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An automated apparatus for dissolution studies

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An automated apparatus for dissolution rate studies of solid dosage forms under sink conditions at constant volume has been developed. Sink condition was maintained in the small volume of the buffer by continuous elimination of the solution and replacement with fresh buffer. A mathematical treatment of the dissolution-dilution system for the apparatus is given. The validity of the calculations has been proved using clomipramine solution and tablets.

The *in vitro* release of drug from solid dosage forms has been subject to intensive studies in recent years (Morrison & Campbell, 1965). A variety of techniques is used to determine *in vitro* dissolution rates of medicaments from these dosage forms. Hersey (1968) has classified the methods in three groups: (*a*) natural convection, non-sink methods, (*b*) forced convection, non-sink methods, (*c*) forced convection, sink methods.

Noyes & Whitney (1897) had derived a differential equation for a dissolving substance in a medium as

$$\frac{dc}{dt} = KS(C_s - C), \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where dc/dt is the rate at which the substance is dissolving across a surface area S, and $(C_s - C)$ is the concentration gradient between C_s, the concentration of substance in a thin saturated liquid film adjacent to the dissolving surface and C the concentration in the surrounding bulk medium. K is a rate constant for dissolution incorporating the diffusion coefficient and the film thickness. If in the above equation the concentration gradient $C_s - C$ tends towards C_s, the retarding effect on the solubility of the substance becomes negligible. Equation (1) may be rewritten as

$$\frac{dc}{dt} = KSC_s \quad .. \quad .. \quad .. \quad .. \quad (2)$$

This is known more generally as sink condition and may be achieved by removal of the solute from the dissolving medium. The methods to obtain sink conditions are: use of (*a*) an adsorbent, (*b*) an organic phase, (*c*) dialysis.

We have sought to develop an automated apparatus for dissolution rate studies under sink conditions and to find a way for maintaining sink conditions in a single phase system of small volume.

EXPERIMENTAL

Description of the apparatus

Two thermostated glass cylinders C_1 and C_2 (diameter 45 mm) are connected to each other with a tube A in such a way that the dissolution medium can flow from

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C_1 to C_2. A constant volume of dissolution medium is maintained by means of an overflow system S. This consists of an adjustable tube S_1 connected to a pump P_1 leading to the reservoir S_2. The replacement of dissolution medium in S_2 is by the pump P_1 from the main reservoirs S_3 and S_4 respectively.

Tube A is connected to a vacuum pump by means of a T-shaped tap, which permits a rapid removal of dissolution medium from either cylinder or from both. Cylinder C_2 is equipped with a four blade stirrer R (diameter 15 mm) with adjustable speed to maintain a homogeneous solution. From this cylinder the solution is pumped off continuously by pump P_2 (Beckman solution metric pump) through tube B, filtered at F (Millipore type SC) to remove foreign particles, and the absorbance is continuously measured and recorded in the spectrophotometer Sp (Beckman DB-G; W+W recorder type 202). Fig. 1 illustrates the set-up.

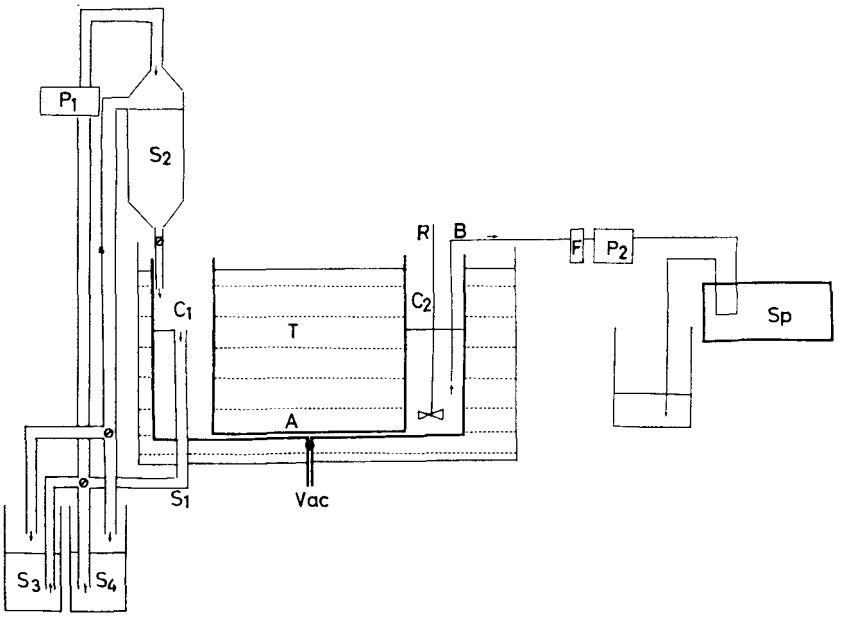

FIG. 1. Design of the apparatus for dissolution studies. C_1, reservoir cylinder. C_2, testing cylinder. P_1, P_2, pumps. S_1–S_4, overflow system. A, B, tubes. R, stirrer. F, filter. Sp, spectrophotometer. Vac., vacuum. T, const. temp. bath.

For the simultaneous determination of several dissolution rates a number of testing cylinders C_2 can be connected to cylinder C_1. All studies were made at 37 $\pm$ 0·1°.

Procedure

Elimination of dissolved drug. A concentrated solution containing a known amount of drug is injected in cylinder C_2 containing 150 ml of distilled water. The solution is stirred at a selected rate and the pump is adjusted to remove the solution at a fixed flow rate.

Clomipramine [3-chloro-5-(3-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenz[b,f]-azepine hydrochloride; Anafranil, GEIGY] was the drug used in the present work. The stirring rate was 200 rev/min and the flow rates were: 2, 5, 8, 11 and 14 ml/min.

Dissolution of drug from tablets. Artificial gastric juice (USP, without enzymes) is adjusted to a volume of 150 ml in cylinder C_2. A tablet to be tested is added.

The flow rate of the eliminating pump is adjusted to a suitable rate and the speed of the stirrer maintained at a constant rate. The absorbance is continuously recorded at a chosen wavelength.

For the present study the flow rate was 2 ml/min, the stirring rates 50, 100, 200, 400 rev/min and the wavelength 252 nm.

Calculation

Rate of elimination of dissolved drug under constant volume condition. Consider that c_0 is the amount of dissolved drug at time Zero and E the rate of elimination of the solution at constant volume. Hence

$$E = \frac{F}{V} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (3)$$

where F = flow rate in ml/min
V = constant volume in cylinder C_2 in ml

The rate of change of concentration in the solution can be expressed as

$$-\frac{dc}{dt} = E \cdot c \quad .. \quad .. \quad .. \quad .. \quad (4)$$

By integrating between the limits c_0 and c_t the above equation becomes

$$\int_{c_0}^{c_t} \frac{dc}{c} = -E \int_{0}^{t} dt \quad .. \quad .. \quad .. \quad .. \quad .. \quad (5)$$

and therefore

$$c_t = c_0 e^{-Et} \quad .. \quad .. \quad .. \quad .. \quad (6)$$

The rate of change of concentration in the solution under constant volume condition is a first order kinetic.

Calculation of drug dissolved from solid dosage forms. This calculation has been done assuming the time interval Δt is small and at no time exceeds 2 min.

The amount of drug released after Δt in a given volume will be

$$C_1 = c_1 + c_1 \Delta t\, E \quad .. \quad .. \quad .. \quad .. \quad (7)$$

where c_1 = amount of drug observed in the solution;

$c_1 \Delta t\, E$ = amount of drug eliminated from the solution during the interval Δt.

After the next interval Δt the amount released is calculated similarly,

$$C_2 = c_2 + c_1 \Delta t\, E + c_2 \Delta t\, E$$
$$C_2 = c_2 + \Delta t\, E\,(c_1 + c_2) \quad .. \quad .. \quad .. \quad (8)$$

and so on, until the peak of the curve is reached, where the amount of drug released will be

$$C_p = c_p + \Delta t\, E\,(c_1 + c_2 \ldots c_p)$$

$$C_p = c_p + \Delta t\, E \sum_{i=1}^{i=p} c_i \quad .. \quad .. \quad .. \quad .. \quad (9)$$

Thus the amount of drug in the solution is equal to c_p.

When there will be no further release of drug from the dosage form, the elimination of the dissolved drug will follow equation (6). However, if the amount observed after the next interval of time is higher than the one calculated according to equation (6), the difference will show a further amount of drug dissolved during this interval.

Thus the drug released after the peak may be calculated for Δt as

$$C_{p+1} = c_{p+1} - c_p\, e^{-E\Delta t} \quad .. \quad .. \quad .. \quad .. \quad (10)$$

where C_{p+1} = amount of drug released in first interval after peak, c_{p+1} = amount observed in the solution, $c_p\, e^{-E\Delta t}$ = amount of drug expected by pure dilution according to equation (6) for interval Δt. The release during the next interval will be

$$C_{p+2} = c_{p+2} - c_{p+1}\, e^{-E\Delta t}$$

or in general form

$$C_{p+n} = c_{p+n} - c_{p+(n-1)}\, e^{-E\Delta t} \quad .. \quad .. \quad .. \quad (11)$$

When

$$c_{p+n} = c_{p+(n-1)}\, e^{-E\Delta t} \quad .. \quad .. \quad .. \quad (12)$$

equation (11) becomes

$$C_{p+n} = 0 \quad .. \quad .. \quad .. \quad .. \quad (13)$$

Thus, at the interval $(p + n)$ the amount observed in the solution being equal to the amount expected by pure dilution, there is no further release of drug.

Hence the total amount of drug released will be

$$C_T = C_p + \sum_{q=p+1}^{q=p+n} C_q \quad .. \quad .. \quad .. \quad .. \quad (14)$$

C_T = Total release, C_p = release of drug before peak, C_q = release of drug after peak. These calculations are conveniently done with an electronic desk-top computer Olivetti Programma 101 according to equations (9) and (14).

RESULTS

Elimination of dissolved drug

The results obtained with the different flow rates plotted on a semilog graph of rest concentration against time showed straight lines with the slopes $-E/2{\cdot}303$.

The experimental and calculated results are compared in Table 1.

Dissolution of drug from clomipramine tablets

The dissolution of drug from tablets containing 25 mg at stirring rates 50, 100, 200, 400 rev/min was examined. At the stirring rate of 50 rev/min a significantly different dissolution behaviour was observed compared with the higher stirring rates. As the results at the rates 200 and 400 rev/min were close, 200 rev/min was used. The results are in Fig. 2.

Tablets containing 11 mg of drug were tested. The results were obtained for a single tablet as well as for three tablets per run. The ultraviolet absorbance for one tablet being approx. 0·3, three tablets were chosen for the determination of average release and control of sink condition. The same effect may be achieved by decreasing the buffer volume. The results are in Fig. 3. Spectroscopic analysis was made in 0·1N HCl.

Table 1. *Comparison of experimental and calculated rest concentrations of dissolved drug under constant volume condition.* Dose 20 mg, volume 150 ml of artificial gastric juice without enzymes USP

Flow rate ml/min	Time (min)	Drug in solution in mg		Slope of the plot
		experimental*	calculated	
2	40	11·7	11·9	0·0058
	80	7·0	7·1	
	120	4·2	4·2	
	160	2·4	2·5	
	200	1·4	1·5	
	240	0·7	0·9	
	280	0·4	0·6	
	300	0·2	0·4	
5	20	10·1	10·2	0·0147
	40	5·2	5·2	
	60	2·7	2·7	
	80	1·3	1·4	
	100	0·5	0·7	
	120	0·2	0·4	
8	20	6·8†	6·7	0·0238
	40	2·4†	2·3	
	60	0·8	0·8	
	70	0·4	0·5	
11	10	9·8†	9·4	0·0331
	20	4·5†	4·4	
	30	2·1	2·1	
	40	0·9	1·0	
	50	0·3	0·5	
14	10	7·6†	7·5	0·0426
	20	2·8	2·8	
	30	0·9	1·1	
	40	0·3	0·5	

* Mean of three determinations.

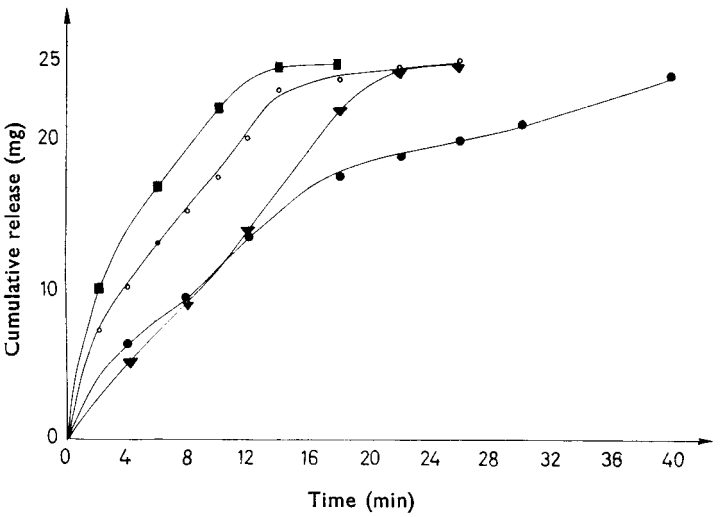

FIG. 2. Cumulative release of clomipramine from 25 mg tablets at different stirring rates. ● 50, ▼ 100, ○ 200, □ 400 rev/min.

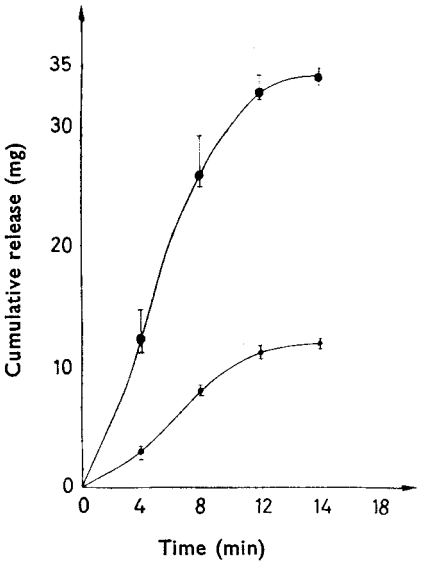

FIG. 3. Cumulative release of clomipramine from 11 mg tablets. ● 3 tablets (mean). • 1 tablet (mean). I maximum–minimum of single values.

From the above results it can be concluded that the apparatus provides reproducible results under sink condition.

DISCUSSION

In the present method it is easy to change from one buffer solution to another either by continuous change or by immediate vacuum removing and refilling. In the method discussed by Pernarowski, Woo & Searl (1968) only the continuous change is possible. The sink condition depends on the flow rate of the pump which may be adjusted if required. However, if at any moment the concentration of drug in solution goes beyond sink condition, the rapid removal and refilling of buffer may be helpful. The method of calculation remains the same.

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