An analogue computer simulation of drug dissolution

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The dissolution rate of salicylic acid from non-disintegrating discs at controlled pH has been determined. A theoretical model of dissolution has been developed in terms of the diffusion layer theory. This model has been programmed on an analogue computer and theoretical dissolution curves have been obtained. Experimental dissolution curves have been compared with simulated curves and the fit of the data has allowed the estimation of drug concentration in the diffusion layer.

The dissolution of salicylic acid from non-disintegrating discs into aqueous dissolution medium has been measured as a function of pH and agitation (Collett, Rees & Dickinson, 1972). Analysis of the data indicated that the system could be described as a diffusion controlled process. Such a system can be regarded as a bulk dissolution medium containing solute at a concentration below its saturation solubility and a diffusion layer, saturated with solute, above the dissolving solid.

The experimental procedure used previously was such that the pH of the bulk dissolution medium was controlled enabling reproducible dissolution rates to be obtained at any one pH. Brownian motion of the solute molecules within the diffusion layer has been reported to govern the dissolution rate of a solid (Nernst & Brünner, 1904). Hence a knowledge of pH and concentration of drug in the diffusion layer becomes important because of its role in controlling dissolution rate. However, in our previous report the pH of the diffusion layer was not known. If the pH of the diffusion layer could be measured then an estimate of the amount of drug present could be obtained from the relation between drug saturation solubility and pH.

The pH of the diffusion layer is not easily measurable with existing equipment and so an indirect method must be used. A suitable indirect method involves the use of an analogue computer.

METHOD

The apparatus and procedure for following the dissolution of salicylic acid from a constant surface area at controlled pH has been reported previously (Collett & others, 1972). Briefly, the apparatus consisted of a Perspex cylindrical dissolution cell in which the non-disintegrating salicylic acid disc (BDH A.R. grade, 1·0 g compressed at 300 MN m^{-2}, diameter 19·05 mm), contained in a titanium disc holder, was fitted in the base of the cell. The dissolution medium was stirred by a three bladed stirrer attached to an 80 rev min^{-1} asynchronous motor (Crouzet Ltd.). pH control was effected by a pH stat assembly (Radiometer, Denmark). Dissolution was followed under "sink" conditions for a limited time period and apparent zero order dissolution rate constants were obtained from slopes of amount of salicylic acid dissolved against time plots. In the present work, dissolution was allowed to

continue almost to equilibrium and first order rate constants were obtained from slopes of log concentration of salicylic acid against time plots at pH 1·0, 2·0, 3·0 and 3·5. Equilibrium concentrations were not attainable in the system within reasonable experimental time periods at pH values greater than pH 3·5.

An Applied Dynamics A.D. 256 computer was used for simulating dissolution rates. Outputs from integrators were recorded on a Bryant X.Y. recorder. To compare computer output with experimentally determined dissolution rates, the concentrations of salicylic acid in the bulk solution at known time intervals were converted to equivalent voltages using appropriate scaling factors. These voltages were plotted on X.Y. recorder paper against the computer time scale. Output of the integrators was systematically changed until potentiometer-generated curves were coincident with experimental results.

THEORY, RESULTS AND DISCUSSION

In terms of diffusion layer theory, dissolution can be considered as:
(1) drug transfer from a non-disintegrating disc to an aqueous diffusion layer saturated with drug,
(2) transfer of the drug from the diffusion layer to the bulk dissolution medium.
Equation (1) represents these processes as a series of reversible reactions.

$$D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S \underset{k_4}{\overset{k_3}{\rightleftharpoons}} M \quad .. \quad .. \quad .. \quad .. \quad .. \quad (1)$$
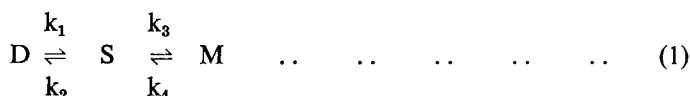
where D is the concentration of drug in the non-disintegrating disc, S is the concentration of drug in the diffusion layer and M the concentration of drug in the bulk dissolution medium, k_1 and k_2 are the rate constants for salicylic acid transfer from the non-disintegrating disc surface to the diffusion layer, k_3 and k_4 are the rate constants for salicylic acid transfer from the diffusion layer to the bulk solution.

The concentration of the drug in the bulk solution, at a controlled pH and time, can be measured and an overall estimate of dissolution rate obtained. Under diffusion-controlled conditions the overall rate of appearance of the drug in the bulk solution should be equal to the rate of drug transfer from the diffusion layer to the bulk solution. Thus, under these conditions the rate of achieving equilibrium drug concentration in the bulk, at any one pH, will depend on the drug concentration (and pH) in the diffusion layer. It is possible to simulate rates of achieving equilibrium in the bulk solution using different equilibrium values of S, whilst maintaining M constant. When the simulated rate of drug leaving the diffusion layer is equal to the real rate of increase in drug concentration in the bulk solution, then the simulated equilibrium concentration in the diffusion layer will be equal to the real equilibrium concentration in the diffusion layer.

The rate of change of amount of salicylic acid in each compartment with time is given by the following equations:

$$-V_d \frac{dD}{dt} = V_s k_2 (Sat - S^1) \quad .. \quad .. \quad .. \quad .. \quad (2)$$

where Sat and S^1 are respectively the equilibrium concentration and concentration at time, t, in compartment S.

$$-V_s \frac{dS}{dt} = V_s k_2 (Sat - S^1) + V_s k_3 S - k_4 V_m M \qquad .. \qquad .. \qquad .. \qquad (3)$$

$$V_m \frac{dM}{dt} = V_s k_3 S - k_4 V_m M \qquad .. \qquad .. \qquad .. \qquad .. \qquad (4)$$

where the volumes, V, of each compartment are denoted by the appropriate sub-scripts.

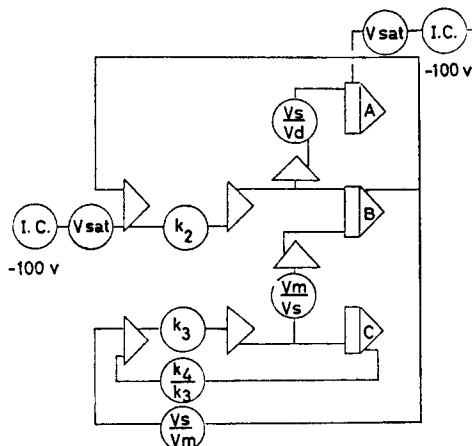The analogue computer program fitting these three equations is shown in Fig. 1.

FIG. 1. Analogue computer program for the simulation of dissolution to equilibrium. Integrators A, B and C represent the three compartments of the model (equation 1). I.C. = initial conditions.

Using the initial concentration of salicylic acid in each compartment, the settings on the initial condition potentiometers were calculated using appropriate scaling factors. The settings were arranged so that M was constant at any one pH but S could be changed to that of a saturated salicylic acid solution at any pH. The remaining potentiometers were set at values calculated using scaling factors.

It was considered most likely that S would be either a saturated solution of salicylic acid in water (pH 2·97, 4·49 kg m^{-3}) or at the pH of the bulk dissolution medium. Experimentally determined first order rate constants for appearance of drug in bulk solution at pH 1·0, 2·0, 3·0 and 3·5 are shown in Table 1. Corresponding simulated first order release rate constants from the diffusion layer at a concentration either equivalent to the bulk medium or pH 2·97 are also shown. Fig. 2 is a typical plot of experimentally determined concentration of salicylic acid in the bulk dissolution medium against time at pH 1·0. The line is computer-simulated for bulk medium at pH 1·0 and the diffusion layer at pH 1·0.

There is close agreement between experimental dissolution rate and release rate from a simulated diffusion layer at the same pH as the bulk medium. When these two rates are equal the indications are that the simulated equilibrium concentration, S, is equal to the real equilibrium concentration in the diffusion layer. When the simulated diffusion layer is at a pH other than the pH of the bulk medium, no correlation is evident. Assuming that dissolution is diffusion controlled, then the diffusion
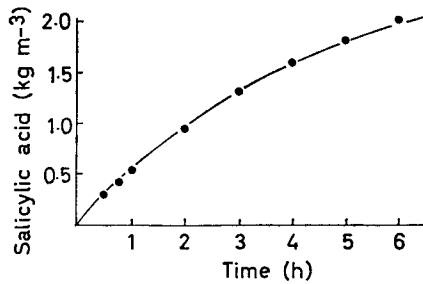
FIG. 2. Plot of concentration of salicylic acid in the bulk dissolution medium at pH 1·0. ● Experimental points. —— Computer simulated line for bulk medium and diffusion layer at pH 1·0.

Table 1. *Experimentally determined dissolution rate constants, and analogue computer determined values of release rates from diffusion layer.*

pH of bulk solution	Experimental dissolution rate constant $(s^{-1}) \times 10^5$	Release rate from simulated diffusion layer $(s^{-1}) \times 10^5$	
		(a)	(b)
1·0	6·62	6·55	6·66
2·0	4·08	4·16	4·44
3·0	2·66	2·77	3·00
3·5	2·41	2·44	5·27

(a) Concentration in diffusion layer equals concentration at bulk pH.
(b) Concentration in diffusion layer equals concentration at pH 2·97.

layer will be at the same pH as the bulk solution. This observation is of importance when considering the design of *in vitro* dissolution tests. In particular an apparatus designed to institute a pH gradient dissolution procedure (Swarbrick, 1970) must take into account the influence due to change of bulk solution pH on diffusion layer pH and its consequent effect on dissolution rate.

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