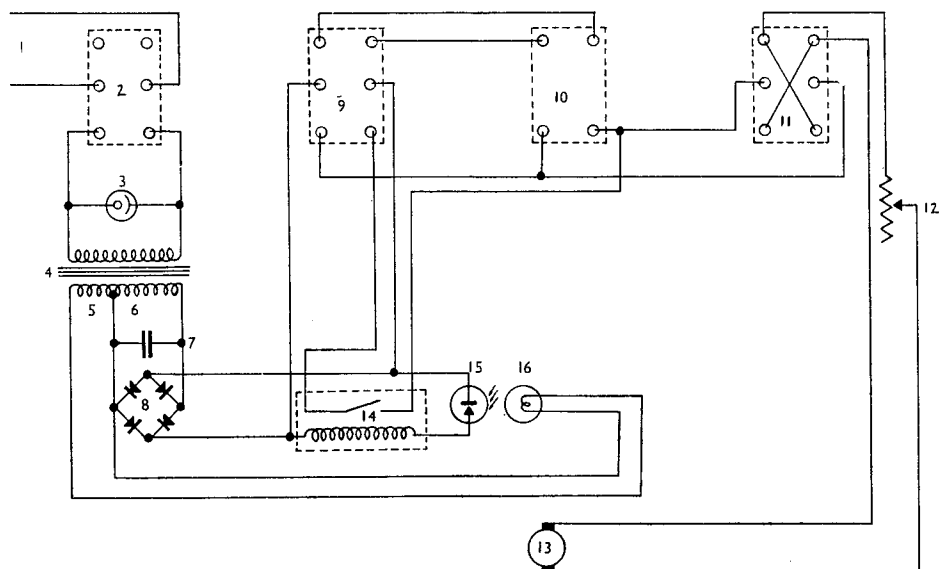

FIG. 3. Circuit diagram for light activated switch. 1–mains inlet. 2–on-off double pole double throw switch. 3–neon indicator light. 4–transformer. 5–6 V outlet. 6–20 V outlet. 7–1000 pF smoothing condenser. 8–rectifier (R.S. components REC 41A). 9–auto-manual select D.P.D.T. switch. 10–manual on-off D.P.S.T. switch. 11–forward/reverse D.P.S.T. switch. 12–motor speed control (100 ΩR.S. components potentiometer). 13–needle valve drive motor, 20 V synchronous. 14–reed relay switch (R.S component, R. R. 12–18V). 15–photodiode. 16–6 V pilot lamp.

Method

After assembly of the apparatus and positioning of the tablet vertically with its centre one inlet-tube diameter above the inlet gauze, the operating conditions are chosen and the pump switched on. Providing the filters at the top of the column are dry the air can be progressively displaced from the device and there is time to adjust the flowrate to a required value before the liquid level in the column reaches the suspended tablet, zero time. The effluent is collected over a period of time, at the end of which the pump is stopped and all the liquid remaining in the column, together with undissolved solid, is withdrawn by downward displacement into a receiver for subsequent analysis by opening the tap (8, Fig. 1) to the outlet 15. It is not therefore necessary to run a dissolution experiment to completion in order to know the content of the tablet under examination, and this proved to be a valuable feature when investigating products which release their content relatively slowly.

RESULTS

Observation with dyed tablets

Lactose compacts (0·7 g) were prepared from spray dried lactose in a single punch instrumented tablet machine at a pressure of 200 MN m^{-2}. Known quantities of malachite green were added to each tablet by allowing small volumes of solution (from an Agla Syringe (Wellcome Foundation)) to evaporate to dryness on the flat surfaces. These tablets were then used to evaluate the flow behaviour of the dissolution apparatus.

At flow rates below 8 ml min^{-1} (Re = 10) there was a tendency for solute to flow back, against the direction of flow. This back flow has been reported by Fee, Grant & Newton (1973). Although the density of the potassium chloride solution used by Fee & others is high in relation to the oxytetracycline solution of interest to us, and the backflow here would probably consist of almost saturated lactose solution, the lower limit for use of our apparatus was regarded as being Re = 10.

Increasing the flow rate showed that streamlines around the suspended tablets were smooth up to Re>100, at which point there was a slight tendency for disturbances to appear immediately downstream of the tablet. Repeated experiments using the dyed lactose tablets showed that recovery of the dye was in excess of 98 % between Re = 10 and Re = 100. This was regarded as satisfactory for our purpose, and suggested that there were no significant "dead spaces" in the apparatus.

Coated oxytetracycline cores

Cores for coated tablets of oxytetracycline were obtained from two manufacturers (details Table 1), together with examples of the final coated product made from the same batch of cores. Dissolution rates were measured at Re 17·5 in the Clark and Lub HCl/KCl buffer solution, pH 2·0, at 37°. Results are shown in Table 1. There is a surprising degree of uniformity of results within a batch of cores which suggests that the variability due to instrument and assay effects is small.

Table 1. *Dissolution times of replicate runs on coated 250 mg oxytetracycline tablets and cores in pH 2·0 buffer at 37° and Re 17·5.* (t_{50} estimated from dissolution curves plotted on log-probit plot, 16 replicates).

Sample		Mean t_{50} min	Standard error
Batch A	Core (chloride equivalent to 250 mg base)	20·5	1·85
	Film coated	20·3	0·83
Batch B	Core (dihydrate equivalent to 250 mg base)	34·4	3·3
	sugar coated	90·5	14·5

The effect of flow rate on dissolution behaviour

The results in Table 1 support the suggestion that the variability of results seen previously (Groves, 1973) may be largely due to the sugar coat. A separate batch (C) of tablets containing the dihydrate, and sugar coated, appeared to have completely different dissolution characteristics when compared by the stirred beaker method
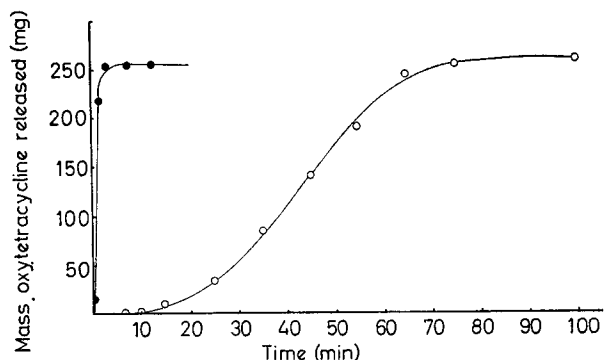
FIG. 4. Dissolution profiles of oxytetracycline tablets by a stirred beaker method (Groves, 1973), 250 mg tablets in pH 2·0 buffer at 37° stirred at 50 rev min⁻¹. ● Film coated tablet (batch A Table 1). ○ Sugar coated tablet (batch C), core containing oxytetracycline dihydrate equivalent, to 250 mg base.

with a batch of film coated oxytetracycline chloride tablets (A), Fig. 4. It was therefore of interest to see how each product would behave at increasing flow rates in the column apparatus. The experiments were carried out between Re 10–70 in the pH 2·0 buffer solution, but at room temperature to simplify the system.

Results are shown in Fig. 5 and are not strictly comparable since the differences in behaviour required that different times should be used for reading the results. However, the anticipated effect of increasing the dissolution rate by increasing the flow rate is clearly shown in Fig. 5a for the film coated tablet. This product disintegrates rapidly once it is wetted so that the results for dissolution at 7 min are obtained effectively on the disintegrated particles. The sugar coated product, C, on the other hand, is very slow to disintegrate and shows the opposite effect. In this case the coat splits and exposes the ends of the core to the solvent action of the liquid continuum but at the 110 min reading time the two flattened surfaces of the coat are still intact. This may be due to an instrument artifact since the arms of the mounting cross are
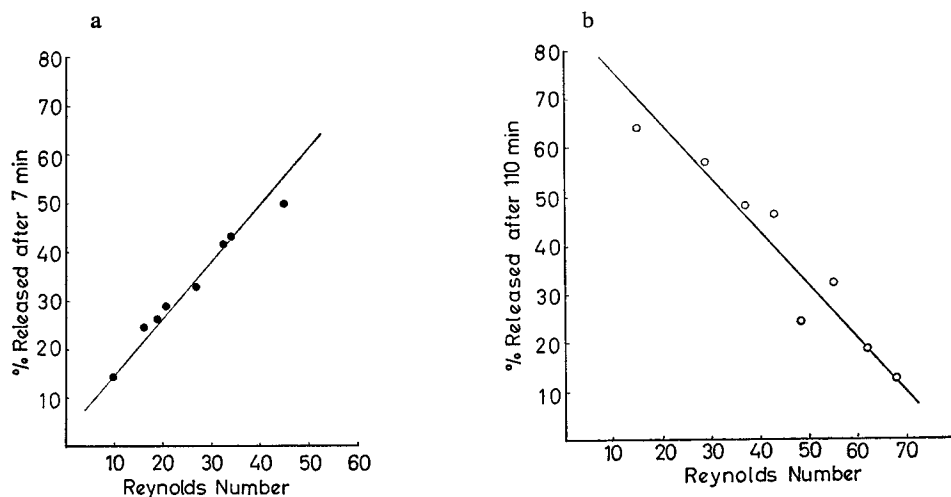

FIG. 5. The effect of flow rate on the % released: a, oxytetracycline tablet A after 7 min (film coated); b, oxytetracycline tablet C, after 110 min (sugar coated).

holding the tablet together within the two clam-like sections of intact coating, and mass transfer can only take place around the exposed rim.   The effect seen in Fig. 5b may be due to almost static liquid accumulating within the burst tablet and re-entrant streamlines downstream of the tablet.   These will slow the apparent release rate down as the velocity of the main liquid increases and the volume of static liquid increases downstream of the, now, irregularly shaped object.

DISCUSSION

Although the present device is another form of dissolution apparatus, the advantages inherent in a column flow method are such that it deserves closer attention.   The influence that flow rate, expressed as Re, can have on the dissolution characteristics on a solid dosage form is well established.   Since Re is influenced by dimensions of apparatus as well as the linear velocity of the liquid itself, any attempt to standardize dissolution measurements on generic formulated drugs will have to specify with some precision the various operating conditions, whichever method is employed.   The variability of the USP XVIII rotating basket procedure is such that it is hardly an appropriate procedure for an official method (Withey, 1971) and alternative methods are required.   Tingstad & others (1972) pointed out that the column method could eliminate or greatly reduce the potential difficulties inherent in all variations of the beaker method.

The use of standard and readily available catalogue items of glassware, together with the added convenience of screwed interconnecting pieces which can be used to hold filters in place, would seem to have a considerable advantage over previous attempts to standardize the apparatus (e.g. Tingstad & others, 1972).   The problems associated with blockage of the filtration system represent a limitation of the device since substantial quantities of gelatinous material will block the filters readily. However, the use of a light activated switch to control the flow rate has overcome the need to continually adjust the apparatus manually when used on non-gelatinous disintegrating products.   This has improved the applicability of the device considerably and, in so doing, appears to have increased the accuracy since the main source of fluctuation has been removed.

The importance of bathing the solid dosage form in liquid moving in streamline parallel flow cannot be overemphasized.   In this connection the relevance of the metal gauze at the column inlet, 2, Fig. 2, should be noted since a gauze is the ideal method of restoring streamline flow in a system which may be unstable (Boothroyd, 1971).   To some extent instabilities in the inlet pipe may develop since bends and constrictions are required when bringing the liquid to this point, and cannot otherwise be removed except by making the inlet pipe unrealistically long.

Sources of experimental variation are to be found in the method of assay, the accuracy of the taking of samples, measurement of the sample times, variability of flow rate and temperature within the device, and uncertainty of the recovery procedure i.e. the presence of "dead space" or absorption of the drug into surfaces exposed to the solution.   On top of these must be superimposed the variability of the solid dosage form itself which is completely unknown.   For this reason it is not possible to separate sources of variation due to the instrument from those inherent in the product under test.   However, Table 1 shows that the combined errors are low for at least three of the products tested and this suggests that the instrument error itself is small.

As noted, the column method may not be ideal in some limited applications which involve gelatinous materials, and it is possible that under some circumstances artifacts may develop in the system under test. This may be the explanation for the results shown in Fig. 5B, obtained in the isolated case of a product which was extremely slow to disintegrate and dissolve even when tested by the beaker method. A problem experienced here was the inordinate volume of solution produced for assay during an experiment which could take as long as 6 h for completion. In general, however, this new device is proving a valuable tool for the investigation of the dissolution behaviour of tabletted materials.

Acknowledgements

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